

Studies in the psychopathology, neurobiology and psychopharmacology of schizophrenia.

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Declaration

I, the undersigned, declare that the work contained in this dissertation is my own original work, and has not previously been submitted for a degree in its entirety or in part at any other University for a degree

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Robin Emsley

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Summary

The overall aim of these studies was to investigate selected aspects of psychopathology, neurobiological abnormalities and treatment in schizophrenia.

The following topics were researched:

1. Psychopathology:

We explored the symptom structure of schizophrenia by means of principal components and factor analysis in two separate samples.

- a. The first study investigated the nature of symptoms in patients with a first-episode of schizophrenia, in a large cohort of patients who were participating in a multinational clinical trial. We compared our findings with similar analyses previously conducted in multi-episode schizophrenia patients.
- b. We then assessed the influence of culture on the symptom structure of schizophrenia by conducting a principal components and factor analysis of the symptom ratings in a large sample of South African Xhosa patients with schizophrenia, and comparing the results with those in other parts of the world.
- c. We investigated the occurrence of co-morbid depressive and anxiety symptoms, and their demographic and clinical correlates. The sample for this study comprised acutely psychotic patients who were participants in clinical drug trials conducted at our centre.
- d. To explore the relationships between obsessive-compulsive disorder and schizophrenia, we conducted a review of the relevant literature.

2. Neurobiological abnormalities:

- a. We performed a series of studies to investigate disorders of water homeostasis and vasopressin secretion in schizophrenia. To test the hypothesis that acutely psychotic patients have disordered regulation of water homeostasis, we applied a dynamic suppression test - a water loading test, with assessment of excretory capacity (including arginine vasopressin assay) in acutely psychotic patients. To evaluate whether a subset of patients with schizophrenia and co-morbid disordered water homeostasis sustained cerebral damage as a consequence of water intoxication we did the following experiment: We identified a cohort of subjects with schizophrenia and disordered water homeostasis and compared them with patients with schizophrenia without disordered water homeostasis in terms of cerebral ventricular size and cognitive function. To assess the prevalence of disordered water homeostasis in a long-term inpatient sample of psychiatric patients we conducted serum sodium screening tests. Those subjects with dilutional hyponatraemia were then further investigated for dysregulation of water homeostatic mechanisms.
- b. We studied neurological soft signs in a sample of subjects with first-episode schizophrenia followed up over a two year period. We investigated their occurrence, relationships to psychiatric symptoms and medication effects, their

temporal stability and their outcome correlates. We also investigated their potential to predict outcome in schizophrenia

3. Treatment aspects

A great deal of our work has focussed on the pharmacological treatment of schizophrenia. The following aspects of treatment are included in this thesis:

a. Treatment effects on psychiatric symptoms:

- i. To assess the effects of ethnicity on treatment outcome in schizophrenia we compared the acute response to antipsychotic treatment in 3 ethnic groups, namely blacks, coloureds and whites. We included patients in this analysis who had participated in clinical trials in our department as well as the Department of Psychiatry in the University of the Free State. Patients had been treated under blinded conditions over a 6-week period.
- ii. After discussions with the late Dr David Horrobin, who had pioneered possible applications of the omega-3 fatty acids in the treatment of various psychiatric disorders, we became interested in further investigating the potential of this group of compounds as an affordable adjunct to treating schizophrenia. We assessed the antipsychotic potential of the omega-3 fatty acid, ethyl-eicosapentaenoic-acid (e-EPA) supplementation versus placebo supplementation in a small sample of subjects with schizophrenia who had been only partially responsive to antipsychotic treatment previously. We also conducted a review of the literature to evaluate the evidence for efficacy for the omega-3 fatty acids in schizophrenia according to published studies.

b. Treatment effects on neurological abnormalities:

- i. In a single-blinded controlled study we compared a new generation antipsychotic to a conventional antipsychotic in the treatment of tardive dyskinesia (TD). This was a long-term (1 yr) study in patients with chronic schizophrenia and established tardive dyskinesia.
- ii. We also assessed the effect of omega-3 fatty acid (e-EPA) supplementation in treating TD. This was conducted in a larger sample (n=84) of patients with chronic schizophrenia and established TD. The blinded, placebo-controlled phase was 12 weeks. This was followed by an open-label extension for 40 weeks.

c. Conventional versus new generation antipsychotic agents.

Several evidence-based literature reviews of the efficacy and tolerability of the new generation of antipsychotics compared to the conventional agents were conducted. Some multinational, randomised, controlled clinical trials in which the author was principal investigator, are included in this thesis. Also, studies addressing patients with partial treatment refractoriness are included, as well as studies of the effects of antipsychotics on depressive symptoms,

body mass and glycaemic control. Finally, we have included a pharmacoeconomic study comparing a conventional antipsychotic (haloperidol) with a new generation antipsychotic (quetiapine) in partially refractory patients in a South African setting.

Findings and conclusions:

1. Psychopathology:

Our studies demonstrated that the factor structure for the symptoms of schizophrenia is replicable across samples, and is not greatly influenced by ethnic and cultural factors. However, changes in the factor structures do occur over time. There are symptom domains that are present in first-episode schizophrenia but disappear as a distinct entity as the illness becomes chronic. Particularly, a motor component is evident in untreated patients, but disappears after initiation of treatment. We found that depression and anxiety are common co-morbid symptoms in schizophrenia, and have important clinical and outcome correlates. Depressive symptoms in the acute psychotic phase of schizophrenia are associated with a favourable prognosis and diminish as the symptoms of psychosis improve in response to antipsychotic treatment. However, persistent depressive symptoms are associated with a poorer prognosis, and require additional therapeutic intervention.

2. Neurobiological abnormalities:

We investigated the occurrence of disordered water regulation in a population of psychiatric inpatients, and conducted further investigations on those identified, in order to establish mechanisms involved. Polydipsia and the syndrome of inappropriate antidiuretic hormone secretion (SIADH) were found to occur in a subset of patients with schizophrenia, and are associated with acute psychosis, as well as with some psychotropic medications. These patients are characterised by more severe cognitive impairment and evidence of cerebral atrophy. The condition can become life-threatening in the presence of other factors impeding water excretion, particularly thiazide diuretics.

Neurological soft signs were investigated in a sample of patients with a first-episode of schizophrenia. These soft signs appear to be trait-like (present early in the illness, and stable over time), except for a motor sequencing factor. Patients performing poorly on this latter group of tests have a longer duration of untreated psychosis, and are at significant risk for developing TD.

3. Treatment aspects:

Our studies suggest that there are important ethnic differences in antipsychotic treatment response, but that these differences could be explained by a number of environmental and biological factors. As was found with many studies worldwide, we found that the new

generation antipsychotics have important efficacy and safety advantages over their predecessors. Risperidone was as effective as haloperidol in first-episode psychosis, but with a more favourable side-effect profile in terms of reduced extrapyramidal symptoms. Quetiapine treatment in partially refractory patients resulted in more responders compared to haloperidol, and fewer extrapyramidal symptoms. However, evidence of a different side-effect profile is emerging. Of particular concern is the finding that some of the new antipsychotics cause weight gain, glucose intolerance and dyslipidaemias. We found that one novel antipsychotic, quetiapine, was not associated with significantly more weight gain or disordered glucose metabolism than a conventional agent, haloperidol. The omega-3 fatty acids, particularly EPA may have a role in the treatment of various psychiatric disorders. Our studies provided mixed results – the first found a significant beneficial effect on psychotic symptoms and dyskinesia scores for EPA supplementation, while the second failed to demonstrate a beneficial effect on TD or psychotic symptoms. We explored the early treatment response in first-episode psychosis and found, unlike that reported in multi-episode patients, some patients took a long time to respond. We also found that early treatment response was a significant predictor of later remission, as was duration of untreated psychosis, educational level and baseline excitement factor scores. Finally, our pharmacoeconomic study conducted for South African circumstances in patients with a partial response to conventional antipsychotic treatment showed cost-neutrality or cost-benefits for quetiapine compared with haloperidol treatment for direct costs.

Opsomming

Die oorkoepelende doel van hierdie studies was om geselekteerde aspekte van psigopatologie, neurobiologiese abnormaliteite en behandeling in skisofrenie te ondersoek. Die volgende onderwerpe is nagevors:

4. Psigopatologie:

Ons het die simptoomstruktuur van skisofrenie ondersoek deur middel van hoofkomponent- en faktoranalise in twee aparte steekproewe.

- a. Die eerste studie het die aard van simptome in pasiënte, met 'n eerste-episode van skisofrenie, ondersoek in 'n groot kohort van pasiënte wat deelgeneem het aan 'n multi-nasionale kliniese proefneming. Ons het ons bevindinge vergelyk met soortgelyke analyses wat voorheen gedoen is in multi-eposode skisofrenie pasiënte.
- b. Hierna het ons die invloed van kultuur op die simptoom struktuur van skisofrenie geassesseer deur 'n hoofkomponent- en faktoranalise van die simptoomtellings uit te voer in 'n groot steekproef van Suid-Afrikaanse Xhosa pasiënte met skisofrenie en die resultate te vergelyk met bevindinge in ander dele van die wêreld.
- c. Ons het die voorkoms van ko-morbiede depressiewe en angssimptome ondersoek, asook hul demografiese en kliniese korrelate. Die steekproef vir hierdie studie het bestaan uit akute psigotiese pasiënte wat deelnemers was in 'n kliniese geneesmiddel proef wat uitgevoer is by ons sentrum.
- d. Om die verband tussen obsessief-kompulsiewe steurnis en skisofrenie te verken, het ons 'n oorsig van die relevante literatuur gedoen.

5. Neurobiologiese abnormaliteite:

- a. Ons het 'n reeks studies uitgevoer om steurnisse in water homeostase en vasopressie sekresie in skisofrenie te ondersoek. Om die hipotese dat akute psigotiese pasiënte versteurde regulering van water homeostase het te ondersoek, het ons 'n dinamiese onderdrukkingstoets toegepas – 'n water ladingstoets, met assessering van ekskresiekapasiteit (insluitend arginien vasopressie essai) in akute psigotiese pasiënte. Om te evalueer of 'n onderafdeling van skisofrenie pasiënte met ko-morbiede versteurde water homeostase serebrale skade opgedoen het as gevolg van water intoksikasie, het ons die volgende eksperiment uitgevoer: Ons het 'n kohort deelnemers met skisofrenie en versteurde water homeostase geïdentifiseer en hulle vergelyk met skisofrenie pasiënte sonder versteurde water homeostase in terme van serebrale ventrikulêre grootte en kognitiewe funksionering. Om die voorkoms van versteurde water homeostase in 'n langtermyn binne-pasiënt steekproef van psigiatriese pasiënte te bepaal, het ons serum natrium siftingstoetse uitgevoer. Deelnemers met hiponatremie is hierna verder ondersoek vir disregulering van water homeostatiese meganismes.

- b. Ons het neurologiese sagte tekens in 'n steekproef van deelnemers met eerste-episode skisofrenie bestudeer en opgevolg oor 'n twee jaar tydperk. Ons het hulle voorkoms, verwantskappe met psigiatriese simptome en medikasie effekte, hulle temporale stabiliteit en hul uitkoms korrelate ondersoek. Ons het ook hulle potensiaal om die uitkoms in skisofrenie te voorspel, ondersoek.

6. Behandelings aspekte

'n Groot meerderheid van ons werk het gefokus op die farmakologiese behandeling van skisofrenie. Die volgende aspekte van behandeling is ingesluit in hierdie tesis:

- a. Behandelingseffekte op psigiatriese simptome:
 - i. Om die effek van etnisiteit op behandelingsuitkoms in skisofrenie te assesser, het ons die akute respons op anti-psigotiese behandeling in 3 etniese groepe vergelyk, naamlik swart, gekleurd, en wit. Ons het pasiënte wat deelgeneem het aan kliniese proefnemings in ons departement sowel as die Departement Psigiatrie van die Universiteit van die Vrystaat ingesluit in hierdie analise. Pasiënte is behandel onder geblinde toestande oor 'n tydperk van 6 weke.
 - ii. Na besprekings met wyle Dr David Horrobin, wie die moontlike toepassings van omega-3 vetsure in die behandeling van verskeie psigiatreie steurnisse gepionier het, het ons begin belangstel in verdere ondersoek na die potensiaal van hierdie groep samestellings as 'n bekostigbare toevoeging in die behandeling van skisofrenie. Ons het die anti-psigotiese potensiaal van die omega-3 vetsuur, etiel-eikosapentanoësuur (e-EPA) suplementasie versus plasebo suplementasie ondersoek in 'n klein steekproef van deelnemers met skisofrenie wat slegs gedeeltelik responsief was op anti-psigotiese behandeling in die verlede. Ons het ook 'n literatuuroorsig gedoen om die bewyse vir die effektiwiteit vir die omega-3 vetsure in skisofrenie te evalueer volgens gepubliseerde studies.
- b. Behandelingseffekte op neurologiese abnormaliteite:
 - i. In 'n enkelblinde kontrole studie het ons 'n nuwe generasie anti-psigotiese medikasie vergelyk met 'n konvensionele anti-psigotiese medikasie in die behandeling van tardiewe diskinesie (TD). Hierdie was 'n langtermyn (1-jaar) studie in pasiënte met chroniese skisofrenie en vasgestelde TD.
 - ii. Ons het ook die effek van omega-3 vetsuur (e-EPA) suplementasie geassesseer in die behandeling van TD. Dit was gedoen in 'n groter steekproef (n=84) van pasiënte met chroniese skisofrenie en vasgestelde TD. Die blinde, placebo kontrole fase was 12 weke. Dit is gevolg deur 'n nie-geblinde ekstensie vir 40 weke.
- c. Konvensionele versus nuwe generasie anti-psigotiese agente.

Verskeie bewys-gebaseerde literatuuroorsigte oor die effektiwiteit en toleransie van die nuwe generasie anti-psigotiese agente in vergelyking met die konvensionele agente, is gedoen. Sommige multi-nasionale, ewekansige, kontrole kliniese proefnemings waarin die outeur die hoofnavorsers was, is ingesluit in hierdie tesis. Verder, studies wat die pasiënte met gedeeltelike behandelingsweerstandigheid aanspreek, is ingesluit, sowel as studies oor die effekte van anti-psigotiese agente op depressiewe simptome, liggaamsmassa en glisemiese kontrole. Laastens, het ons a farmako-ekonomiese studie ingesluit wat die konvensionele anti-psigotiese behandeling (haloperidol) met 'n nuwe generasie anti-psigotiese behandeling (quetiapien) in gedeeltelik weerstandige pasiënte in 'n Suid-Afrikaanse ligging vergelyk.

Bevindinge en gevolgtrekkings:

4. Psigopatologie:

Ons studies het gedemonstreer dat die faktor struktuur vir die simptome van skisofrenie herhaalbaar is oor steekproewe, en dat dit nie grootliks beïnvloed word deur etnisiteit en kulturele faktore nie. Veranderinge vind egter in die faktor strukture wel plaas met verloop van tyd. Daar is simptome domeine wat teenwoordig is in eerste-episode skisofrenie, maar verdwyn as 'n afsonderlike entiteit soos wat die toestand chronies word. Spesifiek, 'n motoriese komponent is duidelik in onbehandelde pasiënte, maar verdwyn na die aanvang van behandeling. Ons het gevind dat depressie en angs algemene ko-morbiede simptome in skisofrenie is en het belangrike kliniese en uitkoms korrelate. Depressiewe simptome in die akute psigotiese fase van skisofrenie word geassosieer met 'n gunstige prognose en verminder soos wat die simptome van psigose verbeter in repons op anti-psigotiese behandeling. Egter, volgehoue depressiewe simptome word geassosieer met 'n swakker prognose en benodig addisionele tereapeutiese intervensie.

5. Neurobiologiese abnormaliteite:

Ons het die voorkoms van versteurde water regulering ondersoek in 'n populasie van psigiatriese binne-pasiënte en verdere ondersoek ingestel op dié wie geïdentifiseer is, om die betrokke meganismes vas te stel. Polidipsie en die sindroom van onvoldoende anti-diuretiese hormoon sekresie (SIADH) is gevind om voor te kom in 'n onderafdeling van pasiënte met skisofrenie, en word geassosieer met akute psigose sowel as met sommige psigotropiese medikasie. Hierdie pasiënte word gekenmerk deur meer ernstige kognitiewe beperking en bewyse van serebrale atrofie. Die toestand kan lewensbedreigend raak in die teenwoordigheid van ander faktore wat water ekskresie hinder, veral tiasied diuretika's.

Neurologiese sagte tekens is ondersoek in 'n steekproef van pasiënte met eerste-episode skisofrenie. Hierdie sagte tekens blyk om kenmerkend (teenwoordig vroeg in die siekte, en stabiel oor tyd) te wees, behalwe vir 'n motoriese volgorde faktor. Pasiënte wat swak vaar op die laasgenoemde groep toetse, het 'n langer durasie van onbehandelde psigose, en het 'n beduidende risiko om TD te ontwikkel.

6. Behandeling aspekte:

Ons studies stel voor dat daar 'n belangrike etniese verskil is in anti-psigotiese behandelingsrespons, maar dat hierdie verskille verduidelik kan word deur 'n aantal omgewings- en biologiese faktore. Soos wat gevind was vir verskeie studies wêreldwyd, het ons gevind dat die nuwe generasie anti-psigotiese agente belangrike effektiwiteit- en veiligheidsvoordele het bo hulle voorgangers. Risperidoon was net so effektief as haloperidol in eerste-episode psigose, maar met 'n meer gunstige newe-effekte profiel in terme van verminderde ekstrapirimidale simptome. Quetiapien behandeling in veral refraktêre pasiënte het gelei tot meer respondeerders vergeleke met haloperidol, en minder ekstra pirimidale simptome. Alhoewel, bewyse van 'n verskillende newe-effekte profiel is besig om na vore te kom. Van spesifieke belang is die bevinding dat sommige van die nuwe anti-psigotiese agente gewigstoename, glukose intoleransie en dyslipidemie veroorsaak. Ons het gevind dat een nuwe anti-psigotiese agent, quetiapien, nie geassosieer was met enige beduidende meer gewigstoename of versteurde glukose metabolisme as 'n konvensionele agent, haloperidol, nie. Die omega-3 vetsure, spesifiek EPA mag moontlik 'n rol in die behandeling van verskeie psigiatriese versteurings hê. Ons studies het gemengde resultate voorsien – die eerste het 'n beduidende voordelige effek op psigotiese simptome en diskinesie tellings vir EPA supplementasie gevind, terwyl die tweede nie 'n voordelige effek op TD of psigotiese simptome gevind het nie. Ons het die vroeë behandelingsrespons ondersoek in eerste-episode pasiënte en het gevind, in teenstelling met dit wat gerapporteer word in multi-episode pasiënte, dat sommige pasiënte 'n lang tyd geneem het om te reageer. Ons het ook gevind dat vroeë behandelingsrespons 'n beduidende voorspeller was van latere remissie, so ook die durasie van onbehandelde psigose, opvoedingspeil, en basisvlak opwindings-faktor tellings. Laastens het ons farma-ekonomiese studie, wat uitgevoer is vir Suid-Afrikaanse omstandighede in pasiënte met 'n gedeeltelike repons op konvensionele anti-psigotiese behandeling, koste-neutraliteit of koste-voordele aangetoon vir quetiapien vergeleke met haloperidol behandeling vir direkte onkoste.

Foreword

This thesis comprises a collection of published studies that were conducted in patients with schizophrenia over the past 20 years. These studies focus on three major aspects of the illness, namely psychopathology, neurobiology and psychopharmacology. As a clinician-researcher, all of the work has a strong clinical focus. I have only included studies in which I was the principal author. Research in the field of schizophrenia, as is the case in most other areas, requires considerable collaboration. Almost all of my work has involved collaborations with various co-workers.

Choosing schizophrenia as the subject of my research was not a difficult task. Being one of *the* major remaining challenges facing medical science, its peculiar complex of symptoms has fascinated and puzzled scientists for many years. There remain many unanswered fundamental questions regarding the illness. For example, no really plausible hypothesis has been forthcoming as to why the illness first overtly manifests itself around about late adolescence or early adulthood. Also, no clearly defined anatomical or functional unit has been identified that can adequately explain the simultaneous occurrence of the apparently diverse symptoms that we have come to recognise as the psychopathology of schizophrenia. For example, how is emotional blunting linked to active auditory hallucinations, catatonic features and disorders of inferential thinking? While some elegant hypotheses have been proposed (for example, "cognitive dysmetria" as consequence of a dysfunction in cortical-subcortical-cerebellar circuitry [Andreasen et al., 1998] or psychosis as a state of aberrant salience [Kapur, 2003]) none have gained general acceptance. Psychiatric disorders are an increasing part of the global health burden, and now rate as one of the largest causes of lost years of quality of life (Sadik, 1992). Schizophrenia forms a significant part of this burden, being ranked the 9th most important cause of disability in the world (Murray & Lopez, 1997), and the most costly illness that psychiatrists treat (Andreasen, 1991). The illness imposes a disproportionately large emotional and economic burden on patients and their families, health care systems and society, because of its early onset, devastating effects, and usually chronic and unremitting course (Glazer and Johnstone, 1997). It has been referred to as youth's greatest disabler, and has even been described as arguably the worst disease afflicting humankind (Aronson, 1997).

To make matters worse, patients with schizophrenia have been stigmatised, marginalised and discriminated against possibly more than any persons, with or without illness. Throughout history misconceptions regarding the illness have prevailed. Sadly, many of these misconceptions are still widely prevalent today. A lack of public awareness, as well as inadequate treatment and care facilities have resulted in the marginalisation of vast numbers of patients with schizophrenia. The costs both in terms of the economic burden and human suffering are staggering. Eighty percent of patients with schizophrenia are unemployed, 50% seriously contemplate suicide, and 10% successfully complete suicide (Weiden et al, 1996).

Direct (e.g. medication, hospitalisation) and indirect costs (eg. loss of earnings, time taken up by care-givers) are enormous, and in South Africa probably amount to billions of rands each year.

The assessment and management of schizophrenia has undergone important new developments, with the emergence of enhanced diagnostic precision and more effective and better tolerated treatment options. Technological developments over the past decade and more have enabled us to study aspects of schizophrenia in more detail, and in a more sophisticated manner than previously. These developments have raised hopes for an improved outcome, including fewer residual symptoms, reduced functional impairment, better quality of life and reduced emotional distress for patients and their families. Hopefully, important breakthroughs are just around the corner.

Index

Foreword

Summary

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1.a The factor structure for the Positive and Negative Syndrome Scale (PANSS) in recent-onset psychosis

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Abstract

The PANSS is a widely used instrument for measuring severe psychopathology in adult patients with schizophrenia. Data, primarily on chronic patients, have been used to define factors for the PANSS. The present study examines the PANSS factor structure in a large sample of subjects with recent onset schizophrenia, schizophreniform disorder and schizo-affective disorder who had been exposed to very limited antipsychotic medication. Equamax factor analysis was conducted on PANSS baseline assessments from a multicenter, 11 country drug trial that enrolled 535 patients. The forced five-factor solution essentially corresponds to the factors most frequently described previously, namely negative, positive, disorganized (or cognitive), excited and anxiety/depression. In the exploratory analysis a seven-factor solution was obtained, with depression and anxiety symptoms separating and a motor component emerging. The results of this study partially support the use of a five factor model for the PANSS, but suggest that scales for catatonia, depressive and anxiety syndromes should be included in future studies.

1. Introduction

Numerous attempts have been made to elucidate the complexities of schizophrenia by exploring relationships between its various symptoms. The diversity of these symptoms has been difficult to explain, and has led to the proposal of pathophysiological heterogeneity as a conceptual model for the disorder (Buchanan and Carpenter, 1994). A landmark change in our thinking entailed replacing the classical subtypes of schizophrenia with the division of symptoms into positive and negative components. Although this distinction had long been considered (Reynolds, 1896; Jackson, 1931), it was only relatively recently that attention focussed on these two components as possibly representing separate pathological processes in schizophrenia. Strauss, Carpenter and Bartko (1974) described positive, or productive symptoms and negative, or deficit symptoms. Based on this model, Crow (1980) hypothesised that the positive and negative symptoms represent different subtypes of schizophrenia, the former reflecting a hyperdopaminergic state, and the latter a consequence of structural brain-deficit.

In order to investigate this distinction empirically, methods of phenomenologic description and nosologic categorisation were required. The Scale for the Assessment of Negative Symptoms (SANS), and the Scale for the Assessment of Positive Symptoms (SAPS), were developed according to Crow's concept at the time, attempting to group all of the symptoms into positive and negative categories (Andreasen, 1983; Andreasen, 1984). While the original factor analysis of the SANS and SAPS appeared to support the validity of the positive and negative dichotomy, most subsequent studies called the two-dimensional model into question, preferentially yielding a three-factor structure. These factors comprise a negative symptom factor and two positive symptom factors - a "psychosis" dimension and a "disorganisation" dimension (Andreasen and Olsen, 1982; Andreasen and Grove, 1986; Moscarelli et al., 1987; Liddle, 1987; Arndt et al., 1991; Miller et al., 1993; Bilder et al., 1985; Kuhlara et al., 1986; Lenzenweger et al., 1989; Schulzberg et al., 1990; Gur et al., 1991; Minas et al., 1992; Brown

et al., 1992; Peralta et al., 1992). Andreasen et al. (1995) summarised the results of the published factor analytic studies for the SANS and SAPS, noting strong similarities in the findings. These similarities were all the more striking considering that they included patients meeting various diagnostic criteria, at different stages of the illness, and with varying medication status. In addition, samples were often small and a variety of statistical techniques were employed. These factors have also been found to be stable over the course of time (Arndt et al, 1995), and to be resistant to cultural influences (Emsley et al, 2000).

The Positive and Negative Syndrome Scale (PANSS) was later developed in an attempt to provide a more comprehensive assessment of the symptoms of schizophrenia (Kay, Fisbein and Opler, 1987; Kay, Opler and Lindenmayer, 1988; Kay, Opler and Lindenmayer, 1989). The scale comprises 30 items, and was designed to assess three main domains: the positive subscale (7 items), the negative subscale (7 items) and the general psychopathology subscale (14 items). The scale includes all of the items from the BPRS (Brief Psychiatric Rating Scale) (Overall and Gorham, 1988) and select items from the Psychopathology Rating Scale (Singh and Kay, 1987) The PANSS is widely used in clinical and research settings, and is regarded as a reliable means of symptom assessment (Bell, et al 1992; Muller, et al 1998). To assess the factorial validity of the PANSS, the authors conducted a principal component analysis with equamax rotation on 240 schizophrenic inpatients (Kay and Sevy, 1990). The two main components to emerge were the negative and positive syndromes. These two factors were very robust, with eigenvalues of 7.08 and 3.74 respectively, and together accounted for 36.1% of the total variance. They also found five additional components of significance: excitement, depression, cognitive dysfunction, suspiciousness/persecution, and stereotyped thinking. Of the 7 components, the first four had eigenvalues > 2 and explained 52.3% of the total variance. They were clearly distinct, and statistically unrelated. Also, these 4 components embraced 5 or more items each, while the other 3 components together had only 5 items. For these reasons, they decided to retain only the first 4 components. However, subsequent studies (Lepine et al, 1989; Dolfus et al, 1991; Lindstrom and von Knorring, 1993; Bell et al, 1994; Lindenmeyer et al, 1994; Kawasaki et al, 1994; Lindenmeyer et al, 1995; Marder et al, 1997; White et al, 1997; Lancon et al, 1998; Lancon et al, 1999; Lancon et al, 2000; Lykouras et al, 2000; Mass et al, 2000; Wolthaus et al 2000), as well as a re-analysis of the original sample of Kay and Savy (Lindenmeyer et al, 1995) overwhelmingly favoured a five-factor solution – i.e. negative, positive, disorganised (or cognitive), excited and depression/anxiety factors. As was the case with the SANS and SAPS, the PANSS factor structure does not appear to be affected by age, severity of symptoms, chronicity of illness (White et al, 1997), or by short-term medication withdrawal (Lindenmeyer et al, 1995). However, all but one (Wolthaus et al 2000) of the published analyses were conducted in subjects who were mostly medicated and in a chronic phase of the illness. The present study examines the PANSS factor structure in a large sample of subjects with recent-onset schizophrenia, schizophreniform disorder and schizo-affective disorder who had been exposed to very limited antipsychotic medication, and compares the results with previously published studies.

Methods

The RIS-INT-35 is a randomized, double-blind, multicenter, international trial comparing the effect of treatment with risperidone or haloperidol on the long-term outcome of early psychotic patients. Subjects are receiving trial medication for at least one year and are followed-up for a minimum of two and a maximum of four years. The key inclusion criteria were: aged < 45 years, having a DSM-IV diagnosis of schizophrenia, schizophreniform disorder or schizoaffective disorder for at most 12 months, having had a maximum of two lifetime psychiatric hospitalizations for psychosis, having persistent current psychotic symptoms requiring long-term neuroleptic treatment, and having had 12 weeks or less of cumulative lifetime exposure to neuroleptic medications.

Recruitment started in November 1996 and ended in December 1999. The study is being conducted according to Good Clinical Practice. Investigators ($N=49$) underwent training and inter-rater reliability testing at an investigator meeting prior to the start of the study, and further training was provided at follow-up meetings. Before enrolling patients into the study, raters were trained to administer the PANSS and achieved an inter-rater reliability of 0.80 or greater. Blinded follow-up of the remaining subjects in the trial is still ongoing. This article

presents (blinded for treatment) baseline data. The total study sample includes randomized subjects from 11 countries. Approval was obtained from Institutional Review Boards, and subjects provided informed, written consent to participate in the study.

2.1 Sample

The sample comprised 535 subjects (380 men and 155 women) after excluding two persons who left the trial before treatment but after randomisation, and 21 patients from a centre removed from the trial in the early stages of the trial due to inconsistent data reporting. The mean (\pm SD) age was 26.0 (\pm 6.9) yrs, and duration of illness 435.1 (\pm 1136) days. The sample was composed of patients assigned the following diagnoses: schizophrenia (n=270), schizophreniform disorder (n=243) and schizoaffective disorder (n=43). Thirty-one percent (n=167) had no previous exposure to antipsychotic medication. Most patients were Caucasian (n=400) and the rest Black (n=40), Hispanic (n=17), Oriental (n=11) or members of other groups (n=43).

2.2 Statistical analysis

A principal components factor analysis using equamax rotation was performed. The equamax rotation was chosen to be consistent with many previous studies of the PANSS. The first round of analysis did not limit the number of factors. A second round limited the number of factors to five. Items were allocated to factors according to their highest loading. Internal consistency for each of the components was determined by calculating Cronbach's alpha coefficients (Cronbach, 1951). A further five-factor analysis was performed on the 167 subjects who had never been exposed to antipsychotic medication.

3. Results

The mean (\pm SD) PANSS scores for the sample were as follows: PANSS total 82.5 (\pm 20.2); PANSS positive subscale 20.3 (\pm 6.2); PANSS negative subscale 21.5 (\pm 7.1); and PANSS general psychopathology subscale 40.7 (\pm 10.5). In two cases the PANSS was not completed thus results are presented on 533 persons. Table 1 presents the results of the rotated principal component matrix with the factor loadings for the analysis limited to five factors for the 533 subjects. Descriptive names have been assigned to each of the factors. Our factor loadings are compared with those of other published studies in Table 2. While many items have strong loadings and are consistently related to a particular factor across studies, others are less specific, loading with more than one factor in the same analysis, or loading with different factors in different studies. The following items are inconsistently associated with specific factors. In the negative factor: disturbance of volition (G13); in the disorganized factor: stereotyped thinking (N7), mannerisms (G5), preoccupation (G15); in the positive factor: suspiciousness (P6); and in the depressive/anxiety factor: somatic concern (G1), and tension (G4). We repeated the forced five-factor analysis after removing these items in order to examine whether their exclusion affected the specificity of the PANSS factors. Alpha values and percentage variance were almost identical to what they had been when these variables were included in the analysis, these results are as follows: Negative factor 0.88 and 17.1%; disorganized factor 0.72 and 11.5%; positive factor 0.75 and 11.4%; excited factor 0.71 and 10.7%; and anxiety/depression factor 0.64 and 8.7%.

The five-factor analysis for the 167 neuroleptic-naïve subjects produced a solution similar to the entire sample that explained 53.7% of the total variance and identified the following factors: Negative factor: N4, N2, N1, N3, N6, G16 and G7 (alpha= .87 , % variance 14.6); disorganized factor: G11, P2, N5, G10, G15, N7 and G13 (alpha=.79, % variance=11.8); excited factor: P7, P4, G14, G8 and G1 (alpha=.68 ,% variance=9.4%); positive factor: P1, G9, P5, P6 and P3 (alpha=.70 , % variance= 9.1); and anxiety/depression: G2, G4, G3, G6, G12 and G5 (alpha=.66 ,% variance=8.8).

Table 3 presents the results of the exploratory factor analysis for the entire sample. The 7 components shown had eigenvalues greater than unity, and accounted for 61.7% of the variance. The forced five-factor solution essentially corresponds to the five factors most frequently described previously, namely negative, positive, disorganized (or cognitive), excited and anxiety/depression. However, in the exploratory seven-factor solution depression

and anxiety symptoms have separated, and a motor component has emerged.

4 Discussion

The forced five-factor solution provides an adequate model insofar as it accounts for 54.7% of the total variance, and the internal consistency for each factor is good, with the exception of the depression/anxiety component, which is modest. As shown in Table 4, most published studies favour a five-factor solution. The factors identified in our study are essentially the same as those described in the majority of other studies, namely negative, positive, disorganized (or cognitive), excited and depression/anxiety. As was the case in the majority of the chronic schizophrenia samples, we found that the negative factor was the most robust, accounting for 15.4% of the total variance. This was somewhat surprising, considering that negative symptoms, although present, are less prominent in first-episode schizophrenia than in chronic samples (Mayerhof et al, 1994; Emsley et al, 1999). The disorganized and positive dimensions formed the second and third factors respectively. Once again this corresponds with the findings in the majority of chronic schizophrenia samples where the negative, positive and disorganized components accounted for most of the variance. These 3 factors also match the 3 factors identified by the SANS and SAPS global item analyses.

While 14 of the 16 reported PANSS factor analytical studies (Table 4) reported a five-factor solution, the criteria used to select the number of factors differed from study to study, and in fact 4 of the studies *only* reported a forced five-factor model (Marder et al, 1997; Lancon et al, 1998; Lancon et al, 1999; Lancon et al, 2000). Other studies, using the conventional method of selecting factors with eigenvalues > 1 , actually obtained more than 5 factors, and then discarded the additional factors for various reasons (Lindstrom and von Knorring, 1993; Bell et al, 1994; Kawasaki et al, 1994; Lykouras et al, 2000). Thus, the choice of the number of factors is arbitrary, and the apparent uniformity of the findings somewhat misleading. Some PANSS items do not appear to contribute significantly to the symptom structure of schizophrenia. Exclusion of the less specific items (P6, N7, G1, G4, G5, G13, and G15) does not substantially affect alpha values and percentage variance of the five factors, indicating that omission of these items in future studies is not likely to significantly alter the PANSS factor structure.

The seven factors with eigenvalues greater than unity that were obtained from the exploratory factor analysis are of considerable interest. The emergence of a motor component was unanticipated, and to our knowledge, has not been described in previous PANSS factor analytical studies. Although comprising only two items, with an internal consistency of 0.55, it accounts for 7.6% of the total variance. The items making up this factor, mannerisms and posturing (G5) and motor retardation (G7) are characteristic of catatonic symptoms. Although once thought to have dramatically decreased in prevalence (Magrinat et al, 1983), catatonic symptoms are now recognized with increasing frequency in clinical practice (Johnson, 1993). The decline in catatonic symptoms is likely to have been related to the advent of antipsychotic agents – either as part of the response to treatment, or alternatively due to extrapyramidal side-effects masking these symptoms. This would explain why previous PANSS factor analyses did not identify a catatonic or motor component, as they were conducted largely in medicated samples.

Motor symptoms have been well documented in neuroleptic-naïve patients with first-episode schizophrenia (Puri et al, 1999), as well as in elderly never-medicated subjects with schizophrenia (McCreadie et al, 1996), suggesting that these symptoms are an integral part of the illness, rather than just medication side-effects. In previous PANSS factor analyses conducted in medicated and chronic samples, catatonic items loaded with either the negative or disorganized factor (Table 2). In the only other PANSS factor analysis of a first-episode psychosis sample (Wolthaus et al, 2000), the motor retardation item (G7) loaded with the negative factor, while the mannerisms and posturing item (G5) was excluded because it did not load by ≥ 0.50 on any of the components. However, other studies using rating scales covering a broader range of symptoms have reported a catatonic factor (Andreasen and Olsen, 1982; Kitamura et al, 1995; McGorry et al, 1998). Indeed, a recent article examining the complexities of the symptom structure of schizophrenia argues for the inclusion of catatonia as an additional symptom dimension (Peralta and Cuesta, 2001(a)), and a set of empirical diagnostic criteria for catatonia have been proposed (Peralta and Cuesta, 2001(b)).

The other finding of interest with the 7-factor solution was that depressive and anxiety symptoms separated into 'purer' components. Depression and anxiety symptoms loaded as a single factor in the original PANSS analysis of Kay and Sevy (1991), as well as in the majority of subsequent studies. However separate anxiety and depression factors were also reported by Peralta and Cuesta (1994) when they reported an 8 factor solution, and Dollfus et al (1991) found an anxiety factor without a depressive factor. It is not clear how clinically meaningful this separation of anxiety and depression items is. Depressive symptoms are common in first-episode schizophrenia (Koreen et al, 1993; Emsley et al, 1999) and when present, are usually associated with a full depressive syndrome (Barnes et al, 1989). There is considerable evidence that depression may in fact be a core feature of the illness (Koreen et al, 1993). Anxiety symptoms are also frequently encountered. There are many possible explanations for symptoms of depression and anxiety in schizophrenia, including the following: Response to adverse life events (e.g. involuntary hospitalisation, unemployment, broken relationships); reaction to terrifying psychotic experiences; substance intoxication or withdrawal; neuroleptic-induced (either directly, e.g. akathisia, or indirectly e.g. in reaction to the distressing experience of developing acute dystonia); or co-morbid major depression or anxiety disorders (Emsley et al, 2001).

Interpretation of our findings is subject to certain limitations. The sample was selected according to specific criteria for a randomised clinical trial, and may not accurately represent subjects encountered in clinical practice. Further, many subjects had been exposed to small quantities of antipsychotics, so that the sample cannot be regarded as medication-naïve. Also, because of the large number of sites, many investigators were involved in PANSS assessments, subjects differed widely in terms of language and culture, and the different versions of the PANSS were not validated. Finally, the inherent limitations of factor-analysis (Peralta and Cuesta, 2001a) need to be kept in mind.

The symptom structure of schizophrenia and other psychoses appears to be more influenced by the measurement instrument than any other factor (Peralta and Cuesta, 2001a). Also, many studies are flawed by research designs orientated towards confirmation rather than exploration ((McGorry et al, 1998). Finally, the symptom domains of schizophrenia and other psychoses that have been described so far have yet to be externally validated by means of neurobiological and other strategies. Our results suggest that future assessments of symptom domains in schizophrenia should, in addition to the PANSS, include an assessment scale for catatonic symptoms, as well as instruments to identify specific anxiety and depressive syndromes.

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Table1. Factors and factor loadings (the factor on which each item had its highest loading) of PANNS items for 533 subjects, for the forced five factor solution using the equamax method.

Factor and Items	Variable	Factor Loadings
<i>1: Negative</i>	Alpha=.89	
Passive social withdrawal	N4	.80
Emotional withdrawal	N2	.78
Blunted Affect	N1	.74
Lack of spontaneity	N6	.71
Poor rapport	N3	.69
Active social avoidance	G16	.67
Motor retardation	G7	.62
Disturbance of Volition	G13	.51
% of variance (rotation sums of squares)		15.4%
<i>2: Disorganized</i>	Alpha=.80	
Poor attention	G11	.74
Stereotyped thinking	N7	.63
Conceptual disorganization	P2	.62
Difficulty in abstract thinking	N5	.56
Preoccupation	G15	.50
Disorientation	G10	.40
Mannerisms and posturing	G5	.38
% of variance (rotation sums of squares)		11.4%
<i>3: Positive</i>	Alpha=.78	
Delusions	P1	.84
Unusual thought content	G9	.74
Hallucinatory behavior	P3	.65
Suspiciousness	P6	.63
Grandiosity	P5	.45
Lack of judgment and insight	G12	.41
% of variance (rotation sums of squares)		10.8%
<i>4: Excited</i>	Alpha=.71	
Hostility	P7	.80
Poor impulse control	G14	.69
Excitement	P4	.63
Uncooperativeness	G8	.57
% of variance (rotation sums of squares)		9.0%
<i>5: Anxiety & Depression</i>	Alpha=.66	
Anxiety	G2	.81
Tension	G4	.67
Depression	G6	.59
Guilt feelings	G3	.56
Somatic concern	G1	.43
% of variance (rotation sums of squares)		8.4% (cumulative 54.7%)

Table 2. Comparison of component loadings for the 30 PANSS items for the present study with other published studies*.

Factor and Item	Study								
	Present study	Kay & Sevy, 1990	Lindenmayer et al, 1994	White et al, 1997	Marder et al, 1997	Lancon et al, 1999	Lancon et al, 2000	Mass et al, 2000	Lykouras et al, 2000
1. Negative factor:									
N1 blunted affect	1	1	1	1	1	1	1	1	1
N2 emotional withdrawal	1	1	1	1	1	1	1	1	1
N3 poor rapport	1	1	1	1	1	1	1	1	1
N4 passive social withdrawal	1	1	1	1	1	1	1	1	1
N6 lack of spontaneity	1	1	1	1	1	1	1	1	1
G7 motor retardation	1	1	1	1	1	1			1
G13 disturbance of volition	1	2	2	2	1				1
G16 active social avoidance	1	1		1	1	1	1	1	4
2. Disorganised factor:									
P2 conceptual disorganisation	2	2		2	2	2	2	2	2
N5 difficulty in abstract thinking	2	2	2	2	2	2	2	2	2
N7 stereotyped thinking		4	2	3	4				2
G5 mannerisms	1	2	1	2	2		4		1/2
G10 disorientation	2	2		2	2	2			2
G11 poor attention	1	2	2	2	2	2	2	2	2
G15 preoccupation	5	5	2	2	1				1
3. Positive factor:									
P1 delusions	3	3	3	3	3	3	3	3	3
P3 hallucinations	3	3	3	3	3	3	3	3	3
P5 grandiosity	3	3	3	3	3	3	3	4	3
P6 suspiciousness		3		3	3	3	3		3
G9 unusual thought content	3	3	3	3	3	3	3	3	3
G12 Lack of judgement	3	3		3	3	3			3/5
4. Excited factor:									
P4 excitation	4	4	4	4	4	4	4	4	4
P7 hostility	4	4	4	4	4	4	4	4	4
G8 uncooperativeness	4	4	4	4	4			4	4
G14 poor impulse control	4	4	4	4	4	4	4	4	4
5. Depressive & anxiety factor:									
G1 somatic concern	5	5	5	3	3				4
G2 anxiety	5	5	5	5	5	5	5	5	5
G3 guilt feelings	5	5	5	5	5	5	5	5	5
G4 tension	4	4	5	5	4	4	4	4	4
G6 depression	5	5	5	5	5	5	5	5	5

*Published studies with samples ≥ 240 and where component loadings are reported are included.

Numbers depict the factor in which that item had its highest loading in the study in question. (1=negative factor; 2=disorganised factor; 3=positive factor; 4=excited factor; 5=depressive/anxiety factor.)

Table 3. Factors and factor loadings (the factor on which each item had its highest loading) of PANNS items for 533 subjects, for the unlimited factor solution using the equamax method.

Factor and Items	Variable	Factor Loadings
<i>1: Negative</i>	Alpha=.88	
Passive social withdrawal	N4	.77
Emotional withdrawal	N2	.73
Poor rapport	N3	.68
Active social avoidance	G16	.68
Lack of spontaneity	N6	.68
Blunted Affect	N1	.62
Disturbance of Volition	G13	.41
% of variance (rotation sums of squares)		12.4%
<i>2: Positive</i>	Alpha=.80	
Delusions	P1	.83
Unusual thought content	G9	.75
Hallucinatory behavior	P3	.63
Suspiciousness	P6	.59
Grandiosity	P5	.50
Lack of judgement and insight	G12	.41
Preoccupation	G15	.38
% of variance (rotation sums of squares)		10.0%
<i>3. Disorganized</i>	Alpha=.77	
Disorientation	G10	.75
Poor attention	G11	.64
Difficulty in abstract thinking	N5	.59
Conceptual disorganization	P2	.56
Stereotyped thinking	N7	.54
% of variance (rotation sums of squares)		9.8%
<i>4. Excited</i>	Alpha=.71	
Hostility	P7	.80
Poor impulse control	G14	.72
Excitement	P4	.64
Uncooperativeness	G8	.52
% of variance		8.4%
<i>5. Motor</i>	Alpha=.55	
Mannerisms and posturing	G5	.72
Motor retardation	G7	.55
% of variance (rotation sums of squares)		7.6%
<i>6. Depression</i>	Alpha=.53	
Depression	G6	.77
Guilt feelings	G3	.68
% of variance		6.8%
<i>7. Anxiety</i>	Alpha=.62	
Somatic concern	G1	.72
Anxiety	G2	.60
Tension	G4	.57
% of variance (rotation sums of squares)		6.7% (cumulative 61.7%)

Table 4. Details of published PANSS factor analytical studies.

Authors	N	Sample	Medication status	Statistical methods	No. of factors	Criteria for choosing no. of factors	% variance
Kay & Sevy, 1990	240	Schizophrenia, with psychotic symptoms	All but 2 medicated	PCA, equamax rotation	4	Eigenvalues>1 gave 7 factors: 3 discarded	52%
Dollfus et al, 1991	70	Schizophrenia, acute or stabilised.	All but 1 medicated	PCA, varimax rotation	5	Eigenvalues>1	56%
Lindstrom & von Knorring, 1993	120	Schizophrenia, chronic.	Not specified	PCA, varimax rotation	5	Eigenvalues>1 gave 9 factors: 4 discarded	70%
Peralta & Cuesta, 1994	100	Schizophrenia, exacerbation, 20% first-admission.	All medicated	PCA, varimax rotation, CFA	8	Eigenvalues>1	69.9%
Lindenmeyer et al, 1994	240	Re-analysis of Kay & Sevy, 1990 sample	All but 2 medicated	PCA, orthogonal rotation	5	Eigenvalues>1	57.5%
Bell et al, 1994	146	Schizophrenia, schizo-affective mostly outpatients	Not specified	PCA, equamax rotation	5	Eigenvalues>1 gave 8 factors: 3 discarded	52.3%
Kawasaki et al, 1994	70	Schizophrenia, active symptoms.	All but one medicated	PCA, varimax rotation	5	Eigenvalues>1 gave 6 factors: 1 discarded	68.7%
Lindenmeyer et al, 1995	517	Schizophrenia, chronic in-patients	Medicated, then after 1 week washout	PCA, equamax rotation	5	Scree plot examination	51.7%
White et al, 1997	1233	Schizophrenia or schizo-affective, diverse	Not specified	PCA, varimax rotation and CFA	5	Eigenvalues>1	51%
Marder et al, 1997	513	Schizophrenia, chronic, PANSS score 60 to 120	Medicated, washout up to 7 days	PCA, equamax rotation	5	Forced 5 factors	Not reported
Lancon et al, 1998	205	Schizophrenia, long-term maintenance.	All medicated	PCA, varimax rotation	5	Forced 5 factors	57%
Lancon et al, 1999	342	Schizophrenia, 217 acute relapse, 125 chronic.	All medicated	PCA, varimax rotation	5	Forced 5 factors	57.5%
Lancon et al, 2000	342	Schizophrenia, 118 acute relapse, 224 chronic.	All medicated	PCA, varimax rotation	5	Forced 5 factors	64.3% ^{acute} 62.1% ^{chr}
Lykouras et al, 2000	258	Schizophrenia, acute or stable.	All medicated	PCA, varimax rotation, CFA	5	Eigenvalues>1 gave 7 factors: scree plot gave 5 factors	59.85%
Mass et al, 2000	253	Schizophrenia, mainly multi-episode	94.5% medicated	PCA, varimax rotation	5	Eigenvalues>1	72.3%
Wolthaus et al, 2000	138	Schizophrenia, recent onset and spectrum disorders	Not specified	PCA, varimax and equamax	5	Scree plot	Not reported

PCA = principal-component analysis
CFA = confirmatory factor analysis

1.b The factor structure for positive and negative symptoms in South African Xhosa patients with schizophrenia.

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Abstract

Most studies investigating the symptom dimensions of schizophrenia utilising the Scale for the Assessment of Negative Symptoms (SANS) and the Scale for the Assessment of Positive Symptoms (SAPS) favour a three factor model. This study sought to investigate the factor structure of both the global and individual items of the SANS and SAPS in a large sample of South African Xhosa patients with schizophrenia. A total of 422 subjects participated. Both principal components and factor analytical procedures were applied. For the global items, a two-factor solution representing positive and negative symptoms accounted for 59.9% of the variance. Alternatively, the three dimensional model of negative, psychotic and disorganisation factors was supported by a five factor solution if the more heterogeneous items of attention and alogia were ignored. Analysis of the individual items yielded a five-factor solution with the negative symptoms splitting into diminished expression and disordered relating, and the positive symptoms separating into factors for psychosis, thought disorder and bizarre behaviour. Our findings are very similar to those in other parts of the world, providing evidence that the factor structure for the symptoms of schizophrenia is relatively resistant to cultural influences. This is particularly true for negative symptoms.

1. Introduction

Considerable attempts have been made to elucidate the heterogeneity of schizophrenia by exploring the relationships between its various symptoms. The Scale for the Assessment of Negative Symptoms (SANS) and the Scale for the Assessment of Positive Symptoms (SAPS) were developed specifically for this purpose (Andreasen, 1983; Andreasen, 1984), and have been extensively used in research settings. The SANS contains 20 items that are summarised in five global ratings: affective flattening, alogia, avolition/apathy, anhedonia/asociality and attention. The SAPS comprises 30 items that are summarised in four global ratings: hallucinations, delusions, bizarre behaviour and positive formal thought

disorder. Taken together, these two scales provide a comprehensive assessment of the symptoms of schizophrenia (Andreasen, 1989). The scales were organised according to Crow's (1980) concept at that time of two broad dimensions - positive and negative symptoms - that represented different subtypes of schizophrenia. However, most subsequent studies have called this model into question and preferentially yielded a three-factor structure. These factors comprise a negative symptom factor (SANS global ratings for avolition/apathy, anhedonia/asociality and affective flattening) and two positive symptom factors (a "psychosis" dimension consisting of SAPS global ratings for hallucinations and delusions and a "disorganisation dimension" comprising SAPS global ratings for bizarre behaviour and formal thought disorder) (Andreasen and Olsen, 1982; Andreasen and Grove, 1986; Moscarelli et al., 1987; Liddle, 1987; Arndt et al., 1991; Miller et al., 1993; Bilder et al., 1985; Kulhara et al., 1986; Lenzenweger et al., 1989; Schuldberg et al., 1990; Gur et al., 1991; Minas et al., 1992; Brown et al., 1992; Peralta et al., 1992).

Andreasen et al. (1995) summarised the results of the published factor analytic studies, and noted the strong convergence towards a three dimensional model. The similarities in the findings are all the more striking considering that these studies included patients from various parts of the world, often with small sample sizes, and using a variety of factor analytic techniques. Also, study samples varied considerably regarding the stage of the illness and medication status. Although commonly reproduced, the validity of the three factor model has been questioned, largely due to inadequate measurement at the symptom level (Stuart et al., 1999). The majority of these studies analysed the global ratings of the two scales - a practice that runs the risk of missing relationships between individual symptoms. Indeed, two studies that analysed the individual items rather than the global scores found evidence that the dimensionality could be increased to five factors. In the first of these studies, Minas et al. (1994), utilising a principal components analysis of individual items on a sample of 114 patients with psychotic disorders, found that the structure could be summarised by three major components labeled negative symptoms, thought disorder and delusions/hallucinations. However, they also found that dimensionality could meaningfully be increased to five components - the negative symptoms factor was found to separate into two components that they labeled negative signs and social dysfunctions, and the delusions/hallucinations factor separated into two components, delusions and hallucinations, with "loss of boundary delusions" being related to both factors. In the second study, Toomey et al. (1997) applied factor analysis to the item-level ratings to a heterogeneous sample of 549 psychiatric patients. This revealed two negative symptom factors (diminished expression and disordered relating), two positive symptom factors (bizarre delusions and auditory hallucinations), and a disorganisation factor. Thus, the findings of these two studies analysing individual items are also remarkably similar.

It is not clear whether ethnicity and culture have any influence on these factor structures. Although previous studies included patients from different language and cultural groups (United States, Spain, Italy, England, Australia), all but one (India) (Kulhara et al., 1986) studied Caucasian populations. Other cross-cultural studies, although not looking specifically at factor structures, have reported varying degrees of inter-ethnic variation in the symptoms of schizophrenia. Some studies found Schneiderian first-rank or core symptoms to be similar across cultures (Ndeti and Singh, 1983 A; Sartorius et al., 1986; Gureje, 1987; Malik et al., 1990; Ensink et al., 1998) and negative symptoms also to be similar (Dassori et al., 1998). However, others report cross-cultural differences: A lower prevalence of first-rank or core symptoms has been found in developing countries (Chandrasena et al., 1987), in subjects less proficient in English (Coffey et al., 1993), and in minority groups (Breke and Barrio, 1997), while a higher prevalence of visual hallucinations has been reported in Kenyans (Ndeti and Singh 1983 B). To effectively address the question of whether the factor structure for the symptoms of schizophrenia is influenced by culture and ethnicity, it would be important to investigate subjects from a very different background and in a relatively non-aculturated setting. African subjects are an appropriate group to study as they are culturally and genetically distinct (Cavalli-Sforza et al., 1994). Symptoms of schizophrenia have been investigated in African subjects, with no differences in core symptoms being found in Kenyans (Ndeti and Singh., 1983 A), Nigerians (Gureje, 1987) and South African Xhosas (Ensink et al., 1998) while one study reported visual hallucinations to be more common in Kenyans (Ndeti and Singh 1983 B).

This study investigated the factor structure of the symptoms of schizophrenia in South African Xhosa patients. To our knowledge such a study has not previously been undertaken in African patients. The large sample allowed us to analyse not only the global items, but also the individual items of the SANS and SAPS scales. Both principal components and factor analytical procedures were applied.

2. Methods

2.1 Subjects

Subjects were recruited from in-patient and out-patient hospital services and community clinics throughout the Western and Eastern Cape Provinces of South Africa. Potential participants had to be of Xhosa ethnicity, and have a diagnosis of schizophrenia. The Xhosas are the southernmost indigenous African population. Belonging to the Nguni language group, the characteristic clicking sounds attest to their ancestral links with the Khoisan people (Cavalli-Sforza et al., 1994). Particularly the rural Xhosa people have maintained purity of language and traditional custom including ancestor worship and traditional medicine (Cheetham and Cheetham, 1976). The study protocol was presented to the local mental health workers, who were then asked to identify possible participants. All candidates were then screened by one of us (DJHN or NIM) for suitability. The study group included subjects at various stages of the illness, and with various levels of symptoms. Patients were diagnosed according to DSM IV criteria (A.P.A., 1994). Subjects with known organic aetiology were excluded. Patients were included in the study if they met the criteria and approval for participation was obtained from the treating mental health workers and their care-givers. In addition, all patients provided written, informed consent. These procedures yielded 422 patients. Because of missing observations, 396 patients were included in the global ratings analysis and 347 patients were included in the item ratings analysis.

2.2 Ratings

The ratings of positive and negative symptoms used for analysis in this study were taken from the SANS and SAPS scales in the Diagnostic Interview for Genetic Studies (DIGS), version 2.0 (Nurnberger et al., 1994). The DIGS is a comprehensive clinical interview designed for the assessment of major mood and psychotic disorders and their spectrum conditions. Ratings were performed by either a psychiatrist (DJHN) or a trained Xhosa psychiatric nurse with extensive experience in an academic psychiatric hospital (IM). For patients who were not fluent in English, interviews were conducted in Xhosa – either by the interviewer (NIM) or through an interpreter (DJHN). Interviewers rated individual items and also made global ratings to reflect the overall impairment in each area. Patients were recruited over a two-year period. In order to attain optimal rating consistency all subjects were assessed by both raters together during the first year of the study. Thereafter the raters partook in regular calibration meetings.

A study of the inter-rater reliability for the global and individual items was made in which 18 subjects were assessed by both of the raters. In the case of the SANS items the mean, minimum and maximum correlation coefficients were, respectively 0.826; 0.539; and 0.958, and for the SAPS items 0.828; 0.314; and 1.000. The question of relative bias of the raters was also examined. While in some items there were significant differences in mean scores, overall there was no detectable tendency for the raters to assign significantly different scores.

2.3 Data analysis

Various analyses of the data were undertaken. Factor analysis of the global ratings, and of the individual items, was performed by the method of maximum likelihood. This is a well established, standard statistical procedure. It requires the number of factors to be specified, and principal component analysis was performed as a guide for choosing the number of factors. We chose to use two criteria for the global items – that eigenvalues should be greater than unity (Andreasen et al, 1995), and that the number of factors specified should account for at least 60% of the total variation. The initial maximum likelihood factor solution was rotated using the varimax procedure.

3. Results

The sample comprised 317 men and 105 women with a mean (\pm SD) age of 38.2 (9.43) yrs. Their mean (\pm SD) educational status was 7.4 (3.1) yrs and the duration of illness 13.5 (9.4) yrs.

3.1 Global items:

The mean (\pm SD) scores for the global items were as follows: Affective flattening 2.22 (\pm 1.25); alogia 2.16 (\pm 1.55); avolition 2.77 (\pm 1.28); anhedonia 2.94 (\pm 1.25); attention 0.44 (\pm 0.95); hallucinations 1.22 (\pm 1.62); delusions 1.30 (\pm 1.68); bizarre behaviour 0.91 (\pm 1.48); and thought disorder 0.86 (\pm 1.38). The results of the principal components analysis are given in Table 1. The first two factors had eigenvalues greater than unity and accounted for 60% of the variation. The first five principal components accounted for 85% of the total variation. Table 2 gives the results of the two-factor analysis for the global ratings after the factors were rotated using the varimax rotation procedure. The first factor reflects the negative symptom dimension and accounts for 26.7% of the variance. Anhedonia, avolition, alogia and affective flattening all load highly with this factor, while attentional impairment loads almost equally on both factors. The second factor comprises a positive symptom dimension, with hallucinations, delusions, bizarre behaviour and to a lesser extent thought disorder loading here. The second factor accounts for 23.2% of the variance. The results of the five-factor analysis are given in Table 3. The first two factors – i.e. negative and positive symptoms - are substantially the same as in the two-factor analysis. Factors three and four are largely determined by global items attentional impairment and alogia. Factor five, a disorganizational factor, comprises largely the global items bizarre behaviour and to a lesser extent thought disorder.

3.2 Individual items:

The first five principal components accounted for 55% of the total variation, and the first 20 principal components for 85%. The first 10 components had eigenvalues of greater than one. We chose to report a five-factor model because the two previous analyses of individual items (Minas et al., 1994; Toomey et al., 1997) had favoured such a model. Table 4 gives details of a maximum likelihood five-factor analysis. Hallucinations and delusions form a single factor with the exception of delusions of jealousy. The second factor essentially corresponds with the “diminished expression” factor of Toomey et al. (1997) except that the items impersistence at work or school and physical anergia also load here in our analysis. The third factor comprises the items for positive formal thought disorder, as well as inappropriate affect, blocking and aggressive and agitated behaviour. The fourth factor corresponds with the “disordered relating” factor of Toomey et al. (1997), with the addition of poverty of content of speech. The fifth factor consists of the bizarre behaviour items (excluding aggressive and agitated behaviour) plus grooming and hygiene and delusions of jealousy.

4. Discussion

Global ratings:

As was the case in the study of Toomey et al. (1997), our factor analysis of the SANS and SAPS global ratings did not obviously replicate the three factor solution most frequently reported in the literature. This may be due to differences in the statistical methods that were applied. As pointed out by Toomey et al. (1997), previous studies favoured principal component analysis rather than factor analysis, with the former method running the risk of measurement error contributing to the findings. Our analysis yielded a two factor solution representing positive and negative symptoms that together accounted for a large portion of the variance, namely 59.9%. Attention was the only global item not to fit clearly into one of these two categories - a finding in keeping with previous studies indicating that this item has the least robust correlation and may in fact be heterogeneous (Andreasen et al., 1995).

However, while the two factor model appeared to fit well, the five factor model was also of interest, and yielded a solution that is consistent with previous work. Thus, the first two factors of the five factor analysis are essentially the same as with the two factor analysis (negative and positive dimensions) while factors three and four are largely determined by global items attentional impairment and alogia respectively. If, as was the case with Andreasen et al. (1994), these latter two factors are excluded, then our results are similar to those authors and to the majority of other studies in favouring a three factor solution comprising psychoticism, negative symptoms and disorganisation. Considering the diversity of the patient samples in

the various published studies as well as the existence of other methodological differences mentioned previously, the consistency of these findings with the previous studies is striking.

Individual items:

When comparing our individual item analysis with the two previously published studies (Minas et al., 1994; Toomey et al., 1997) there are once again strong similarities. The two negative symptom factors and a thought disorder (or disorganisation) factor were common to all three studies. The five factor item-level model split the negative symptom factor into two separate factors reflecting diminished expression and disordered relating. This latter term was coined by Toomey et al. (1997), who proposed that deficits in personal relationships constitute a dimension that is independent from the other negative symptoms. The positive symptoms were split in the item-level analysis into factors for psychosis (hallucinations and delusions), thought disorder and bizarre behaviour. Thus, the disorganisation factor reported in the 3 factor solution for the global items has split into thought disorder and bizarre behaviour factors in the individual item analysis. The thought disorder factor corresponds to the one reported by Minas et al. (1994) and Toomey et al. (1997). As was the case with these authors, as well as with Miller et al. (1993), we found that inappropriate affect loaded with this thought disorder factor. However, unlike them, we did not find that hallucinations separated from delusions, or that delusions differentiated into those that were bizarre and those that were non-bizarre. Also, our fifth factor, "bizarre behaviour", has not previously been reported as a separate factor, although the possibility was raised in one study (Andreasen et al., 1986).

There are various possible explanations for these observed differences. For example, both of the previous studies examined a much more heterogeneous sample than ours. Also, there may have been important treatment-related differences between the samples such as duration of symptoms prior to treatment, duration of treatment and current medication status. Another possibility is that cultural factors are responsible for these differences. Thus, the three factors of diminished expression, disordered relating and disorganisation may be relatively resistant to cultural influences, whereas the positive symptoms of delusions and hallucinations and in particular bizarre behaviour may be more susceptible to such influences. In this regard it is interesting to note that black Xhosa patients with schizophrenia have previously been reported by their relatives to have more bizarre behaviour than that reported by the relatives of their white English-speaking counterparts (Ensink et al., 1998).

If diminished expression, disordered relating, and disorganisation are more resistant to cultural influences, this may also argue for these symptoms of the illness being more genetically mediated than the other symptoms. With this in mind it would have been of interest to compare our findings with the studies conducted in Kenyan samples (Ndeti and Singh, 1983 A and 1983 B). While linguistically distinct from each other, the genetic distance between the Xhosa (south-east bantu) and the predominant Kenyan ethnic groups (other bantus and nilotics) is very small (Cavalli-Sforza et al., 1994). Unfortunately, comparisons are not possible as different methods of assessment were used and negative and disorganised symptoms were not reported in the Kenyan studies.

Interpretation of the results of this study is subject to a number of limitations: First, the patient ratings were cross-sectional, and important historical information may have been missed. Second, the assessment instruments were not translated into Xhosa. Third, the sample was of low education. Fourth, patients were not assessed at the same stage of their illness. This could have influenced our results, as the symptom dimensions of schizophrenia have been shown to have different patterns of exacerbation and remission during the course of the illness (Arndt et al., 1995). And fifth, the sample size was less than optimal for analysing the individual items. In spite of these limitations our solutions explained a high percentage of the variance in this study, suggesting that the results are indeed valid.

Previous studies of cultural differences in the symptoms of schizophrenia have often been limited by small samples, lack of specific diagnostic criteria and non-standardised symptom assessment. The present study addressed these issues. We found close similarities between the factor structures of Xhosa patients with schizophrenia and those from other parts of the world. The results are very similar to previously reported studies regarding negative symptoms – i.e. a single negative factor for the global items that separated into factors for diminished expression and disordered relating in the individual item analysis. However, the

positive symptoms did not show the same degree of stability at the individual item level – delusions and hallucinations did not split, while bizarre behaviour emerged as a separate factor. Our findings provide compelling evidence that the symptom dimensions of schizophrenia are relatively resistant to cultural influences. This is particularly true for negative symptoms, and provides further support for their inclusion in international cross-cultural studies (Dassori et al., 1998).

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Table 1 Principal component analysis for the SANS and SAPS global ratings*

Symptom	PC1	PC2	PC3	PC4	PC5
Affective flattening	-0.381	0.224	0.156	0.316	-0.010
Alogia	-0.337	0.382	0.076	-0.305	-0.373
Avolition	-0.374	0.296	-0.227	0.147	0.363
Anhedonia	-0.346	0.390	-0.311	0.153	0.002
Attention	-0.252	-0.077	0.811	0.261	-0.158
Hallucinations	-0.292	-0.476	-0.242	0.274	-0.360
Delusions	-0.328	-0.445	-0.286	0.094	-0.201
Bizarre behaviour	-0.325	-0.343	0.141	-0.106	0.725
Thought disorder	-0.345	-0.128	0.063	-0.774	-0.092
Eigenvalue	3.7356	1.6516	0.9392	0.7088	0.5858
Proportion	0.415	0.184	0.104	0.079	0.065
Cumulative	0.415	0.599	0.703	0.782	0.847

* The first five components are reported

SANS indicates Scale for the Assessment of Negative Symptoms

SAPS indicates Scale for the Assessment of Positive Symptoms

Table 2 Two factor structure for SANS and SAPS global ratings.

Symptom	Negative Symptoms	Positive Symptoms	Communality
Affective flattening	0.668	-0.255	0.512
Alogia	0.712	-0.083	0.513
Avolition	0.757	-0.200	0.613
Anhedonia	0.781	-0.118	0.624
Attention	0.264	-0.260	0.137
Hallucinations	0.059	-0.788	0.625
Delusions	0.121	-0.853	0.743
Bizarre behaviour	0.216	-0.582	0.386
Thought disorder	0.369	-0.450	0.338
Variance	2.4059	2.0842	4.4902
% Variance	26.7	23.2	49.9

The strongest correlations on a factor for a given item are given in bold face

SANS indicates Scale for the Assessment of Negative Symptoms

SAPS indicates Scale for the Assessment of Positive Symptoms

Table 3 Five factor structure for SANS and SAPS global ratings.

Variable	Negative Symptoms	Positive Symptoms	Attention	Alogia	Disorganisation	Commnlty
Affective flattening	0.573	-0.171	-0.260	0.244	0.155	0.509
Alogia	0.474	-0.013	-0.119	0.871	0.045	1.000
Avolition	0.788	-0.117	-0.051	0.129	0.187	0.689
Anhedonia	0.800	-0.105	-0.005	0.210	0.001	0.695
Attention	0.113	-0.119	-0.969	0.105	0.151	1.000
Hallucinations	0.111	-0.766	-0.114	-0.011	0.146	0.633
Delusions	0.131	-0.843	-0.030	0.088	0.229	0.788
Bizarre behaviour	0.149	-0.367	-0.164	0.035	0.775	0.786
Thought disorder	0.228	-0.335	-0.125	0.319	0.337	0.396
Variance	1.9302	1.6124	1.0802	1.0011	0.8723	6.4962
% Variance	21.4	17.9	12.0	11.1	9.7	72.2

The strongest correlations on a factor for a given item are given in bold face
 SANS indicates Scale for the Assessment of Negative Symptoms
 SAPS indicates Scale for the Assessment of Positive Symptoms

Table 4 Five factor analysis for SANS and SAPS individual items.

SANS Item	Psychotic Symptoms	Diminished Expression	Thought-disorder	Disordered Relating	Bizarre Behaviour	Commnlty
1 unchanging facial expression	0.013	0.845	-0.009	0.007	0.148	0.737
2 decreased spont. movements	0.064	0.882	-0.035	0.086	-0.032	0.792
3 paucity of expressive gestures	0.046	0.933	-0.041	0.055	0.033	0.879
4 poor eye contact	0.034	0.732	0.132	0.258	0.074	0.625
5 affective nonresponsivity	0.100	0.849	0.006	0.238	0.013	0.787
6 inappropriate affect	0.079	0.028	0.511	0.071	0.228	0.325
7 lack of vocal inflections	0.066	0.844	-0.026	0.169	0.102	0.756
9 poverty of speech	-0.027	0.677	0.050	0.277	-0.053	0.541
10 poverty of content of speech	0.113	0.388	0.348	0.455	-0.149	0.514
11 blocking	0.135	0.201	0.210	0.128	-0.034	0.121
12 increased latency of response	0.010	0.255	0.132	0.202	-0.054	0.126
14 grooming and hygiene	-0.098	0.318	0.123	0.264	0.350	0.318
15 impersistence	0.004	0.454	0.136	0.421	0.246	0.463
16 physical anergia	0.070	0.508	-0.005	0.460	0.103	0.485
18 recreational interests	0.041	0.460	0.101	0.681	0.122	0.703
20 intimacy and closeness	0.158	0.432	0.201	0.736	0.031	0.794
21 relationships	0.079	0.437	0.120	0.726	0.087	0.747
23 social inattentiveness	0.037	0.302	0.170	-0.034	0.231	0.176
SAPS Item						
1 auditory hallucinations	0.627	0.064	0.093	0.026	0.572	0.733
2 voices commenting	0.590	0.077	0.165	0.078	0.524	0.662
3 voices conversing	0.591	0.052	0.106	0.077	0.572	0.696
4 somatic/tactile hallucinations	0.567	-0.010	0.035	0.040	0.394	0.479
5 olfactory hallucinations	0.563	0.042	0.144	0.106	0.239	0.408
6 visual hallucinations	0.491	-0.034	0.285	0.010	0.327	0.430
8 persecutory delusions	0.472	0.150	0.237	0.067	0.446	0.505
9 delusions of jealousy	0.096	-0.074	0.108	-0.110	0.175	0.069
10 delusions of guilt or sin	0.673	0.050	0.031	-0.043	-0.096	0.468
11 grandiose delusions	0.476	-0.061	0.187	0.114	0.205	0.321
12 religious delusions	0.391	0.037	0.237	0.054	0.268	0.285
13 somatic delusions	0.570	0.012	0.147	0.074	0.180	0.384
14 delusions of reference	0.549	0.102	0.248	0.082	0.299	0.470
15 delusions of being controlled	0.689	0.073	0.145	0.043	0.150	0.526
16 delusions of mind reading	0.796	0.101	0.139	0.020	0.026	0.664
17 thought broadcasting	0.809	0.044	0.078	-0.007	-0.104	0.673
18 thought insertion	0.761	0.015	0.169	-0.041	-0.202	0.651
19 thought withdrawal	0.731	0.014	0.155	-0.005	-0.076	0.564
21 clothing and appearance	0.073	0.187	0.218	0.199	0.306	0.221
22 social and sexual behaviour	0.008	0.048	0.264	-0.012	0.339	0.187
23 aggressive, agitated behaviour	0.176	0.025	0.273	-0.015	0.217	0.154
24 repetitive behaviour	0.074	0.063	0.091	0.044	0.129	0.036
26 derailment	0.182	0.056	0.819	0.096	0.178	0.748
27 tangentiality	0.137	0.140	0.866	0.104	0.208	0.843
28 incoherence	0.213	0.169	0.779	0.193	0.064	0.723
29 illogicality	0.212	0.126	0.840	0.137	0.163	0.811
30 circumstantiality	0.220	0.133	0.657	0.236	-0.000	0.553
31 pressure of speech	0.035	-0.054	0.314	0.056	0.168	0.134
32 distractible speech	0.216	0.005	0.506	-0.038	0.055	0.307
33 clanging	0.050	-0.042	0.214	-0.031	-0.002	0.051
Variance						
Variance	6.9285	6.5031	4.8526	2.7582	2.6037	23.6462
% Variance	14.4	13.5	10.1	5.7	5.4	49.3

The highest correlations on a factor for each item are given in bold face

1.c Depressive and anxiety symptoms in patients with schizophrenia and schizophreniform disorder

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ABSTRACT

Background: Symptoms of depression and anxiety are frequently encountered in the course of schizophrenia, and are of considerable clinical importance. They may compromise social and vocational functioning, and are associated with an increased risk of relapse and suicide. Various treatment approaches have been reported to be successful.

Methods: The sample comprised 177 patients with schizophrenia or schizophreniform disorder who were participants in multinational clinical drug trials at our academic psychiatric unit over a 7 year period and who were assessed by means of the Positive and Negative Syndrome Scale (PANSS). Analysis was performed on baseline PANSS scores. The depression/anxiety score was compared in the men and women, first-episode and multiple episode patients, and those with predominantly positive and negative syndromes. Correlations were sought between depression/anxiety scores and age, total PANSS score, positive score, negative score, general psychopathology score and treatment outcome. Multivariate analysis was applied to determine contributions of individual variables toward depression/anxiety and outcome scores.

Results: Depression and anxiety symptoms were more severe in women ($p = 0.007$), first-episode patients ($p = 0.02$), and those with predominantly positive symptoms ($p < 0.0001$). Depression/anxiety scores were significantly correlated to age ($r = -0.31$, $p < 0.0001$), PANSS positive scores ($r = 0.39$, $p < 0.0001$) and treatment outcome ($r = 0.25$, $p = 0.006$). Multivariate analysis bore out these results, with the exception that first episode was not a significant predictor of depression and anxiety scores.

Conclusions: Depressive/anxiety scores were generally low in our sample, perhaps because patients with schizoaffective disorder were excluded. The finding that these symptoms were more prominent in women and first-episode patients is in keeping with previous literature. The higher scores in first-episode patients are likely due to the higher positive symptom scores in these patients. The association between depressive/anxiety scores and positive symptoms but not with negative symptoms points to a specific relationship between affective symptoms and the positive symptom domain of schizophrenia. The presence of depressive and anxiety symptoms may predict a more favorable outcome to treatment, although this may only apply to the acute exacerbations of the illness.

INTRODUCTION

Symptoms of depression and anxiety are frequently encountered during the course of schizophrenia. They may occur during any phase of the illness, and are not always easy to recognize. Depressive symptoms may mimic the negative symptoms of schizophrenia¹ and neuroleptic-induced akinesia, while anxiety symptoms may be indistinguishable from akathisia.^{2,3} Possible causes of depression and anxiety in schizophrenia include response to adverse life events⁴, substance abuse,¹ co-morbid major depression or anxiety disorders, neuroleptic-induced dysphoria⁵ or the possibility that these symptoms are a core feature of the schizophrenic illness.⁶ The prevalence of depressive symptoms in schizophrenia has been reported as between 7% and 70%, depending on the criteria applied and populations studied.⁷ Depressive symptoms are very common in first-episode schizophrenia,⁶ the majority occurring concurrently with the psychotic symptoms and resolving as the psychosis remits. The majority of depressive symptoms appear to be related to the psychotic symptoms. Although not clear-cut, the presence of depressive symptoms in the acute phase of the illness may be associated with a favorable outcome,^{7,8} while in the chronic course they may be negative prognostic indicators.^{9,10} Koreen et al⁶ found that depressive symptoms in their first-episode patients did not significantly affect the prognosis.

Anxiety symptoms in schizophrenia have been less well studied, although reports of co-morbid anxiety disorders and syndromes including obsessive-compulsive disorder,¹¹ panic attacks,¹² social anxiety¹³ and posttraumatic stress disorder¹⁴ have appeared in the literature. Kay¹⁵ found that depressive and anxiety symptoms clustered together as a distinct factor in patients with schizophrenia. Whatever their origins, depressive and anxiety symptoms in schizophrenia are of considerable clinical relevance. They may compromise social and vocational functioning, and are associated with an increased risk of relapse¹⁶ and suicide.¹⁷ The importance of recognizing these symptoms is further underlined by the fact that they may be responsive to various therapeutic interventions. Most depressive symptoms accompanying an acute psychosis resolve with neuroleptic treatment of the psychosis.⁶ Tricyclic antidepressants, although not effective in treating depressive symptoms in actively psychotic patients,¹⁸ were successful in treating post-psychotic depression,^{19,20} as was lithium carbonate.²⁰ Decreased depression and suicidality was reported with clozapine treatment of neuroleptic-resistant schizophrenia.²¹ More recently, olanzapine was found to be superior to haloperidol in reducing depressive signs and symptoms in schizophrenia, and this effect was independent of reduction of psychotic symptoms.¹ Alprazolam has been reported to be effective in schizophrenia with panic anxiety,²² as has cognitive-behavioral therapy.²³

This study further investigates depressive and anxiety symptoms in a large sample of patients with schizophrenia and schizophreniform disorder. The patients comprise participants in multinational clinical drug trials at our academic psychiatric unit who were assessed by means of the Positive and Negative Syndrome Scale (PANSS)¹⁵ over a 7 year period.

PATIENTS AND METHODS

Patients meeting DSM-III-R²⁴ or DSM-IV²⁵ criteria for schizophrenia or schizophreniform disorder who had participated in multinational clinical trials within our department and in whom the PANSS had been used to assess symptom severity were included. All patients had provided informed, written consent to participate in the trials, and the studies were approved by the Ethics Committee of the University of Stellenbosch. The trials took place between 1991 and 1998 at an academic psychiatric hospital under a single principal investigator (RAE). The other investigators were experienced psychiatrists who had undergone training and inter-rater reliability testing for using the PANSS. Subjects were aged between 18 and 65 years, had no concomitant significant medical conditions and did not meet criteria for substance abuse. Schizoaffective disorder was an exclusion criterion for all of the trials. Analysis was performed on baseline PANSS scores of all of the patients who had been randomized to one of the trials. The following PANSS groups were selected, according to previously specified criteria:¹⁵ Total PANSS score (30 items); positive scale (items P1-P7); negative scale (items N1-N7); composite score (positive scale score minus negative scale score); and general psychopathology scale (items G1-G14). Patients were also divided into those with predominantly positive syndromes (score of 4 or more on at least three of the positive items and on fewer than three on the negative scale) and those with predominantly negative syndromes (score of 4 or more on at least three of the negative items and on fewer than three on the positive scale), and into those suffering from their first psychotic episode

and those suffering from recurrent psychotic episodes. Depressive and anxiety symptoms were examined in these different groups. The depression/anxiety factor comprised the sum of the scores from PANSS items G1 (somatic concern), G2 (anxiety), G3 (guilt feelings) and G6 (depression). Finally, correlations were sought between depression/anxiety scores and the following variables: Age, total PANSS score; positive score; negative score; composite score; and treatment outcome as assessed by the change from baseline in total PANSS scores (minus depression/anxiety items) at 6 weeks (or the closest assessment to 6 weeks, ranging from 5 – 9 weeks).

Statistical analysis:

Student's t-test (2-tailed) and Pearson's Product Moment Correlation Coefficient were used for differences and correlations between numeric variables. To determine the contributions of individual variables toward depression/anxiety and outcome scores, significant univariate results were followed with regression analysis with simultaneous entry, using the method of least squares. The significance level was set at 0.05.

RESULTS

The sample comprised 177 subjects of whom 113 (64%) were men and 64 (36%) women. The mean \pm sd age was 35.6 ± 13.36 years. Sixty (34%) were first-episode patients. The median (interquartile range) number of psychotic episodes in the multiple episode group was 2 (3). DSM diagnoses were as follows: Paranoid schizophrenia (n=41), disorganized schizophrenia (n=28), catatonic schizophrenia (n=2), undifferentiated schizophrenia (n=48), residual schizophrenia (n=27) and schizophreniform disorder (n=29). For the entire sample mean PANSS scores were as follows: positive scale 20.5 ± 6.82 ; negative scale 24.5 ± 6.71 ; general psychopathology scale 38.6 ± 9.06 ; total PANSS score 83.6 ± 17.61 ; composite score -4 ± 9.66 ; and depression/anxiety factor 7.8 ± 3.05 .

We were initially interested in looking at anxiety and depressive symptoms separately. To determine whether these were in fact separate entities we selected the items that we considered to represent "pure" anxiety (G2. Anxiety + G4. Tension) and depressive (G3. Guilt feelings + G6. Depression) symptoms and correlated them. A highly significant correlation ($r = 0.5$, $p < 0.0001$) was found between these factors, indicating that depression and anxiety symptoms largely occurred together in our sample of patients. This is in keeping with the original principal component analysis of Kay, in which the depressive and anxiety symptoms of the PANSS scale formed a single component.¹⁵ We therefore examined depression and anxiety symptoms as one factor, using the items identified by Kay¹⁵ (G1, G2, G3 and G6). Figure 1 shows the various PANSS scores for men and women, and Figure 2 shows the various PANSS scores for first-episode and multiple episode patients. Thirty-four patients met criteria for a predominantly positive syndrome, and 59 for a predominantly negative syndrome. The depression/anxiety scores for these two groups were, respectively, 8.2 ± 2.5 and 6.3 ± 2.45 . The difference between these groups was highly significant ($p = 0.0004$). The depression/anxiety score was found to correlate significantly with age ($r = -0.31$, $p < 0.0001$), PANSS positive score ($r = 0.39$, $p < 0.0001$), treatment outcome ($r = 0.25$, $p = 0.006$) but not with the PANSS negative score ($r = -0.07$, $p = 0.4$).

Because the depression/anxiety factor was related to both first-episode and positive symptom scores, and first-episode patients had significantly higher positive symptom scores, multiple regression, using the method of least squares was performed. The depression/anxiety score was the dependent variable and age, sex, first episode, positive score, negative score and the interaction of positive score and first-episode were the independent variables. The overall regression was significant [$F(6,168) = 8.54$, $p < 0.0001$, adjusted $R^2 = 0.21$], suggesting that 21% of the variance in depression/anxiety scores was associated with the model. Significant predictors were younger age ($p = 0.02$), female gender ($p = 0.005$) and positive symptoms ($p = 0.04$).

To identify the contributions of age, sex, first-episode and depression/anxiety score to predicting outcome, multiple regression was performed with outcome as the dependent variable and the other variables as predictor variables. The symptoms included in the depression/anxiety factor (G1, G2, G3 and G6) were excluded from the total PANSS scores.

The overall regression was significant [$F(4,117) = 4.46, p < 0.002, \text{adjusted } R^2 = 0.10$], suggesting that 10% of the variance in outcome could be explained by these variables. The only significant predictor was anxiety/depression score ($p = 0.04$).

DISCUSSION

The major findings of this study were that depressive and anxiety symptoms were more prominent in women, those with predominantly positive symptoms and those suffering from their first psychotic episode. There was a significant negative association with age, and a significant positive association with positive symptoms. Generally, symptoms of depression and anxiety were present only to a moderate degree, even in the first-episode patients. This is in contrast to the findings of Koreen et al⁶ (although direct comparisons are not possible because different scales were used to assess symptom severity). This discrepancy could be due to the fact that patients with schizoaffective disorder were excluded from our sample.

The finding that depressive and anxiety symptoms are more prominent in women is in keeping with previously reported gender differences in schizophrenia.²⁶ Bardenstein and McGlashan,²⁷ after reviewing the literature, concluded that women with schizophrenia are more likely to experience affective symptoms, while men are likely to have more prominent negative symptoms. Häfner et al²⁸ found more depressive symptoms in women than in men in first-admission patients with schizophrenia. However, it is possible that these results could reflect differences in men and women that are not related to schizophrenia.²⁸ Also, the differences, although significant are small, and may not be clinically meaningful.

As with the studies of House et al²⁹ and Koreen et al,⁶ our study showed that depressive and anxiety symptoms were more prominent in patients experiencing their first-episode of schizophrenia. Again however, the differences although significant are small, and may not have clinical relevance. On the other hand, the additional clear-cut differences between first-episode and multiple-episode patients regarding positive symptoms, negative symptoms and general psychopathology scores indicate that the psychopathology of first-episode schizophrenia is different from multiple-episode schizophrenia. Multivariate analyses indicate that the higher positive symptom scores in first-episode patients are likely to account also for the higher levels of depressive and anxiety symptoms encountered in first-episode compared to multiple-episode patients.

Whereas Koreen et al⁶ found depression to be significantly correlated with both positive and negative symptoms, we found a significant correlation with positive symptoms only. Our findings are thus consistent with other studies^{30,31} indicating an association between depression/anxiety and positive symptoms, with independence of negative symptoms. This points to a specific association between these affective symptoms and the positive symptom domain of schizophrenia. There are several possible explanations for this association. First, it could be that depressive and anxiety symptoms are secondary to the positive symptoms. Second, in the stress-diathesis context, these affective symptoms may themselves constitute a stressor that triggers a psychotic episode.³² Third, affective symptoms and positive symptoms may represent common clinical manifestations of the same underlying pathological process. This latter possibility is consistent with the proposal that depression is a core part of schizophrenia that occurs at the height of psychosis and decreases over the course of treatment.⁶

The finding that depression and anxiety scores correlated with treatment response is consistent with that reported by Kay,¹⁵ who found that this factor emerged as the only clinical variable to reliably predict good outcome. This is particularly interesting considering that both our study and that of Kay excluded patients with schizoaffective disorder. Thus, the better prognosis in patients with schizophrenia with affective symptoms cannot be explained on the basis that these patients were actually suffering from schizoaffective disorder. However, the fact that most of our patients were experiencing acute exacerbations of their illness is consistent with other studies indicating that the favourable outcome associated with depressive symptoms may only apply to the acute phase of the illness.^{7,8}

There are a number of limitations to this study. Firstly, we only looked at *symptoms* of depression and anxiety, and not at specific co-morbid mood and anxiety *disorders*. Secondly, side-effects of medication taken prior to the onset of the trials were not assessed. Although patients had undergone a washout period of 3 to 7 days before the PANSS assessment was done, extrapyramidal or other side-effects from previously taken medication could have influenced the results. However, medication effects are unlikely to have played a major role, considering that previous studies failed to show a strong association between depression and extrapyramidal symptoms.^{6,29} Thirdly, the various investigators may have rated symptoms differently. The fact that regular inter-rater reliability training took place, and the same principle investigator was present for all of the studies, decreases the likelihood of this possibility. Finally, the correlations with treatment outcome need to be interpreted with caution, as patients obviously received different treatments. Details of medication were not available to us, as a number of the studies had not been unblinded at the time of our analysis.

In conclusion, the assessment of depressive and anxiety symptoms in patients with schizophrenia is of considerable importance. These symptoms may be core features of the illness, and may be of value in predicting the treatment outcome in patients suffering acute exacerbations of the illness.

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Table 1. Mean \pm SD PANSS Scores for Men and Women With Schizophrenia or Schizophreniform Disorder.

	Men (n=113)	Women (n=64)	p value
Depression/anxiety score	7.29 \pm 2.95	8.6 \pm 3.09	0.007
Positive score	20.4 \pm 6.70	20.8 \pm 7.08	NS
Negative score	24.7 \pm 7.25	24.2 \pm 5.68	NS
GPS	38.3 \pm 8.75	39.1 \pm 9.62	NS
PANSS total score	83.4 \pm 17.07	84.1 \pm 18.65	NS
Composite score	-4.3 \pm 10.45	-3.4 \pm 8.14	NS

GPS = General psychopathology score

NS = not significant

Table 2. Mean \pm SD PANSS Scores for First Episode and Multiple Episode Patients With Schizophrenia or Schizophreniform Disorder.

	First episode (n=60)	Multiple episode (n=115)	p value
Depression/anxiety score	8.5 \pm 3.32	7.4 \pm 2.84	0.02
Positive score	23.7 \pm 5.15	18.7 \pm 6.94	< 0.0001
Negative score	23.3 \pm 8.06	25.3 \pm 5.79	0.05
GPS	41.4 \pm 10.19	37.2 \pm 8.08	0.003
PANSS total score	88.4 \pm 19.2	81.2 \pm 16.33	0.01
Composite score	0.42 \pm 9.24	-6.5 \pm 8.89	< 0.00001

GPS = General psychopathology score

1.d Co-occurrence of schizophrenia and obsessive-compulsive disorder – a literature review

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Introduction

Similarities between schizophrenia and obsessive-compulsive disorder (OCD) have long been recognised. Obsessive-compulsive symptoms in patients with schizophrenia were first described by Westphal over 100 years ago.¹ The disorder was considered to be a variant of schizophrenia. Since that time the relationship of OCD to schizophrenia and psychosis has been the subject of considerable debate. Unfortunately, only a few methodologically sound studies have investigated this relationship. Associations between the two disorders have been investigated in two ways – on the one hand the frequency of obsessions and compulsions in patients with schizophrenia has been assessed, and on the other hand the occurrence of psychotic symptoms in patients with OCD has been investigated. This article reviews the literature concerning the co-occurrence of schizophrenia and OCD. Clinical implications are highlighted, and avenues for further research are suggested.

OCD IN PATIENTS WITH SCHIZOPHRENIA

Several studies have investigated the occurrence of OCD symptoms in patients with schizophrenia, with the reported frequency ranging from 3.5% to 25%.²⁻⁴ In a retrospective chart review, Rosen² found prominent features of OCD in 30 (3.5%) of 848 patients with schizophrenia. These symptoms either preceded or coincided with the onset of the schizophrenic symptoms. He emphasised the depressive and paranoid features of these patients, and considered them to have a good prognosis. In another retrospective chart review Fenton and McGlashan³ found that 21 (12.9%) of 163 *DSM-III*-diagnosed schizophrenic patients had prominent OCD symptoms. Berman *et al.*⁴ interviewed the treating physicians of 108 patients with chronic schizophrenia and found prominent OCD symptoms in 27 (25%). However, in a well-designed study on 77 patients with schizophrenia or schizo-affective disorder, Eisen *et al.*⁵ found that only 6 (7.8%) also met *DSM-III-R* criteria for OCD. This prospective study employed the Structured Clinical Interview for *DSM-III-R* and the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), as well as chart review and contact with the treating clinicians. Of the above studies, the latter is most likely to reflect the true incidence of OCD in patients with schizophrenia. The occurrence of OC symptoms in patients with schizophrenia is likely to be considerably higher. In a study limited by its small sample size, Yaryura-Tobias *et al.*⁶ reported unexpectedly high scores on the Y-BOCS and the Self-Rated Symptom Scale for OCD in 13 patients with schizophrenia, and found great similarities in thought process impairment and perceptual deficits when compared with 22 OCD patients. Little is known about the clinical, neurobiological and treatment aspects of these patients. The need for further carefully planned prospective studies is obvious.

OCD WITH PSYCHOTIC FEATURES

Clinical observations indicate that not all OCD patients recognise their obsessions as being irrational or excessive. Their ideas have usually been described as overvalued or delusional. Kozak and Foa⁷ have examined the matter of insight in OCD and conclude that OCD ideas cannot be dichotomised into those with and those without insight. They suggest that a continuum of strength of OC beliefs is more appropriate, and emphasise that the relationship between the degree of OC conviction and outcome of treatment remains unclear. In 1875 du Saulle⁸ reported psychotic symptoms in some of the 27 OCD patients he described. The patients with psychotic features also had poor insight and severe psychopathology. Janet⁹

found psychotic symptoms in 7.7% of patients with OCD. In a review of the literature of OCD with psychotic features, Insel and Akiskal¹⁰ list 9 studies¹¹⁻¹⁹ of patients who were initially diagnosed as OCD and in whom a relatively high incidence of psychosis was found. Incidence rates for schizophrenia in these studies range from 0.7% to 12.3%. The authors point out that these findings should be interpreted with caution, as these were all retrospective studies, with the diagnoses being made by chart review. Also, standardised criteria for diagnosing schizophrenia were not used. Rudin¹² and Muller¹³ found that a relatively high percentage of their patients had schizophrenia, while other studies considered their OCD patients to be psychotic only in the presence of paranoid thinking, or transient loss of insight. Interestingly, many of the OCD patients with psychotic features reportedly had a relatively good outcome.

Insel and Akiskal¹⁰ emphasise that the deterioration often seen in patients with schizophrenia is extremely rare in OCD patients with psychotic features. The literature suggests that psychotic features in OCD patients may often be due to a paranoid state or a mood disorder rather than a schizophrenic illness. More recently, Eisen and Rasmussen²⁰ assessed 475 patients with *DSM-III-R* OCD. Sixty-seven (14%) were identified as having 'psychotic' symptoms. However, the only psychotic symptom in 27 (6%) was lack of insight, and 14 (3%) were actually diagnosed as schizotypal personality disorder. The remainder of the patients met criteria for specific psychotic disorders. Eighteen (4%) met criteria for schizophrenia, and 8 (2%) had a delusional disorder. OCD patients with psychotic features were more likely to be male, single, to have received treatment earlier, and to have had a deteriorating course. In contrast to some earlier studies, therefore, these authors found that OCD patients with features of schizophrenia had a poor outcome. Clearly, there is considerable heterogeneity among OCD patients with psychotic symptoms.

The co-occurrence of OCD and schizophrenia appears to be greater than would be expected by chance. Taken together, the evidence points to a small but significant subset of patients sharing OCD and schizophrenia symptoms. Whether this represents a distinct clinical entity, or the extremes of a continuum, is not clear. Further prospective studies are required to clarify this issue as well as to determine such matters as whether these patients have other distinctive features, whether they respond differentially to standard treatment, and whether other treatment options – e.g. serotonin reuptake inhibitors (SRIs) combined with antipsychotics – may be effective.²¹

SEROTONIN AND DOPAMINE

There is considerable evidence suggesting that serotonergic and dopaminergic pathways may have particular relevance both for patients with OCD and for those with schizophrenia. SRIs are the first-line treatment for OCD,²¹ and dopamine-blocking agents have been the mainstay of the treatment of schizophrenia for many years.²² Furthermore, preclinical and clinical findings have reported that dopamine plays a role in OCD and possibly related disorders such as Tourette's syndrome.^{23,24} Also, in treatment-resistant OCD augmentation with haloperidol has been successful, particularly if tics are present.²⁵ The advent of the new antipsychotics has brought renewed interest because of their combined dopaminergic and serotonergic blocking properties. In this regard several studies, although uncontrolled, have reported a favourable augmentative effect with the new antipsychotic risperidone in treatment-resistant OCD.²⁶⁻³⁰ Paradoxically, several anecdotal reports have arisen of OCD symptoms emerging in patients with schizophrenia during treatment with both clozapine³¹⁻³⁶ and risperidone.³⁷⁻³⁹ The frequency of this occurrence is unknown and it may be extremely rare, as a retrospective review of hospital files in 142 randomly selected patients on clozapine treatment failed to identify a single case of OCD symptoms worsening or emerging during treatment.⁴⁰ Also, in a prospective study of patients with schizophrenia those taking another new antipsychotic, olanzapine, did not experience more OC symptoms than those taking placebo.⁴¹

These findings again point to a complex interrelationship between serotonin and dopamine in the pathogenesis of OCD and schizophrenia. It may be that the emergence of OCD symptoms during treatment with the new antipsychotics is a coincidental occurrence, or it may represent a rare idiosyncratic reaction. On the other hand it may be that patients with coexisting psychosis and OCD and patients with resistant OCD represent two distinct

subgroups with different underlying disorders of serotonergic and dopaminergic function. Patients with OCD and psychosis may therefore experience exacerbation of OCD symptoms with combined dopamine and serotonin blockade, while patients with refractory OCD may respond favourably to this intervention. The differential response for symptoms of OCD and schizophrenia in patients with both disorders is not entirely unexpected, as functional brain-imaging studies have suggested an opposite pattern of frontal lobe activity,⁴² and neuropsychological investigations report a double dissociation of frontal lobe functioning in OCD and schizophrenia.⁴³ Whatever the underlying mechanisms, increasing evidence points to the involvement of serotonergic and dopaminergic neurotransmitter systems in patients with coexisting OCD and schizophrenia.²¹ Future controlled trials with drugs acting on these two systems in different ways may shed more light on the underlying mechanisms, and may offer better therapeutic options for these patients. The new antipsychotics in particular may have a role to play and may deserve exploration – not only in schizophrenia, but also in OCD and related disorders such as Tourette's syndrome.

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2.a Water Excretion and Plasma Vasopressin in Psychotic Disorders

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Abstract

To investigate the pathogenesis of water intoxication in psychotic disorders, a standard water load test was given to 23 unmedicated patients with schizophrenic or schizoaffective disorders. Levels of plasma arginine vasopressin were measured concurrently. Compared with 28 healthy volunteers, the psychotic patients had significantly smaller cumulative urine output and higher minimum urine osmolalities. Patients whose current illness had lasted less than 24 weeks exhibited the most severe antidiuretic state and also had the highest plasma arginine vasopressin levels. Water intoxication in acute exacerbations of psychosis may develop as a result of impaired excretory mechanisms.

Self-induced water intoxication is a well-recognized complication in certain patients with psychotic disorders, particularly of the schizophrenic type (1-3). Initially, polydipsia was emphasized in the pathogenesis (4), but it was later recognized that impaired excretory mechanisms may also play a role. Lack of maximal urinary diluting capacity in the presence of serum hypotonicity in some cases suggested an excessive secretion of arginine vasopressin. In fact, the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) has subsequently been documented by direct assay of arginine vasopressin in a number of psychotic patients with water intoxication (5,6). In a further development, Raskind et al. (7) reported elevated plasma arginine vasopressin levels in unmedicated, acutely psychotic patients without water intoxication. This led us to investigate the existence of an antidiuretic state in psychotic patients by measuring their responses to a standard water load test (8) and estimating concurrent levels of plasma arginine vasopressin. Reference data were obtained by simultaneously studying a group of healthy volunteers.

METHOD

The psychotic patients consisted of 16 men and seven women between the ages of 18 and 42 years (median=27 years) who met the Research Diagnostic Criteria (9) for a schizophrenic (N=15) or schizoaffective (N=8) disorder. All of them manifested features of active psychosis, had been free of psychotropic medication for at least 4 months, and were tested within 4 days of admission to a psychiatric ward. At the time of the study, each patient was rated on the Brief Psychiatric Rating Scale (BPRS) (10). The healthy volunteers were recruited from hospital staff and their families; there were 21 men and seven women between the ages of 18 and 55 years (median=25.5 years). Subjects in both groups were in good physical health, did not display polydipsia, and had no other disorders associated with an abnormal fluid balance or with SIADH. None gave a history of excessive alcohol consumption or drug abuse or was taking any medication. All subjects gave informed consent.

The subjects fasted and abstained from smoking from the previous evening until completion of the test, during which they remained recumbent. Blood and urine samples were obtained before the administration of a standard water load test. Blood was analyzed for sodium, potassium, creatinine, urea, osmolality, glucose, albumin, globulin, conjugated and unconjugated bilirubin, γ -glutamyltransferase, hematocrit, thyroid-stimulating hormone, T_3 , T_4 , 9-hour cortisol, plasma renin activity, and β_2 microglobulin (as an indicator of glomerular function). Urine was analyzed for osmolality and β_2 microglobulin (as an indicator of renal tubular function).

For the water load test, subjects consumed 20 ml/kg of body weight of cool tap water within 15 minutes. Each hour during the next 4 hours, blood pressure was recorded and samples of blood and total urine output were collected. These were analyzed for electrolyte and osmolality concentrations. Blood for arginine vasopressin assay was drawn at 0, 2, and 4 hours and was collected in ice-cooled EDTA Vacutainer tubes. These were immediately transported on ice to the laboratory, and the plasma was separated in a cold centrifuge at 4°C. The separated plasma was stored at -20°C. Arginine vasopressin was measured by means of a radio-immunoassay kit (Immuno Nuclear Corp.). Interassay and intra-assay coefficients of variation were 12.5% and 11.2%, respectively.

To determine the relationships between the variables of anxiety, psychotic symptoms, and response to the water load test, the following procedure was followed. A total anxiety factor, consisting of the sum of the scores from the BPRS scales of anxiety, agitation, and excitement, and a psychosis factor, consisting of the sum of the scores from the BPRS scales of suspiciousness, hallucinations, unusual thought content, and conceptual disorganization (7), were calculated. Correlations were then sought between these scores and the percentage water load excreted, the minimum urine osmolality obtained, and plasma arginine vasopressin values at 0, 2, and 4 hours.

Because of small sample sizes, the median and interquartile ranges were used to summarize the continuous measurements within the groups. Pairwise comparisons were done with the Mann-Whitney U test or, when there were many tied values, the Median test (11). Spearman correlation coefficients (ρ) for selected continuous variables were calculated within each group. A significance level of 0.05 was used throughout.

RESULTS

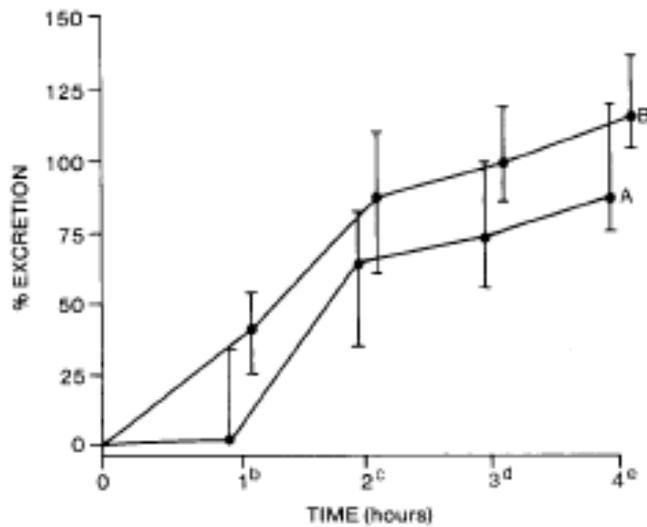
Values for baseline blood and urine studies were within normal limits in all of the subjects. The percentage water load excreted and the minimum urine osmolalities obtained in the two groups of subjects are shown in figures 1 and 2. Compared with healthy volunteers, the psychotic patients excreted a significantly lower cumulative volume (for healthy volunteers, median=115% and interquartile range=32; for psychotic patients, median=86% and interquartile range=44). The psychotic patients also had significantly higher minimum urine osmolalities (for healthy volunteers, median=72 mmol/kg of water and interquartile range=18; for psychotic patients, median=112 mmol/kg and interquartile range=161). Figure 3 shows plasma arginine vasopressin levels measured at 0, 2, and 4 hours. Median and interquartile range values at 0, 2, and 4 hours for the psychotic patients were 1.30 and 1.80 pg/ml, 0.90 and 0.70 pg/ml, and 1.00 and 0.90 pg/ml, respectively; for the healthy volunteers, they were 1.15 and 0.58 pg/ml, 0.90 and 0.63 pg/ml, and 0.99 and 0.84 pg/ml, respectively. There were no significant differences between the two groups.

Baseline serum sodium levels for the psychotic patients (median=142 mmol/liter and interquartile range=3) were similar to those of the healthy volunteers (median=142 mmol/liter and interquartile range=5). At 4 hours, serum sodium values had reverted to baseline levels in the healthy volunteers (median=142 mmol/liter and interquartile range=5) but remained significantly lower (median test, $\chi^2=8.64$, $df=1$, $p=0.003$) in the psychotic patients (median=139 mmol/liter and interquartile range=4). The median value and interquartile range for serum osmolality before loading for the psychotic patients were 284 and 14 mmol/kg of water, and for the healthy volunteers, 285.5 and 6 mmol/kg. At 4 hours, the medians and interquartile ranges were 279 and 8 mmol/kg of water for the psychotic patients and 281.5 and 7 mmol/kg for the healthy volunteers.

The only significant correlations were between total anxiety scores and plasma arginine vasopressin at 0 hours ($\rho=0.54$, $N=23$, $p=0.007$) and at 2 hours ($\rho=0.51$, $N=23$, $p=0.01$).

On separating the psychotic patients according to duration of the current illness, those with a duration of less than 24 weeks ($N=12$) showed the most pronounced antidiuretic state. Thus, compared with the healthy volunteers, all 12 were below the 0.25 centile of 104% for cumulative urine output, 10 were above the 0.75 centile of 81.5 mmol/kg of water for minimum urine osmolality, and seven were above the 0.75 centile of 1.40 pg/ml for baseline arginine vasopressin levels.

Figure 1. Percentage Water Load Excreted for 23 Psychotic Patients (group A) and 28 Healthy Volunteers (group B)^a



^aThe closed circles represent group median values; the lower bars, 0.25 centiles; and the upper bars, 0.75 centiles.

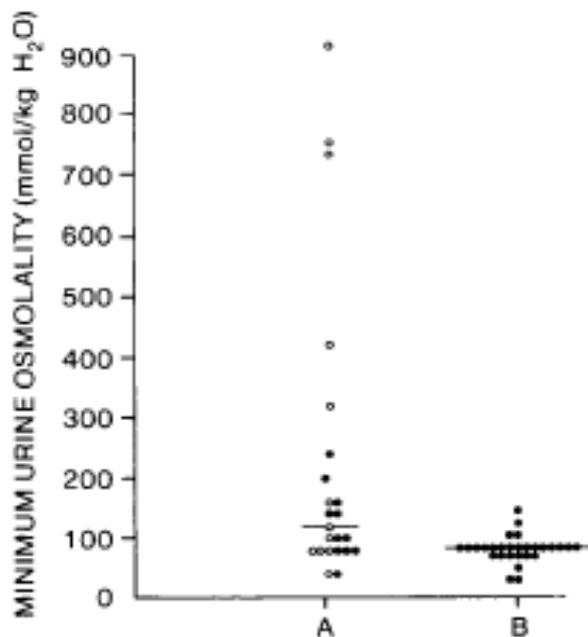
^bSignificant difference between the two groups (Mann-Whitney $U=13.37$, $df=1$, $p=0.0003$).

^cSignificant difference between the two groups (Mann-Whitney $U=7.75$, $df=1$, $p=0.005$).

^dSignificant difference between the two groups (Mann-Whitney $U=9.12$, $df=1$, $p=0.003$).

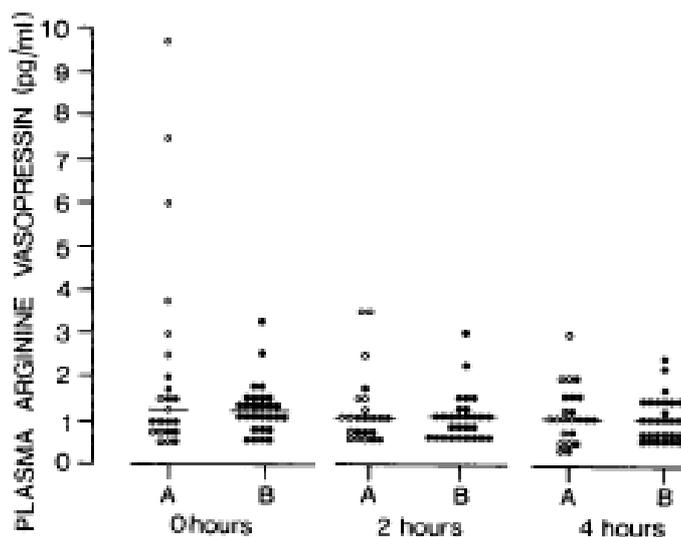
^eSignificant difference between the two groups (Mann-Whitney $U=12.8$, $df=1$, $p=0.0003$).

Figure 2. Minimum Urine Osmolalities After Water Loading for 23 Psychotic Patients (group A) and 28 Healthy Volunteers (group B)^a



^aThe open circles represent individual values for patients whose current illness lasted less than 24 weeks. The horizontal bars represent group median values. Significant difference between the two groups (Mann-Whitney U=16.42, df=1, p=0.0001).

Figure 3. Plasma Arginine Vasopressin Levels at 0, 2, and 4 Hours During Water Loading for 23 Psychotic Patients (group A) and 28 Healthy Volunteers (group B)^a



^aThe open circles represent individual values for patients whose current illness lasted less than 24 weeks. The horizontal bars represent group median values. There were no significant differences between the two groups at 0, 2, and 4 hours.

DISCUSSION

The results of this study indicate that an antidiuretic state exists in some patients with schizophrenic and schizoaffective disorders and that this is most pronounced in those whose current illness is of less than 24 weeks' duration. We attribute this abnormality to an arginine vasopressin mediated effect, since other, recognized causes of water excretion, such as renal, hepatic, or cardiac failure, hypothyroidism, and adrenal insufficiency (8), were not evident. Arginine vasopressin hypersecretion is suggested by the fact that the highest baseline plasma arginine vasopressin levels were found in the patients with the most pronounced antidiuretic state. However, the possibility of enhanced renal sensitivity to arginine vasopressin cannot be excluded, because levels of the hormone did not differ significantly between the psychotic patients and the healthy volunteers. In a study of water metabolism in medicated psychotic patients with polydipsia and hyponatremia (12), similar findings in conjunction with a shift in the relation between urine osmolality and plasma arginine vasopressin levels led the authors to suggest the existence in their patients of enhanced renal sensitivity to arginine vasopressin. The cause was not readily apparent. Our patients did not have polydipsia or hyponatremia and were not receiving neuroleptics. Nevertheless, enhanced renal sensitivity to arginine vasopressin remains a possible explanation for their antidiuretic state.

Seven of the 12 patients whose current illness had lasted less than 24 weeks had baseline arginine vasopressin levels above the 0.75 centile for the control subjects. Hyperosmolality, the normally overriding physiological stimulus to arginine vasopressin release, cannot be implicated because serum sodium levels were not raised. (The use in this context of serum sodium values rather than values for serum osmolality is in accordance with recommendations (8) when, as in our case, the method for determining osmolality uses serum rather than plasma and vapor pressure osmometry rather than freezing point depression). The recognized nonosmolar stimuli of hypovolemia, hypotension, nausea, and hypoglycemia (8) were not present, while the activity of plasma renin – implicated in the control of arginine vasopressin release (13) – was not elevated. Pathways subserving osmoregulation may have been deranged. Thus, although preservation of osmoreceptor control was indicated by a fall in plasma arginine vasopressin levels at 2 and 4 hours that was appropriate to the reduced concentration of serum sodium (figure 3), the higher baseline plasma arginine vasopressin levels could be explained by a resetting of osmoreceptors, with a downward shifting of the threshold at which arginine vasopressin is released (14). In this regard, it is noteworthy that in the psychotic patients with polydipsia and hyponatremia studied by Goldman et al. (12), the osmotic threshold for arginine vasopressin release was shown to be lowered.

Nonspecific emotional stress has been proposed as a stimulus to arginine vasopressin release (15). Whereas the evidence is tenuous and may depend on the development of hypotension (16), our findings of significant correlations between total anxiety scores and plasma arginine vasopressin levels at 0 and 2 hours suggest that emotional stress may have been relevant in this instance. Finally, some process other than the recognized osmolar and nonosmolar regulatory mechanisms may have been responsible. Raskind et al. (7) have suggested that a disturbance of CNS function may produce the symptoms of a psychotic disorder and simultaneously alter central arginine vasopressin regulation.

The finding of higher baseline plasma arginine vasopressin levels in patients with an illness of short duration accords with the fact that many reported cases of water intoxication occurred at the time of an acute psychotic episode. It could be that excessive release of arginine vasopressin is a necessary factor. Occurring during acute exacerbations and thereby rendering such individuals susceptible, the actual development of water intoxication may depend on the presence of additional factors that compromise water homeostasis. Factors that may be particularly relevant include increased fluid intake (primary polydipsia) (1), defects in urinary dilution (12), and drugs considered to be causative agents in SIADH, such as the nicotine from tobacco smoking (17), carbamazepine (18), thiazide diuretics (19), and, possibly, neuroleptic drugs (20).

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2.b Disordered water homeostasis in schizophrenia and cerebral ventricular size

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Summary

Background: A possible association between disordered water homeostasis and cerebral ventricular size in patients with schizophrenia was investigated.

Method: In a cross-sectional study of hospitalised patients, cerebral ventricular size was measured in 16 schizophrenic patients with disordered water homeostasis and 16 matched schizophrenic controls by magnetic resonance imaging.

Results: Ventricle to brain ratio, third ventricular index, bicaudate index and bifrontal index tended to be greater in those with schizophrenia with disordered water homeostasis, although differences were significant only for the bifrontal index ($P < 0.05$). Strong negative correlations were found between ventricular size and performance on neuropsychological testing in the disordered water homeostasis group.

Conclusion: These results provide evidence for an association between structural brain abnormality and disordered water homeostasis in a subset of schizophrenic patients.

Disordered water homeostasis is a well-recognised complication of schizophrenia (Ferrier, 1985), its estimated prevalence in state psychiatric hospitals being between 7% and 18% (Jose & Perez Cruet, 1979; Blum & Friedland, 1983). The disorder comprises polydipsia and/or impaired urinary excretion due to the syndrome of inappropriate antidiuretic hormone secretion (Riggs *et al*, 1991). In approximately 50% of cases the disorder is severe enough to cause periodic episodes of water intoxication (Jose & Perez Cruet, 1979) – a potentially lethal and under-recognised medical emergency.

Recent studies provide evidence to suggest that disordered water homeostasis in schizophrenia is associated with structural brain abnormality. Kirch *et al* (1985) reported that eight polydipsic schizophrenics who had developed hyponatraemia showed brain scan evidence of ventricular enlargement, and cognitive impairment on IQ testing. Lawson *et al* (1985) found that although schizophrenics with polydipsia and polyuria were more likely to have good premorbid histories and positive treatment responses, those who developed hyponatraemia showed tardive dyskinesia and enlarged ventricles on CT scanning. Schnur *et al* (1993) found that schizophrenic patients with polydipsia and hyponatraemia performed significantly worse on the Mini-Mental State examination than did a schizophrenic comparison group. They suggested that their findings could be explained by repeated episodes of hyponatraemia causing brain damage in these patients. We recently reported the findings of a study of 16 schizophrenics with severely disordered water homeostasis and 16 carefully matched schizophrenic controls, where neuropsychological tests were applied to each subject (Emsley *et al*, 1993). Significantly more cognitive impairment was found in the patients with disordered water homeostasis relative to the control group. We now report results of measurement of the cerebral ventricular size in these subjects by magnetic resonance imaging (MRI).

Method

Subjects

The patients with severely deranged water homeostasis (Group A) were all long-term in-patients of a state psychiatric hospital who met DSM-III-R criteria (American Psychiatric Association, 1987) for schizophrenia. All displayed profound polydipsia and/or hyponatraemia (serum sodium < 130 mmol/l). The polydipsic patients were identified by an experienced psychiatric nurse who visited the wards and interviewed staff members with daily contact with

the patients. We included only patients who had been noticed to consume volumes of fluid obviously much above normal. The patients with hyponatraemia were identified from a survey in which serum sodium levels of all adult patients at the hospital were determined. For those whose levels were below 130 mmol/l, other causes of hyponatraemia were excluded (Robertson, 1987). Excretory capacity was regarded as impaired if concomitant urine samples showed non-maximal urinary dilution – i.e. urine osmolality > 100 mmol/kg H₂O (Robertson, 1987).

The control group (Group B) comprised long-term-care in-patients from the same state psychiatric hospital who met DSM-III-R criteria for schizophrenia, but had never shown evidence of polydipsia or polyuria or had previous episodes of hyponatraemia. Their clinical files were scrutinised, ward staff were interviewed and serum sodium levels measured. These patients were matched with the Group A patients for age, sex, educational status, socio-demographic background and duration of schizophrenic illness. Subjects in both groups were in good physical health, and all provided informed consent.

Magnetic resonance imaging

MR images were acquired with the South African Medical Research Council's Elscint 0.5 T Gyrex V imager. All measurements were performed by one of us (RS) without knowledge of the subject's identity. Routine spin-echo technique protocols were used to demonstrate the brain parenchyma (T1-weighted) and cerebrospinal fluid spaces (T2-weighted). The following multislice sequences were performed: a T1-weighted coronal study (TR500/TE30 ms, slice width 6 mm, slice gap 3 mm) and a T2-weighted axial study (TR2000/TE30, 90 ms, slice width 4.7 mm, slice gap 1.6 mm). The coronal slices were planned at 90° to the orbito-meatal line. The ventricular size was then determined by the following measures.

Ventricle to brain ratio (VBR)

From the T2-weighted axial sequence, we chose the two consecutive slices visually judged to show the largest lateral ventricular area. The margins of the lateral ventricles were defined on the screen by a manual tracing technique and the area was computed using standard in-built image analysis software. The area of the brain was calculated similarly, from the same slices. The VBR was taken as the average of the two measures of the ratio of the area of ventricle to area of brain.

Third ventricular index (TVI)

From the coronal plane T1-weighted image, the slice visually judged to display the maximum width of the third ventricle was chosen. The TVI was obtained by dividing the width of the third ventricle by the transverse distance between the inner tables of the skull at the same level.

Bicaudate index (BCI)

From the coronal slice with the most medially placed caudate heads, the bicaudate distance was measured from the maximum convexity of the caudate nuclei, and this was expressed as a percentage of the internal diameter of the calvarium at the same level.

Bifrontal index (BFI)

In the same coronal slice as the BCI, the greatest transverse distance between the frontal horns of the lateral ventricles was measured and expressed as a percentage of the diameter of the inner skull table at the same level.

The BCI, BFI and TVI measures were adapted from Geremia & Huckman (1992). For the various measures the test/retest reliability was: VBR 0.97, BCI 0.98, BFI 0.98 and TVI 0.97.

Neuropsychological evaluation

The following tests were applied to each subject: Wechsler Adult Intelligence Scale (WAIS); Wechsler Memory Scale (WMS) (logical memory, visual reproduction and associate learning subtests); Rey Complex Figure Test (RCFT) (with delayed recall after 30 min); Trail Making Test (TMT); Auditory Verbal Learning Test (AVLT). Testing and scoring were done in a blind fashion. Because some subjects were unable to understand properly the instructions for Part B of the TMT, these results were excluded. For the AVLT the totals of Trials 1 to 5 were used. Premorbid IQ was estimated by averaging the three highest subtest standard scores of the WAIS (Lezak, 1983).

To assess whether the groups differed in the severity or the nature of their symptoms, the Positive and Negative Syndrome Scale for Schizophrenia (PANSS) (Kay *et al*, 1987) was applied to each subject. This scale yields separate scores along a Positive Scale, Negative Scale, Composite Index (Positive score minus Negative score) and General Psychopathology Scale.

Neuropsychological testing took place in the mornings only, and patients were prevented from drinking fluids before and during testing. The MRI studies were, as far as possible, performed in the mornings only, after an overnight fast and a light breakfast. Because of difficulties in obtaining MRI bookings, two Group A and five Group B patients were scanned in the early afternoon (12.30 p.m.). These patients were given a light lunch, including beverage, beforehand. No other fluids were allowed. None of the subjects exhibited impairment of consciousness or any other symptoms of acute water intoxication (Arieff *et al*, 1976) at the time of neuropsychological testing or MRI. Thus, although serum sodium levels were not determined at the time, we consider it unlikely that our results were influenced by the acute effects of water intoxication.

Statistical methods

Results were expressed as the mean (standard deviation). Since the size of the sample was large enough for the assumptions of the *t*-test to be satisfied and measurements were unimodal and continuous, Student's *t*-test was chosen for comparisons between groups. Correlations for selected variables within groups were performed using the Pearson product moment correlation coefficient. Because of the known effects of age on the size of the cerebral ventricles, partial correlations were computed between MRI measures and neuropsychological tests, adjusting for age.

Results

Relevant demographic and clinical data are given in Table 1. The groups did not differ significantly regarding age, sex, highest school grade obtained, duration of illness, estimated premorbid IQ, dosage of neuroleptics, number receiving anticholinergic medication, previous electroconvulsive therapy, number with tardive dyskinesia, or number of smokers. Serum sodium levels for the hyponatraemia patients ($n = 10$) ranged from 115 to 129 mmol/l (mean 124 mmol/l), and for Group B patients ($n = 16$) from 136 to 145 mmol/l (mean 141 mmol/l). Eight hyponatraemic patients had concomitant urine osmolalities over 100 mmol/kg H₂O (urine samples could not be obtained from the other two). Five Group A patients (and none of the Group B patients) had documented evidence in their files of previous unexplained seizures or episodes of loss or clouding of consciousness. When the ventricular size of these five was compared to the other eleven Group A patients, none of the measurements differed significantly.

There were no significant differences in any of the PANSS scores between the two groups (Table 2).

The measures of ventricular size are given in Table 3. For all four measures the ventricular size tended to be greater in Group A subjects, although this reached significance only for the bifrontal index. Table 4 indicates the partial correlations of individual neuropsychological test scores with the measures of ventricular size for the two groups after adjusting for age. In both

groups there was an inverse relationship between cognitive function and ventricular size, but the correlations were much stronger in Group A. Of the 40 correlations performed, 20 were significant in Group A, while only one was significant in Group B.

Table 1
Demographic and clinical data for the schizophrenics with disordered water homeostasis (Group A) and those without (Group B)

		Group A	Group B
	<i>n</i>	16	16
Age (years)		51.9 (11.5)	52.1 (11.7)
Sex – M:F		14 : 2	14 : 2
Duration of illness (years)		30.9 (11.2)	31.2 (11.8)
Polydipsia (<i>n</i>)	10	-	-
Hyponatraemia (<i>n</i>)	10	-	-
School grade (years)	7.0 (3.1)	7.0 (3.1)	
Premorbid IQ		76.3 (20.9)	82.9 (21.6)
Dosage of neuroleptics (mg) ¹	317 (284)	213 (162)	
Anticholinergic medication (<i>n</i>)	9	4	
Previous ECT (<i>n</i>)		8	10
Tardive dyskinesia (<i>n</i>)	2	3	
Smokers (<i>n</i>)		13	13

Values are expressed as the group mean (standard deviation).

1. Chlorpromazine equivalents.

ECT = electro-convulsive therapy.

Table 2
Test scores : mean values (s.d.)

Test	Group A	Group B	<i>P</i>	Max. score
Positive & Negative syndrome Scale for Schizophrenics (PANSS)				
Positive syndrome	13 (4)	13 (4)		-
Negative syndrome	26 (11)	27 (13)		-
Composite score	-13 (9)	-14 (11)		-
General Psychopathology	80 (28)	78 (28)		-
Wechsler Adult Intelligence Scale (WAIS): total score	61.8 (29.7)	69.2 (19.7)	0.32	-
Wechsler Memory Scale (WMS)				
Logical memory	2.4 (2.6)	4 (3.3)	0.04	14
Visual reproduction	2.4 (2.7)	4.6 (3.2)	0.04	21
Associate learning	4.1 (4.6)	7.3 (5.5)	0.08	36
Rey Complex Figure Test (RCFT)				
Copy score	14.2 (12.6)	21.9 (10.5)	0.07	
Recall score	3.2 (3.8)	5.5 (3.6)	0.08	36
Trail Making Test (TMT) Part A (seconds to complete test)	180.7 (97.8)	94.0 (55.6)	0.009	
Auditory Verbal Learning Test (AVLT)	16.9 (15.0)	23.4 (15.8)	0.24	75

Table 3

Measures of ventricular size for the schizophrenics with disordered water homeostasis (Group A, *n* = 16) and those without (Group B, *n* = 16)

Measure	Group A	Group B	P
TVI	4.75 (2.02)	3.72 (1.85)	0.144
BCI	15.52 (3.86)	14.04 (4.51)	0.329
BFI	29.02 (4.83)	25.62 (4.42)	0.046
VBR	9.41 (4.27)	7.86 (2.79)	0.239

Results are expressed as the mean (standard deviation).

TVI = third ventricular index; BCI – bicaudate index; BFI = bifrontal index; VBR = ventricle-to-brain ratio

Table 4

Partial correlations of ventricular size measures with psychometric indices (controlling for age) for 16 schizophrenic patients with disordered water homeostasis (Group A) and 16 schizophrenics without (Group B)

	TVI		BCI		BFI		VBR	
	A	B	A	B	A	B	A	B
VIQ	-0.56*	-0.15	-0.42	-0.09	-0.62**	-0.31	-0.45	-0.26
PIQ	-0.54*	-0.10	-0.39	-0.11	-0.59*	-0.28	-0.35	-0.30
TIQ	-0.55*	-0.12	-0.41	-0.09	-0.61*	-0.30	-0.40	-0.29
RCFT	-0.63**	0.05	-0.42	-0.07	-0.61*	-0.28	-0.40	-0.21
RCFTREC	-0.54*	0.08	-0.30	-0.01	-0.33	0.05	-0.20	-0.01
WMLOG	-0.58*	-0.28	-0.49	-0.38	-0.58*	-0.24	-0.54*	-0.26
WMVIS	-0.53*	-0.33	-0.26	-0.15	-0.48	-0.45	-0.34	-0.35
WMASS	-0.56*	0.09	-0.31	0.22	-0.47	0.20	-0.33	-0.11
TMTA	0.86***	0.33	0.64*	0.29	0.78***	0.53	0.81***	0.69**
AVLT	-0.59*	0.03	-0.45	0.24	-0.52*	0.19	-0.43	-0.12

P*<0.05; *P*<0.01; ****P*<0.005

TVI = third ventricular index; BCI – bicaudate index; BFI = bifrontal index; VBR = ventricle-to-brain ratio; VIQ = verbal intelligence quotient; PIQ = performance intelligence quotient; TIQ = total intelligence quotient; RCFT = Rey Complex Figure Test; RCFTREC = Rey Complex Figure Test with delayed recall after 30 minutes; WMLOG = Wechsler Memory Scale, logical memory subtest; WMVIS = Wechsler Memory Scale, visual reproduction; WMASS = Wechsler Memory Scale, associate learning; TMTA = Trail Making Test, Part A; AVLT = Auditory Verbal Learning Test.

Discussion

In this study, evidence of enlarged ventricles was found in brains of schizophrenic patients with deranged water homeostatic mechanisms, compared with a control group of schizophrenic patients without such derangement. Although only one of the four measures of ventricular size showed a statistically significant difference between the groups, we consider it unlikely that this is a chance finding, for two reasons. First, ventricular size was greater in Group A patients for the other three measures as well, although not significantly so. The relatively small samples may account for the lack of significant differences for these measures. Second, the stronger correlations found between ventricular size and cognition function in Group A patients suggest that these results are functionally significant. These results provide the first quantitative radiological evidence of structural brain disorder in

schizophrenic patients with co-existing disordered water homeostasis. Together with the findings of our previous study (Emsley *et al*, 1993), they provide compelling evidence for an association between disordered water homeostasis and structural brain disorder in schizophrenic patients.

Although the nature of this association is unclear, three possibilities need to be considered. The first is that the co-existence of disordered water homeostasis and structural brain disorder in schizophrenic patients is a coincidental finding. The second is that disordered water homeostasis may be a consequence of the disease process underlying the schizophrenic disorder. This would be consistent with a proposal by Raskind *et al* (1975) that an underlying cerebral disorder simultaneously produces the symptoms of a psychotic disorder, alters the thirst threshold and stimulates vasopressin secretion. It also accords with the suggestion that the ventricular enlargement observed in schizophrenics with disordered water homeostasis by Kirch *et al* (1985) and Lawson *et al* (1985) might be due to a structural defect involving the hypothalamus (Illowsky & Kirch, 1988). More specifically, Ferrier (1985) has suggested that the dilatation of the third ventricle seen in some chronic schizophrenics might indicate a destructive or degenerative process in the hypothalamus in these patients. The finding in our study that the TVI did not differ significantly between the groups does not support the existence of structural pathology specifically in the hypothalamic area. However, TVI is at best a rough measure of diencephalic structures, so that our findings do not rule out the possibility of a less obvious structural lesion in this region.

The third possibility is that brain damage develops in these patients as a consequence of their disordered water regulation, by way of one or more episodes of water intoxication. The hyponatraemic encephalopathy itself may directly cause irreversible brain damage (Arief *et al*, 1976), or this could occur by way of hypoxaemia and even head trauma associated with the seizures and coma that commonly accompany the condition. Our finding that patients with previous seizures or episodes of impairment of consciousness did not have larger ventricles than other Group A patients is an argument against this. However, the number of patients with previous water intoxication episodes is likely to have been underestimated, as full clinical records were not always available, and previous episodes of water intoxication may have gone unrecognised. Future longitudinal studies will need to assess whether these factors are important.

The possibility that brain damage results from disordered water homeostasis raises an important question: can this mechanism account for some of the ventriculomegaly reported in schizophrenia (Weinberger *et al*, 1983)? If this were so, one would expect the ventricular dilatation to develop after the onset of the schizophrenic illness, and become progressively worse. While it is thought that ventriculomegaly in schizophrenics is static and actually antedates the illness (Weinberger *et al*, 1982), there is in fact evidence to suggest that in a subgroup of schizophrenic patients this may not be so. Haug (1962) reported progressive cerebral atrophy in four of 31 schizophrenics who underwent pneumoencephalography. More recently, Nasrallah *et al* (1986) reported the results of a CT scan follow-up study of ventricular size in schizophrenia. Although no significant change was found in the mean VBR after three years, 4 of 11 patients showed increases of over 50% in individual ratios. We suggest that some of these cases could be explained on the basis of water intoxication, and that this possibility needs to be kept in mind in future studies of ventricular size in schizophrenia.

The limitations of this study include the relatively small sample sizes and the low level of education of the patients. The possibility that differences in hydration between the two groups could have influenced the results cannot be excluded. However, overhydration is unlikely in the group with disordered water homeostasis, as precautions were taken to prevent fluid overload during the MRI studies. Furthermore, overhydration is associated with a decrease in ventricular size, with a return to normal after water restriction (Berginer *et al*, 1985). The possibility of water restriction causing dehydration in the patients with disordered water homeostasis, with resultant cerebral shrinkage, is also unlikely, because of their impaired excretory capacity. Further studies need to address the question of whether the structural brain disorder in these patients is static or progressive, and whether it is related to episodes of actual water intoxication. The need for heightened clinical awareness to the possibility of water intoxication occurring in schizophrenic patients is obvious, as the condition can be

effectively treated, and future episodes prevented. Treatment modalities include fluid restriction, removal of exacerbating factors such as thiazide diuretics or carbamazepine, the use of medications such as demeclocycline (Illowsky & Kirch, 1988) and group therapy (Millson *et al*, 1993).

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2.c Disordered Water Homeostasis and Cognitive Impairment in Schizophrenia

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To investigate a possible association between disordered water homeostasis and cognitive impairment in schizophrenia, neuropsychological tests were applied to 16 schizophrenic patients with severely deranged water homeostasis and to 16 matched schizophrenic controls. The patients with disordered water homeostasis tended to obtain poorer scores than the controls throughout, the differences being statistically significant for two of the tests (Wechsler Memory Scale Visual Reproduction and Trail Marking Test part A). These results were not ascribable to differences in the duration of the illness, premorbid IQ, medication, or electroconvulsive therapy received, or prominence of any particular symptoms. The results suggest the co-existence of disordered water homeostasis and cognitive impairment in a subset of schizophrenic patients.

Introduction

Polydipsia and polyuria were first reported in psychiatric patients 60 years ago (Hoskins and Sleeper 1933). Since then an association between schizophrenia and disorders of water homeostasis has been well established (Riggs et al 1991). Although schizophrenics generally exhibit increased fluid intake and urine output (Lawson et al 1985), and impaired excretory capacity (Emsley et al 1989) compared to controls, 6.6% have a more profound derangement of fluid homeostatic mechanisms (Jose and Perez-Cruet 1979). This latter group is characterized by frank polydipsia and/or inappropriate secretion of antidiuretic hormone, which may periodically lead to episodes of water intoxication (Riggs et al 1991). The pathogenesis of the disorder remains essentially conjectural. One possibility is that both the psychotic illness and the deranged water homeostasis are manifestations of an underlying disturbance of central nervous system function (Raskind et al 1975).

Sleeper and Jellinek (1936), in comparing 12 polyuric schizophrenics with 12 schizophrenic patients with a normal urinary output, reported higher IQs and less emotional deterioration in the polyuric group, and considered the cause to be psychological rather than biological. However, two recent studies provide evidence to suggest that deranged water homeostasis in schizophrenia, if severe, is associated with structural brain damage. Kirch et al (1985) found that the clinical profile in eight polydipsic schizophrenic patients who had developed hyponatremia conformed to type II schizophrenia as described by Crow (1985), which has been associated with structural brain damage. Also, their patients showed computed tomography (CT) brain scan evidence of ventricular enlargement, and cognitive impairment on IQ testing. Similarly, Lawson et al (1985) found that although schizophrenic patients with polydipsia and polyuria were more likely to have good premorbid histories and positive neuroleptic responses, those who developed hyponatremia showed tardive dyskinesia and enlarged ventricles on CT scanning – again conforming to type II schizophrenia (Crow 1985). Although the limited size of the samples in these studies precludes any definitive conclusions, it may be that schizophrenic patients with mild polydipsia and polyuria conform to type I

schizophrenia, whereas those with a more severe disorder of water homeostasis who develop hyponatremia correspond to type II schizophrenia.

Cognitive impairment has been described in a subset of patients with schizophrenia (Watson et al 1987). The present study investigates the possibility that disordered water homeostasis is associated with cognitive impairment in schizophrenia. We have applied a battery of standard neuropsychological tests to schizophrenic patients with severely disordered water homeostasis and compared them with carefully matched schizophrenic patients without any evidence of such derangement.

Methods

The patients with severely deranged water homeostasis (Group A) were selected as follows: All were long-term care inpatients from a State Psychiatric Hospital who met DSM-III-R criteria (American Psychiatric Association 1987) for a schizophrenic disorder. All displayed either profound polydipsia or an impaired excretory capacity, or both. Patients with polydipsia were identified by an experienced psychiatric nurse who visited each ward and interviewed at least one staff member with day-to-day patient contact. Only patients who had been observed to consume vastly excessive volumes of fluid were included. The patients with an impaired excretory capacity were identified as follows: Serum sodium levels of all long-term care adult inpatients were determined. In patients with levels < 130 mmol/L, other causes of hyponatremia were excluded and an impaired excretory capacity was confirmed by demonstration of concomitant nonmaximal urinary diluting capacity (Robertson 1987).

The control group (Group B) comprised long-term care inpatients from the same State Psychiatric Hospital who met DSM-III-R criteria for a schizophrenic disorder, but had never displayed polydipsia, polyuria, or had any previous episodes of hyponatremia, and who were found on testing to have a normal serum sodium. These patients were matched with Group A patients for age, gender, education status, sociodemographic background, and duration of schizophrenic illness. Subjects in both groups were in good physical health, and all provided informed consent.

The following neuropsychological tests were applied to each subject: Wechsler Adult Intelligence Scale (WAIS); Wechsler Memory Scale (WMS) (logical memory, visual reproduction and associate learning subtests); Rey Complex Figure Test (RCFT) (with delayed recall after 30 min); Trail Making Test (TMT); Auditory Verbal Learning Test (AVLT). Testing and scoring were done in a blind fashion. Patients were tested in the morning only, and were prevented from drinking prior to and during testing. None of the subjects exhibited impairment of consciousness or any other symptoms of acute water intoxication (Arieff et al 1976) at the time of testing. Thus, although serum sodium levels were not determined at the time, we consider it unlikely that test performances were influenced by water intoxication. Because some subjects were unable to adequately understand the instructions for part B of the TMT these results were excluded. For the AVLT the totals of trials 1 to 5 were used. Premorbid IQ was estimated by averaging the three highest subtest standard scores of the WAIS (Lezak 1983). To assess whether any differences in test performance between the two groups could be ascribed to differences in the severity or nature of symptoms, the Positive and Negative Syndrome Scale for Schizophrenia (PANSS) (Kay et al 1987) was applied to all subjects. This scale yields separate scores along a Positive Scale, Negative Scale, Composite Index (Positive score minus Negative score) and General Psychopathology Scale.

Because of small sample sizes and skewed data, the median (and interquartile range) were used to summarize the measurements within the groups. Comparisons between groups were performed using the Wilcoxon-Mann-Whitney *U* test.

Results

The patients with disordered water homeostasis (Group A) consisted of 14 men and 2 women between the ages of 23 and 61 years (median 55.0 years). All had either polydipsia ($n=5$), or dilutional hyponatremia with evidence of impaired excretory capacity ($n=6$), or both ($n=5$). The highest school grade obtained ranged from 1 to 10 (median 6) and the duration of the

schizophrenic illness ranged from 3 to 44 years (median 33.5 years). The control group (Group B) comprised 14 men and 2 women aged 23 to 67 years (median 55.5 years). The highest school grade obtained ranged from 0 to 10 (median 6) and the duration of the schizophrenic illness ranged from 2 to 44 years (median 32 years).

Group A and Group B did not differ significantly regarding premorbid IQ [71(31) versus 76(36)], the dosage of neuroleptics [258(400) mg versus 175(200) mg chlorpromazine equivalents], as well as the number receiving anticholinergic medication (9 versus 4) or previous electroconvulsive therapy (8 versus 10), showing evidence of tardive dyskinesia (2 versus 3), or smoking (13 versus 13). None of the subjects were receiving benzodiazepines. An attempt to estimate the number of patients with previous episodes of water intoxication was made by searching their files for previous unexplained seizures, delirium, or documented serum sodium values < 120 mmol/L. Evidence of such episodes was found in 5 of the Group A patients. When these 5 patients were compared to the other 11 patients in Group A they did not show significantly more cognitive impairment, negative symptomatology, or tardive dyskinesia. Results of the neuropsychological tests for the two groups are given in Table 1. Group A patients obtained significantly poorer scores than the Group B controls for the WMS visual reproduction (a test of immediate visual memory) and TMT part A (a test involving visual scanning and visuomotor integration). Although there were no other significant differences between the groups, Group A patients obtained poorer scores than the Group B controls for all of the other tests.

There were no significant differences in any of the PANSS scores between the two groups. These scores – expressed as group median (and interquartile range) – were as follows: Positive Syndrome scores: Group A 11(6), Group B 11(5); Negative Syndrome scores: Group A 21(11), Group B 25(19); Composite scores: Group A -9(13), Group B -11(21); General Psychopathology scores: Group A 34(14), Group B 36(9).

Table 1. Neuropsychological Test Scores for the Schizophrenics with Disordered Water Homeostasis (Group A, n = 16) and those without (Group B, n = 16)^a

Test	Group A	Group B	p value
WAIS			
VIQ	56 (35)	64 (34)	NS
PIQ	62 (31)	72 (29)	NS
TIQ	57 (35)	64 (31)	NS
WMS			
LM	2 (4)	4 (4)	NS
VR	1 (4)	4 (5)	0.04
AL	3 (8)	8 (6)	NS
RCFT			
Copy score	11 (24)	23 (16)	NS
Recall score	2 (6)	5 (6)	NS
TMT (Part A)	170 (123)	64 (43)	0.004
AVLT	14 (27)	23 (20)	NS

^aValues are expressed as the group median (and interquartile range).

WAIS = Wechsler Adult Intelligence Scale; VIQ = verbal intelligence quotient;

PIQ = performance intelligence quotient; TIQ = total intelligence quotient;

WMS = Wechsler Memory Scale; LM = logical memory (maximum score = 23); VR = visual reproduction (maximum score = 14); AL = associate learning (maximum score = 21); RCFT = Rey Complex Figure Test (maximum score = 36); TMT = Trail Making Test (seconds taken to complete the test);

AVLT = Auditory Verbal Learning Test (maximum score = 75). (NS = not significant.)

Discussion

This study suggests that deranged water homeostasis is associated with cognitive impairment in schizophrenic patients. This finding cannot be explained on the basis of differences between the two groups regarding education status, premorbid IQ, duration of illness, medications or electroconvulsive therapy received. Further, the similar PANSS scores indicate that the groups did not differ regarding severity of illness, or prominence of any particular symptoms that could effect their performance on neuropsychological testing. Finally, as far as possible, precautions were taken to avoid the possibility that acute water intoxication could affect test performances.

Our findings of cognitive impairment, together with the findings of Kirch et al (1985) and Lawson et al (1985), provide evidence that in patients with schizophrenia, severely disordered water homeostasis is associated with structural brain damage. To attribute the cognitive deficits demonstrated in this study to lesions in a discrete area is not warranted by the results. Although the significantly lower scores of group A patients for the WMS visual reproduction subtest and the TMT part A may indicate visual information input dysfunction as associated with right hemisphere pathology (Golden et al 1981; Lezak 1983), the trend toward poorer performance throughout in group A patients points rather to a more global impairment of function. Whether the cognitive impairment is static or progressive in these patients remains to be determined in future longitudinal studies. Our study was not designed to investigate whether these patients form a distinct subset of schizophrenics. However, the fact that the PANSS scores were similar for the two groups suggests that they do not constitute a group that is easily distinguishable on clinical grounds. In particular, and contrary to the findings of Kirch et al (1985) and Lawson et al (1985), we did not find that negative symptoms were more common in our patients with water dysregulation. In addition, within the group of patients with disordered water homeostasis, those with previous episodes of water intoxication did not display more negative symptomatology, cognitive impairment, or tardive dyskinesia. This finding needs to be interpreted cautiously, however, because of the possibility of a type II error caused by the small sample. Also, the actual incidence of water intoxication in the group A patients is likely to have been underestimated because of the unavailability of full clinical records together with the possibility of previous episodes of water intoxication having gone unrecognized.

Another possible explanation for our findings is that the cognitive impairment may be a *consequence* of the disordered water homeostasis, by way of previous episodes of water intoxication. Thus, dilutional hyponatremia may intermittently develop in these patients as the result of gross polydipsia, impaired excretory capacity, or most likely, both of these mechanisms (Cheng et al 1990). Rapid development of hyponatremia does not allow for adaptive changes to take place in the brain, and cerebral edema may ensue (Cluitmans and Meinders 1990). The resultant encephalopathy is associated with profound neurological disturbance, which may lead to irreversible brain damage (Arieff et al 1976). Additional mechanisms that could contribute to cerebral damage in these patients include hypoxemia and even head trauma associated with seizures and coma, which often accompany water intoxication. The relative importance of these factors could not be assessed in our study, and needs to be addressed in future longitudinal studies. It is likely that cognitive impairment in schizophrenia is multidetermined, with factors such as premorbid cognitive deficits, symptoms of the illness itself and effects of medication possibly playing a role. However, the implications of our findings are considerable, as they suggest that a potentially preventable condition may contribute to cognitive impairment in schizophrenia. Once diagnosed, water intoxication can be effectively treated and further episodes prevented by restricting fluid intake, removing exacerbating factors and, if necessary, prescribing specific medications (Illowsky and Kirch 1988).

The results of this study need to be interpreted with the relatively small sample sizes as well as the limited educational status of the subjects kept in mind. Further studies to investigate the nature of any underlying structural brain damage in these patients are currently under way.

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2.d Inappropriate antidiuretic state in long-term psychiatric inpatients

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Summary

To investigate the occurrence of an inappropriate antidiuretic state in a long-term psychiatric inpatient population, 690 patients underwent serum sodium determination. Forty-four patients (6,4%) had levels < 133 mmol/l. Fifteen of these patients could be investigated further and the biochemical findings in all were consistent with an inappropriate antidiuretic state. Evidence of previous episodes of water intoxication was found in 80% of these patients. Although more than one possible cause was present in most patients, the two factors most strongly incriminated in the pathogenesis of the inappropriate antidiuretic state were the drugs carbamazepine and hydrochlorothiazide.

Water intoxication is a well-recognised complication in certain patients with psychiatric disorders. The condition is characterised by seizures and confusion, and may progress to coma and death.¹ Most of the cases appear to be 'self-induced', i.e. associated with polydipsia.² However, polydipsia alone does not usually appreciably dilute body fluids because of the great excretory capacity of the kidneys,³ and it is now increasingly recognised that impairment of excretory capacity may be an additional necessary factor for the development of water intoxication. In this regard, an inappropriate antidiuretic state, most probably due to vasopressin hypersecretion, has been documented in a number of such patients.⁴ Factors incriminated in the pathogenesis of the antidiuretic state in psychiatric patients include psychosis,⁵ alcohol withdrawal,⁶ psychotropic medication,⁷ carbamazepine,⁸ thiazide diuretics⁹ and smoking.¹⁰

A study was undertaken to investigate the occurrence of an inappropriate antidiuretic state in long-term psychiatric inpatients, and to identify factors of pathogenic significance.

Patients and methods

All long-term inpatients at Stikland Psychiatric Hospital between the ages of 18 years and 70 years were screened for possible dilutional hyponatraemia. Blood samples for serum sodium estimation were obtained between 14h00 and 17h00, for one ward (containing usually between 30 and 50 patients) at a time. Serum sodium levels were determined on the same day using a Beckman Kline flame photometer.

Patients with hyponatraemia, i.e. serum sodium levels < 133 mmol/l, were kept recumbent, given nothing by mouth and abstained from smoking overnight.

The next morning the hyponatraemic patients were assessed clinically. A detailed examination of the files was undertaken and a physical examination performed. In particular, the following information was noted: psychiatric and associated medical diagnoses; all psychotropic and other medications being taken at the time; and previous episodes of possible water intoxication, as indicated by unexplained seizures or delirium or a previously documented serum sodium value < 120 mmol/l. The ward staff were also questioned about the presence of polydipsia and the smoking habits of the patients.

All patients unable to provide consent or co-operate sufficiently or who had severe medical illness were excluded from further study. For the others, an 18-gauge indwelling catheter was inserted into the anterior cubital fossa, after which the patient was kept recumbent for 30 minutes. Blood samples were then collected for estimation of serum sodium, potassium, urea, creatinine, glucose, thyroid stimulating hormone, tri-iodothyronine, tetra-iodothyronine, cortisol and aldosterone levels and plasma renin activity. Concomitant urine samples were analysed for osmolality. Osmolality was determined by freezing point depression with an Osmomat 030 cryoscopic osmometer.

The following criteria³ were used as indicative of an inappropriate antidiuretic state: (i) body fluid hypotonicity, as indicated by a serum sodium value < 133 mmol/l; (ii) concomitant non-maximal dilution of urine, i.e. urine osmolality > 100 mmol/kg H₂O; and (iii) no evidence of oedema, hypovolaemia, hypotension, hypoglycaemia, nausea or abnormal cardiac, renal, hepatic, adrenal or thyroid function.

Results

Of 690 patients who underwent serum sodium determination, 44 (6,4%) had levels < 133 mmol/l. Twenty-nine of the 44 were excluded from further study for the following reasons: (i) inability to provide informed consent or to co-operate sufficiently ($N = 14$); (ii) concomitant physical illness ($N = 4$); and (iii) resolution of hyponatraemia before further studies could be carried out ($N = 11$). The remaining 15 patients, or 2,2% of the total population screened for hyponatraemia, had biochemical findings consistent with the diagnosis of an antidiuretic state (Table 1). Other blood investigations indicated that no other recognised causes of impaired excretory capacity were present.

In order to establish whether factors implicated in the pathogenesis of the inappropriate antidiuretic state occurred more frequently in these patients, the following comparisons were made: using a chi-square test the 15 patients with an inappropriate antidiuretic state were compared with the 646 patients with normal serum sodium values for the following factors: diagnosis of schizophrenia, smoking, and the taking of psychotropic medication, carbamazepine or hydrochlorothiazide. The only significant differences found were that the patients with an inappropriate antidiuretic state were more often receiving the drugs carbamazepine (chi-square 8,40; $df = 1$; $P < 0.005$) and hydrochlorothiazide (chi-square 3,92; $df = 1$; $P < 0.05$). These two drugs were then discontinued in the 13 patients with an inappropriate antidiuretic state who had been taking them, and their serum sodium levels returned to normal within 2 weeks

TABLE 1. DETAILS OF THE 15 PATIENTS WITH BIOCHEMICAL EVIDENCE OF AN INAPPROPRIATE ANTIDIURETIC STATE

Age (yrs)	Sex	Psychiatric diagnosis	Factors associated with IAS	Polydipsia	Evidence of previous water intoxication	Serum sodium (mmol/l)	Urine osmolality (mm/kg H ₂ O)
67	F	MR	N,C	-	+	124	569
31	F	MR	N,C	+	+	125	476
53	F	MR	N,C	-	+	129	148
34	M	MR	N,C	-	+	125	451
52	M	MR	N,C,S	+	+	127	249
41	M	MR	N,H,S	-	+	127	507
66	M	MR	H	-	+	129	508
48	M	MR	N,C,S	-	+	125	370
33	F	MR	N,C,S	-	+	128	445
54	M	Schiz.	N,S	-	-	128	517
58	M	Schiz.	S	+	+	129	255
65	M	Schiz.	N,H,S	-	-	129	455
68	M	Schiz.	N,H,S	-	+	129	226
61	M	Schiz.	H,S	-	-	128	315
56	F	Schiz.	N,C	-	+	129	276

IAS = inappropriate antidiuretic state; MR = mental retardation; schiz. = schizophrenia; N = neuroleptic medication; C = carbamazepine; H = hydrochlorothiazide; S = smoking.

Discussion

In this study, evidence of an inappropriate antidiuretic state was found in 2,2% of long-term psychiatric inpatients. The actual incidence is likely to be considerably higher, however, since it was not possible to investigate almost two-thirds of the hyponatraemic patients.

In most of the patients more than one possible cause of an inappropriate antidiuretic state was present, suggesting the possibility of a multifactorial aetiology. Cigarette smoking has been associated with vasopressin hypersecretion,¹⁰ as have neuroleptic drugs⁷ and schizophrenic psychosis.⁵ However, the two factors disproportionately over-represented in these patients compared with other long-term psychiatric patients were the drugs carbamazepine and hydrochlorothiazide. Furthermore, the fact that serum sodium levels returned to normal soon after their discontinuation indicates an important pathogenic role for these drugs.

Various mechanisms whereby these drugs induce an inappropriate antidiuretic state have been proposed. Carbamazepine may stimulate vasopressin release,¹¹ enhance renal sensitivity to the hormone⁸ or have a direct effect on the renal tubule.¹² Hydrochlorothiazide may cause an antidiuresis by reducing free-water clearance as a direct consequence of natriuresis¹³ or by stimulating the release of vasopressin.¹⁴

Patients with an inappropriate antidiuretic state are at serious risk for the development of water intoxication – as demonstrated by the fact that 80% of cases in this study had evidence in their clinical files of previous episodes of water intoxication. While previous studies have highlighted the risk of water intoxication in patients with polydipsia,^{2,4,15} in this study 12 of the 15 patients did *not* display excessive fluid intake. This would indicate that even more patients are at risk for developing water intoxication than was previously recognised. Considering the possible consequences (water intoxication may cause irreversible brain damage¹⁶ and was found to be responsible for nearly one-fifth of deaths in schizophrenics aged < 53 years in a state hospital¹⁷), the implications for clinical psychiatry would seem considerable.

Identification of these patients is important, since water intoxication, once diagnosed, can be effectively treated simply by restricting fluid intake.¹⁸ We suggest, therefore, that all long-term psychiatric inpatients at risk for the development of water intoxication be periodically screened for hyponatraemia.

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2.e Neurological abnormalities in first episode schizophrenia: temporal stability and clinical and outcome correlates.

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Abstract

Objective: Neurological abnormalities in subjects with schizophrenia have been regarded as diagnostically non-specific and non-localising. This study assessed the temporal stability of neurological abnormalities in subjects with first-episode schizophrenia over the course of 12 months. We also examined their relationships with psychiatric symptoms, medication effects and treatment outcome. *Method:* The sample comprised 66 largely medication-naïve subjects who were treated according to a fixed protocol. We performed a factor analysis of the Neurological Evaluation Scale (NES) items, and relationships between the NES factors and various clinical and outcome measures were explored. *Results:* Five NES factors were identified, explaining 68.4% of the variance. While the NES total scores did not change significantly over time, poor performance on motor sequencing tests was related to longer duration of untreated psychosis, and showed a tendency to improve as psychiatric symptoms resolved. The most interesting finding was that high scores on the motor sequencing factor predicted the emergence of persistent dyskinesia at 24 months (ANCOVAR $F(1, 20)=19.287, p=0.0002$). *Conclusions:* Two NES factors (motor sequencing and attention) are reasonably replicable across samples, and have potential relevance for the further exploration of the pathogenesis of schizophrenia, as well as possible clinical applications.

1. Introduction

Subtle neurological abnormalities are found more frequently in patients with schizophrenia than in healthy controls (Heinrichs and Buchanan 1988; Buchanan and Heinrichs 1989; Mohr et al. 1996; Egan et al. 2001; Yazici et al. 2002; Shibre et al. 2002; Keshavan et al. 2003) and other psychotic disorders (Keshavan et al. 2003). These so called 'soft' neurological signs are thought most likely to be non-specific markers of neurodevelopmental abnormality, possibly as a consequence of a failure in the integration between sensory and motor systems (Griffiths et al. 1998), or alternatively reflecting deficits in neuronal circuits involving structures such as the basal ganglia and brain-stem (Heinrichs and Buchanan 1988). A recent study has reported associated regional grey matter volume changes, suggestive of perturbed cortical-subcortical connectivity (Dazzan et al. 2004). On the other hand, it has been proposed that they could be secondary to psychiatric symptoms (e.g. impaired attention), or to the side-effects of antipsychotic medication (Lawrie et al. 2001).

Support for the neurodevelopmental marker hypothesis is based on the finding that they are present early in the illness (in medication-naïve first-episode samples) (Gupta et al. 1995; Venkatasubramanian et al. 2003; Shibre et al. 2002; Keshavan et al. 2003; Whitty et al. 2003) and have been reported to be stable over time (Chen et al. 1996; Marcus et al. 1985). However, the temporal stability of neurological signs has been poorly studied. One of these

studies assessed the association between age and neurological signs in a cross-sectional design only (Chen et al. 1996) and the other followed up a cohort of *siblings* of schizophrenics with neurological abnormalities (Marcus et al. 1985). In fact, another study found that neurological soft signs varied with the clinical course (Schroder et al. 1991), and two others reported progression of neurological dysfunction (Madsen et al. 1999; Chen et al. 2000). A recent prospective study in first-episode schizophrenia reported improvement in motor-related and cortical neurological soft signs at 6 months, which was associated with improvement in psychopathology. At the same time, 'harder' signs tended to worsen (Whitty et al. 2003).

Studies investigating relationships between neurological abnormalities and psychiatric symptoms have similarly reported conflicting results. While neurological signs have been associated with prominent negative symptoms (Flashman et al. 1996; Merriam et al. 1990; Wong et al. 1997) and positive symptoms (Browne et al. 2000), other workers have reported no association with positive and negative symptoms (Flyckt et al. 1999) or with global measures of psychopathology (Sanders et al. 1994). A study investigating the relationship between neurological abnormalities and three dimensions of schizophrenia (psychomotor poverty, disorganization and reality distortion) found no significant correlations between neurological abnormalities and either reality distortion or disorganization dimensions, while an extrapyramidal factor was modestly related to psychomotor poverty in males. In female subjects there was a significant relationship between psychomotor poverty and a neurological factor reflecting attention and initiative (Malla et al. 1997). Another study examined the relationships between neurological abnormalities and the symptom domains of hallucinations/delusions, disorganization and the deficit syndrome. Each of the three syndromes was found to have a distinctive relationship pattern to neurological signs. Disorganization was significantly related to the global abnormalities, to sensory integration, and to sequencing of complex motor acts; the deficit syndrome was significantly related only to sensory integration deficits; while negative symptoms (primary and secondary) and hallucinations/delusions were not related to any neurological abnormalities (Arango et al. 2000).

Very few longitudinal studies have investigated the effect of antipsychotic medication on neurological abnormalities. Most studies comparing medicated and unmedicated patients, or patients with and without extrapyramidal symptoms (EPS), report no association between neurological abnormalities and antipsychotic medication or EPS (Ismail et al. 1998b; King et al. 1991b; Mohr et al. 1996; Griffiths et al. 1998; Flyckt et al. 1999; Browne et al. 2000; Arango et al. 2000), although one study suggests that antipsychotics may, directly or indirectly, improve baseline neurological dysfunction (Madsen et al. 1999). Also, King et al (King et al. 1991a) reported an association between neurological abnormalities and TD, and suggested that the former may predict vulnerability to the later development of TD. Neurological abnormalities are not related to cannabis use (Bersani et al. 2002), but they may be influenced by alcohol dependence (Mohr et al. 1996). Neurological signs in schizophrenia have been associated with a poorer outcome, greater cognitive impairment (Arango et al. 2000; Flashman et al. 1996) ventricular enlargement (Mohr et al. 1996) and reduced cortical volumes (Rubin et al. 1994; Arango et al. 2000; Mohr et al. 1996; Wong et al. 1997; Ismail et al. 1998b). The possibility that neurological signs have a genetic origin is suggested by the finding that they are present in non-affected family members of patients with schizophrenia (Ismail et al. 1998a; Niethammer et al. 2000; Egan et al. 2001). However, one study found no association between neurological signs and a positive family-history in patients with schizophrenia (Lawrie et al. 2001), and another found such an association in females while in males neurological signs were associated with obstetric complications but not with a positive family history (Lane et al. 1996).

Another area of uncertainty relates to the validity of the scales used to assess neurological dysfunction. One widely used scale, the Neurological Evaluation Scale (NES) (Buchanan and Heinrichs 1989), was developed to standardize the assessment of neurological abnormalities in schizophrenia. Some of the items were grouped into three putative functional areas of interest, namely sensory integration, motor co-ordination and sequencing of complex motor acts. However, subsequent factor analyses have failed to provide empirical validation for these groupings, although some similarities were found. A study conducted in medicated schizophrenic patients yielded five factors (Malla et al. 1997),

while two later analyses (in unmedicated subjects and treatment-naïve first-episode samples respectively) reported four factor solutions (Sanders et al. 2000;Keshavan et al. 2003).

It has been suggested that neurological signs may be useful in differentiating schizophrenia from other psychotic disorders, on the basis that abnormal scores in cognitively demanding and perceptual tasks from the Neurological Evaluation Scale (NES) were markedly higher in patients with schizophrenia than in subjects with other psychoses and healthy controls. These abnormalities could possibly reflect discrete neuroanatomical alterations in schizophrenia and may have a localizing value, as higher scores for the cognitive-perceptual abnormalities factor were significantly correlated with smaller volumes of the left heteromedial association cortex as assessed by magnetic resonance imaging (Keshavan et al. 2003).

The interpretation of many of the previous studies is complicated by the use of different (and unvalidated) assessment methods of neurological signs, different stages of the illness of samples, varying antipsychotic medication status, small samples and cross-sectional designs. Also, relatively few studies have explored neurological abnormalities in first-episode patients (Rubin 1997;Rubin et al. 1994;Gupta et al. 1995;Sanders et al. 1994;Keshavan et al. 2003).

Thus although neurological abnormalities have been consistently reported in subjects with schizophrenia, little is known about their origins and significance, and findings regarding their relationships to psychiatric symptoms, medication effects and outcome are inconsistent. This study attempts to address these uncertainties by investigating neurological abnormalities over the course of 12 months in a sample of largely medication-naïve subjects with a first-episode of schizophrenia who were treated over a two-year period according to a fixed protocol.

2. Methods

2.1 Subjects.

Subjects were recruited from our Early Psychosis Unit at Stikland Psychiatric Hospital, Cape Town. Inclusion criteria were: In- and out-patients; aged between 16 and 55 years; a DSM-IV diagnosis of schizophreniform disorder, schizophrenia or schizo-affective disorder; and prior antipsychotic exposure of 4 weeks or less. Exclusion criteria were an additional DSM-IV axis I diagnosis other than schizophreniform disorder, schizophrenia or schizoaffective disorder; alcohol or other substance abuse or dependence; prior depot antipsychotic treatment; significant medical illness; and mental handicap. Ethical approval was obtained from the Stellenbosch University Ethics Committee, and patients and/or their families provided written, informed consent to participate in the trial.

2.2 Ratings

Baseline evaluations were performed as far as possible before antipsychotic medication was prescribed. In the few cases where patients were unable to be assessed because of the severity of their illness, the evaluations were conducted as soon as they were deemed well enough to co-operate for the examination. A structured evaluation was performed by means of the Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition (SCID-P) (First et al. 1994). Neurological signs were assessed by means of the NES (Buchanan and Heinrichs 1989). An experienced psychiatrist (HJT) performed all of the NES assessments after undergoing training with the instrument. Additional assessments included the Positive and Negative Symptom Scale (PANSS) (Kay et al. 1987), Simpson-Angus Rating Scale (SAS)(Simpson and Angus 1970), Abnormal Involuntary Movement Scale (AIMS) (Guy 1976) and Barnes Akathisia Scale (BAS) (Barnes 1989). A physical examination was also performed. Investigators participated in regular inter-rater-reliability training sessions. Concordance coefficients for the PANSS, SAS, AIMS and BAS were above 0.8. The NES assessments were conducted at 0, 3, 6 and 12 months. All of the other assessments took place at three monthly intervals for the full 24 months.

2.3 Treatment

Subjects were treated with very low doses of haloperidol in an open label design according to a fixed protocol which has been fully described elsewhere (Oosthuizen et al. 2001). Lorazepam was permitted for sedation, and orphenadrine and benzhexol were

prescribed for treatment of EPS. Eighty-one percent of the subjects were still taking haloperidol at endpoint, at a mean \pm SD daily dose of 1.68 ± 1.02 mg/day. Generally, the treatment was effective and well tolerated, although a high incidence of 12.3% of probable or definite tardive dyskinesia was found at 12 months (Oosthuizen et al. 2003).

2.4 Data analysis

Various analyses of the data were undertaken. Factor analysis was performed by the method of maximum likelihood. It requires the number of factors to be specified, and a principal component analysis was performed as a guide for choosing the number of factors. The criterion chosen to select the number of factors was that eigenvalues should be greater than unity (Andreasen et al, 1995). The maximum likelihood factor solution was rotated using the varimax procedure. The first analysis was performed on the individual items of the NES. A further analysis was conducted on the PANSS items, this time using a forced five factor analysis. To explore relationships between neurological abnormalities and psychiatric symptoms we conducted Pearson Product Moment Correlation tests between the NES factors and the PANSS factors. Multiple regression analysis was performed to determine the significance of the relationships between the PANSS factors 1 to 5 (independent variables) and the NES factors 1 to 5 each as dependent variables. NES factors were correlated with demographic variables, EPS rating scale scores and DUP. **Analysis of covariance was preformed for binary variables.** Student's t-test was used to compare independent variables. A significance level of 0.05 was mainly used except where otherwise stated. Corrections for multiple comparisons were not applied because of the exploratory nature of the study. To examine the stability of the neurological abnormalities over time we conducted an observed cases (OC) analysis at each timepoint, and a repeated measures analysis of variance (RANOVA). Results are reported as the mean \pm SD. Analyses were performed using Statistica version 6 (Statsoft, Inc.) software.

3. Results

The sample comprised 66 subjects (53% women) aged 28.1 ± 8.5 yrs, with an illness duration of 371 ± 787 days and baseline PANSS total scores of 92.1 ± 16.2 . Six subjects were not naïve to psychotropic medication at the start of the study. Five had received small doses of antipsychotic medication, and one an antidepressant. The ethnicity of our sample reflected that of our catchment area, with 47 being of mixed descent, 5 black and 14 white. For the initial factor analysis (conducted on baseline NES scores), we followed the procedure of Malla et al (Malla et al. 1997) and Keshaven et al (Keshavan et al. 2003) by discarding items that were abnormal in <10% of the sample (items 2, 3, 4, 7, 18, 19, 21, 22, 23, 24, 25, 26), as well as the cerebral dominance items (handedness, footedness, eyedness). We were left with 13 items for the analysis. These items were similar, but not identical to the 13 items selected by Keshaven et al (Keshavan et al. 2003). The first five NES factors had eigenvalues greater than unity and accounted for 68.4% of the variance. Table 1 presents the results of the rotated principal component matrix with the factor loadings for the analysis. Descriptive names have been assigned to each of the factors. Baseline scores for the NES items, factors and total scores are given in Table 2. We found the following significant correlations between NES factors age, level of education and race: Age and NES factor 4 (motor sequencing) ($r=0.333$, $p=0.04$); level of education and factor 3 (attention) ($r=0.457$, $p=0.005$) and factor 5 (rhythmicity) ($r=0.337$, $p=0.04$). The number of subjects who underwent NES re-assessment at 3, 6 and 12 months, was 35, 31 and 20, respectively.

3.1 Stability of the neurological abnormalities over time

The NES total scores did not change significantly over time, although compared with baseline scores (OC analysis), the motor sequencing factor score was significantly reduced at 3 months ($p=0.01$), but not at 6 and 12 months. However, the repeated measures analysis of variance revealed no significant changes in NES factor scores over time.

3.2 Relationships between neurological abnormalities and psychiatric symptoms

We conducted a forced 5 factor analysis of individual PANSS item scores after omitting the items that were previously shown to load inconsistently (Emsley et al. 2003). This solution explained 64.3% of the variance and comprised the following factors: Negative (items N1, 2, 3, 4, 6 and G 7); disorganised (items P 3, 4, N 5, G 10, 11 and 14); depression/anxiety (items G 2, 3, 6, 16); excitement (items P 7 and G 8) and positive (items P 1, 5 and G 9)

factors. The only significant correlations between NES and PANSS factors were between NES factor 1 (balance) and PANSS factor 5 (positive) ($r=0.298$, $p=0.04$) and NES factor 2 (rapid movements, convergence) and PANSS factor 3 (depression/anxiety) ($r=0.286$, $p=0.05$). However, the R^2 values in the regression analysis were low (0.097 and 0.11, respectively), indicating that relatively little variance is shared between PANSS and NES factors.

3.3 Relationships between baseline neurological abnormalities and emergent acute EPS and dyskinesia

When correlations were sought between NES factors and SAS, AIMS and BAS scores at 3, 6, 9, 12, 15, 18, 21 and 24 months, we found that the NES balance factor was significantly correlated with SAS total scores at 6 ($r=0.58$, $p=0.03$) and 24 months ($r=0.59$, $p=0.02$). Analysis of covariance of NES factors and AIMS scores controlling for age and level of education revealed a highly significant association between the NES motor sequencing factor and the emergence of TD at 24 months ($F(1, 20)=19.287$, $p=0.0002$). The patients with emergent dyskinesia met Schooler and Kane criteria (Schooler and Kane 1982) for TD. When the NES factor scores were compared in patients with and without TD, significantly higher scores were found in the TD patients for the motor sequencing factor (3.2 ± 2.0 vs 1.6 ± 1.9) ($p=0.01$). While many individual NES items showed significant correlations with EPS at the 0.05 level, the only highly significant correlation was that of item 14 (rapid alternating movements) with baseline Simpson Angus scores ($r=0.77$, $p=0.001$).

3.4 Relationships between baseline neurological abnormalities and duration of untreated psychosis

None of the NES factors were significantly correlated with DUP. However, when subjects with a DUP > 1 month were compared to those with DUP \leq 1 month, the former had significantly higher NES motor sequencing factor scores ($p=0.02$).

3.5 Relationships between baseline neurological abnormalities and outcome

No significant correlations were found between the NES factors and outcome as assessed by percentage change in PANSS total and subscale scores at 12 months, response rates (>50% improvement in PANSS total score) at 12 and 24 months, and relapse rates (defined as hospitalization, or an unscheduled visit due to increase in PANSS score) at 12 and 24 months.

4. Discussion

A five-factor model provided the best solution for the NES item factor structure in our sample, accounting for 68.4% of the variance. Substantial similarities were found between our factor analysis and some of the other studies, indicating reproducibility of certain factors across samples. Our results were quite similar to those of Sanders et al (Sanders et al. 2000) and Keshaven et al (Keshavan et al. 2003) insofar as we also identified factors for balance, attention and motor-sequencing. Three of the motor sequencing items (fist-ring test, fist-edge-palm test, Ozeretski test) factored together in all three of the other published NES factor analyses (Malla et al. 1997; Sanders et al. 2000; Keshavan et al. 2003), and two attentional items (memory, extinction) in two others (Sanders et al. 2000; Keshavan et al. 2003). Interestingly, it was these motor sequencing and attentional abnormalities that have been reported to be more specific to schizophrenia (Keshavan et al. 2003). Impairment on motor-sequencing tasks is indicative of problems with the initiation and organization of action, specifically suggestive of perseveration, and is a cardinal feature of frontal dysfunction (Ovsiew 1994). While not reported in previous studies, the association of rapid alternating movements and convergence to form the second factor can be understood from a neuro-anatomical point of view. Impairment of rapid alternating movements is a feature of abnormal coordination, typically as a result of disturbance in corticospinal or cerebellar pathways. Supranuclear control of vergence is likely to be influenced by widely distributed networks, similar to those controlling pursuit eye movements (Leigh and Zee 1991). Additional deficits or dysfunction in control of vergence may result from dysfunction in cerebellar-brainstem pathways (Gamlin 1999).

The neurological abnormalities displayed considerable temporal stability, suggesting a trait-like nature (Lawrie et al. 2001). However, the fact that some variation occurred over

time, suggests that factors such as psychiatric symptom changes and the effects of medication may play a role. The significant improvements observed in the motor sequencing factor in the OC analysis suggest that these abnormalities may at least in part be secondary to psychiatric symptoms, with improvement occurring as the psychiatric symptoms resolve. To further explore this possibility we searched for correlations between PANSS individual items and NES factors. The NES rhythmicity factor was significantly correlated with PANSS items P2 (conceptual disorganization) ($r=0.45$, $p=0.003$) and G11 (poor attention) ($r=0.43$, $p=0.006$). These findings suggest that impairment on some NES tests (motor sequencing and rhythmicity) may be secondary to psychiatric symptoms. The only item score to worsen over time was item 14 (rapid alternating movements), at 3 months. Together with the finding of a strong correlation between this item and symptoms of parkinsonism, this strongly suggests that this is a secondary effect of antipsychotic medication.

It is also possible that the improved performance on the motor sequencing tests could be due to a direct beneficial effect of treatment, particularly considering that impairment on this factor was greater in subjects with a longer DUP. Both of these findings are consistent with the 'toxic psychosis' hypothesis proposing that ongoing psychotic symptoms are indicative of a progressive underlying morbid process, and that antipsychotic medication acts as a neuroprotective factor (Lieberman et al. 1993). (This hypothesis is based on a reported association between longer DUP and poorer overall outcome in patients with schizophrenia (McGlashan 1999; Malla et al. 2002).) Of further interest in this regard is that Madsen et al (Madsen et al. 1999) reported an increase in neurological abnormalities in patients with schizophrenia 5 years after their first presentation that was more marked in those patients who had not received antipsychotic medication over this period. These authors proposed a hypothetical protective effect of antipsychotics on neurological dysfunction. Little shared variance was observed between neurological signs and psychiatric symptoms, counting against the possibility of common biological underpinnings.

A striking finding in our study was the relationship between motor sequencing abnormalities at baseline and the later development of TD. This was unanticipated, although it had previously been suggested that the presence of neurological abnormalities may predict vulnerability to the later development of TD (King et al. 1991). This finding may be of clinical relevance insofar as it could represent a clinical marker for predicting those at risk of developing TD. Such a marker would indeed be helpful, as to date no reliable baseline clinical features have been identified that predict TD in first-episode schizophrenia (Chakos et al. 1996a; Oosthuizen et al. 2003). Thus, the presence of motor sequencing abnormalities, particularly in the presence of additional putative risk factors, should alert the clinician to the risk of TD, and prescribing an antipsychotic with the lowest risk of producing EPS in such cases would seem prudent. Other reported risk factors for TD include poor treatment response (Chakos et al. 1996b), medication-free intervals (Jeste et al. 1979), being of African descent (Glazer et al. 1994), increasing age (Morgenstern and Glazer 1993; Kane and Smith 1982), female gender (Chakos et al. 1996b) and the development of EPS during the acute treatment phase (Chatterjee et al. 1995). It is also of interest to note that motor sequencing abnormalities have been found to be significantly correlated with smaller right and left caudate volumes (Keshavan et al. 2003). This raises the possibility that a neuroanatomical basis exists for a subset of patients with schizophrenia who may be identifiable by motor abnormalities and who are at risk for developing TD.

The attentional factor may represent a stable marker for schizophrenia. While the two items of this factor, the memory and extinction tests, cannot be regarded as highly specific, the factor remained stable over time. Scores did not improve as the psychosis remitted, and they were not influenced by medication-effects. That this factor is a stable characteristic of some individuals with schizophrenia is further supported by the recent finding of Keshavan et al (Keshavan et al. 2003) who identified a similar factor that was found to be specific for schizophrenia insofar as scores were markedly higher in patients with schizophrenia compared to other psychoses and healthy volunteers, and were correlated with smaller volumes of the left heteromedial association cortex.

Similar to a previous report (Johnstone et al. 1990), we were not able to identify any associations between neurological abnormalities and treatment outcome.

Generalization of our findings may be limited by the sample size, particularly at follow-up, and by the inherent limitations of factor analysis (McGorry et al. 1998). The unexplained negative loading on some of the factors in a sense shows inconsistency of the data. Also, improvement on some of the tests could be ascribed to a learning effect. Nevertheless, when taken in conjunction with previously published studies, certain tentative inferences may be drawn. It would appear that two NES factors are reasonably replicable across samples, and have potential relevance for the further exploration of the pathogenesis of schizophrenia, as well as possible clinical applications. Impairment on the motor sequencing factor may be progressive while psychotic symptoms remain untreated, and improve as the symptoms resolve with treatment. Also, impairment on this factor may be an important predictor of vulnerability to TD. The cognitive/perceptual or attentional factor appears to be stable over time, diagnosis specific, and possibly reflects a stable characteristic of schizophrenia with specific neuroanatomical underpinnings.

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Table 1. The factor structure for the NES items.

Item number and description	Factor				
	1 Balance	2 Rapid movements, convergence	3 Attention	4 Motor sequencing	5 Rhythmicity
1 Tandem walk	<i>0.827094</i>	0.027646	0.260490	0.160499	-0.089155
6 Audio-visual integration	-0.055468	0.078780	0.272793	0.280807	<i>0.776058</i>
8 Graphesthesia	-0.621741	-0.016411	0.324952	0.048104	-0.119486
9 Fist-ring test	0.209653	0.052447	0.379532	<i>0.731771</i>	-0.004955
10 Fist-edge-palm test	0.130619	-0.554852	-0.163520	<i>0.589595</i>	0.084821
11 Ozeretski test	-0.080285	0.111193	-0.092655	<i>0.816276</i>	0.152403
12 Memory	0.019871	-0.026882	<i>0.736503</i>	-0.117030	0.127643
13 Ryhthm tapping test	-0.010556	0.021590	0.017907	-0.011399	<i>0.905431</i>
14 Rapid alternating movements	-0.171688	<i>0.728850</i>	-0.069402	0.167228	0.116818
15 Finger-thumb opposition	0.267354	0.477651	-0.245194	0.265210	0.372777
16 Mirror movements	-0.510251	0.245081	0.197664	<i>0.560421</i>	0.256501
17 Extinction	-0.076806	-0.034127	<i>0.811045</i>	0.234276	0.064696
20 Convergence	0.471211	<i>0.651951</i>	0.032437	-0.071837	-0.071125
Explained Variance	1.730941	1.577047	1.732846	2.142588	1.718682
Proportion of Total	0.133149	0.121311	0.133296	0.164814	0.132206

The strongest correlations on a factor for a given item are given in bold face and italics.

Table 2. Baseline scores for the NES individual items, factors and total scores

NES Item	Mean	Std.Dev.
1 Tandem walk	0.3208	0.51041
6 Audio-visual integration	0.7222	0.85598
8 Graphesthesia	1.2778	0.85598
9 Fist-ring test	0.5660	0.72083
10 Fist-edge-palm test	0.8302	0.82592
11 Ozeretski test	0.3922	0.66569
12 Memory	0.6000	0.83299
13 Rythm tapping test	0.9811	0.93007
14 Rapid alternating movements	0.1481	0.45172
15 Finger-thumb opposition	0.1111	0.37197
16 Mirror movements	0.3333	0.58277
17 Extinction	0.1698	0.42679
20 Convergence	0.3962	0.59935
Factor 1	0.3208	0.51041
Factor 2	0.5472	0.79822
Factor 3	0.7959	1.06026
Factor 4	2.0800	1.79387
Factor 5	1.7170	1.53645
TOTAL NES Score	6.7222	3.74376

3.a.i Ethnicity and Treatment Response in Schizophrenia: a Comparison of Three Ethnic Groups

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ABSTRACT

Background: Numerous cultural and ethnic factors may directly and indirectly influence treatment outcome in schizophrenia. The present study compared the response to antipsychotic treatment in three ethnic groups of patients with schizophrenia.

Methods: Fifty Black, 63 Coloured (mixed descent) and 79 White patients with schizophrenia or schizophreniform disorder who were participants in multinational clinical drug trials were assessed by means of the Positive and Negative Syndrome Scale (PANSS). Treatment response was measured by the change in PANSS total scores, and the change in positive, negative and general psychopathology subscale scores from baseline to 6 weeks. Also, the percentage of responders (defined as $\geq 40\%$ reduction in PANSS total scores) was calculated for each group.

Results: Baseline PANSS scores differed significantly, being higher for Blacks and Coloureds. Coloureds showed the greatest mean \pm SD percentage reduction in PANSS total score (29.4 ± 21.6) followed by Blacks (28.4 ± 14.7) and Whites (11.4 ± 27.6). Analysis of covariance revealed a significant effect of ethnicity on the reduction in PANSS total scores ($p < 0.0001$). The numbers of responders were: Coloureds 20 (32%), Blacks 12 (24%) and Whites 7 (9%) ($p = 0.002$).

Conclusions: Significant ethnic differences in acute antipsychotic treatment response are demonstrated by this study. Factors such as diet, nutritional status, body mass, and substance use could be important, as well as genetically determined ethnosppecific pharmacokinetic and pharmacodynamic differences. Delayed help-seeking may account for the higher baseline scores in the Blacks and Coloureds.

Introduction

The field of ethnopsychopharmacology has become a focus of considerable attention. While psychotropic drugs appear to be effective across cultural and ethnic boundaries,^{1,2} it is increasingly recognised that cross-cultural or cross-ethnic variations in responses to psychotropic agents do occur.^{3,4} The discovery of widespread ethno-specific polymorphisms in genes governing pharmacokinetic and pharmacodynamic aspects of psychotropic drugs may explain some of these variations.^{2,5} However, numerous other factors that are either directly or indirectly related to culture and ethnicity may be equally important. These include diet and nutritional status, exposure to various substances (eg. alcohol, tobacco), body mass, accessibility of services, compliance, social support, and co-morbid medical conditions.⁶

Differences in the doses of antipsychotics prescribed for the treatment of psychotic disorders in different ethnic groups have been consistently reported. African Americans are more likely

than Caucasians to receive higher doses.⁷⁻¹³ This may in part be due to delayed help-seeking, greater body weight, or biased therapist attitudes.¹¹ Several retrospective studies have reported that Asian patients receive lower doses of antipsychotics than Caucasians,¹⁴⁻¹⁶ although one study¹⁷ failed to find such differences. Also, Asians have been found to have higher plasma concentrations of antipsychotics than Caucasians.^{18,19} Ruiz et al²⁰ examined a sample of 58 Caucasian, 135 African American, and 11 Hispanic patients who received conventional antipsychotics. The mean dose of antipsychotics was similar for the Caucasian and African American groups (16.2 and 15.5 mg haloperidol equivalents/day, respectively), while for the Hispanic patients it was considerably lower (7.6 mg haloperidol equivalents/day). In a similar study involving the atypical antipsychotics (clozapine, risperidone and olanzapine), African Americans were prescribed the highest mean doses, followed by Hispanics and Caucasians. The doses prescribed for Asian Americans were much lower than for the other groups. These results may have been confounded by large differences that were found in mean body weights between the groups.²¹

While previous studies comparing ethnic differences in antipsychotic treatment have concentrated on examining the doses of antipsychotics prescribed, there is little information regarding the actual treatment responses of different ethnic groups. The present study compares the response to antipsychotic treatment in three ethnic groups of patients with schizophrenia, and considers some factors that may contribute to differences in outcome.

Methods

Subjects

Subjects were recruited from in-patient and out-patient hospital services. They comprised patients who had participated in multinational randomised clinical trials from two academic psychiatric hospitals in South Africa (Stikland Hospital, Cape Town, and Oranje Hospital, Bloemfontein) where the Positive and Negative Syndrome Scale (PANSS)²² had been used to assess symptom severity. They all met DSM-IV²³ criteria for schizophrenia or schizophreniform disorder, and belonged to one of three ethnic groups: Blacks, Whites or Coloureds. The Blacks were mainly from the Sotho (Sesotho and Setswana) ethnic group, with the rest from the Nguni group (Zulu and Xhosa). The Coloureds have developed from indigenous people living in the tip of Africa (San and Khoi), from slaves from Malaya and Madagascar, and from White European settlers.²⁴ The Whites were largely of European descent. The trials were undertaken between 1991 and 2000. Subjects were men and women aged between 18 and 65 years, with no concomitant significant medical conditions, and who did not meet criteria for substance abuse. All participants provided written, informed consent to participate in the clinical trials. Approval was obtained from the Ethics Committees of the Universities of Stellenbosch and Free State. The trials compared novel with conventional antipsychotics, and none had a placebo arm.

Ratings

All of the investigators were experienced psychiatrists who had undergone training and inter-rater reliability testing for the PANSS. Analyses were performed on the PANSS scores at baseline, and at 6 weeks (or the closest assessment to 6 weeks that was performed, ranging from 5 to 9 weeks). The following PANSS scores were selected, according to previously specified criteria²²: Total PANSS score (30 items); positive subscale score (items P1 to P7); negative subscale score (items N1 to N7); and general psychopathology subscale score (items G1-G14). Treatment response was assessed by the following means: Change from baseline to 6 weeks for PANSS total, positive subscale, negative subscale, and general psychopathology subscale scores. Also, the percentage of responders was calculated for each group. Responders were defined as those showing a 40% or greater reduction in PANSS total scores between baseline and 6 weeks.

Data analysis

The Chi square test was used for comparing categorical variables. All tests were 2-tailed. For differences between groups, one-way ANOVA or a chi-square test were performed where appropriate. To control for effects due to gender and age differences between the groups, ANCOVA was employed, with ethnicity and gender as categorical predictors and age as

covariate. Tukey's HSD for unequal group sizes was used for post-hoc pairwise comparisons. The significance level was set at 0.05.

Results

The sample comprised 50 Blacks, 63 Coloureds and 79 Whites. The mean \pm SD age of the Coloureds (29.3 \pm 10.7 years) was significantly lower than that of the Blacks (36.9 \pm 9.9 years) ($p=0.005$) and the Whites (38.6 \pm 13.2 years) ($p < 0.0001$). The baseline PANSS scores for the three groups are given in Table 1. There were significant differences among the groups for all of the PANSS scores. After controlling for age and gender, there was still a significant effect ($p<0.001$) of ethnicity on baseline PANSS total scores ($F_{2,189}=17.53$), PANSS positive scores ($F_{2,189}=11.3$) and PANSS General Psychopathology scores ($F_{2,189}=21.04$), but not the PANSS negative scores. Pairwise comparisons of PANSS total scores revealed significant differences between all ethnic groups ($p<0.009$). The PANSS positive subscale scores for the Whites differed significantly from those for the Coloureds and Blacks ($p<0.0001$), and PANSS General Psychopathology subscale scores differed significantly between all three groups (Black vs. White $p<0.0001$; Black vs. Coloured $p=0.004$; and Coloured vs. White $p=0.03$).

Figures 1 to 4 depict the change in PANSS total, positive, negative and general psychopathology subscale scores between baseline and week 6. Although the Blacks and Coloureds had significantly higher baseline PANSS total, positive and general psychopathology subscale scores, their endpoint scores were similar to, and in some cases lower than, those for the Whites. Coloureds showed the greatest percentage reduction in PANSS total scores (29.4 \pm 21.6), followed by Blacks (28.4 \pm 14.7) and Whites (11.4 \pm 27.6). Analysis of covariance, with ethnicity and age as categorical predictors and age as covariate revealed a significant effect of ethnicity on percentage reduction in PANSS total scores ($F_{2,189}=9.55$; $p<0.0001$). Pairwise comparisons showed that Whites differed significantly from Coloureds ($p<0.0001$) and from Blacks ($p=0.008$), but that Blacks and Coloureds did not ($p=0.96$). The response rates ($\geq 40\%$ reduction in PANSS total scores) for each group were: Coloured 20 (32%), Black 12 (24%) and White 7 (9%) (chi-square 12.2; df 2; $p=0.002$).

Discussion

This study demonstrates important ethnic differences in the acute response to antipsychotic treatment in patients with schizophrenia and schizophreniform disorder. Compared to Whites, the Coloured and Black subjects showed a much greater reduction in symptoms and had significantly better response rates. Whether these differences in acute treatment response are maintained in the longer term and result in better overall outcome remains to be determined. This would appear to be likely though, as responsiveness to biological treatments is reported to be predictive of good outcome.²⁵ Also, initial reductions in positive, and particularly negative symptoms are independently associated with reduced service use and improved quality of life after two years of treatment.²⁶

There is considerable evidence to suggest that the clinical course of schizophrenia varies across cultures - the outcome in developing countries being generally more favourable,²⁷ although the evidence is not conclusive.²⁸ The reasons for these variations in outcome are not clear. While personal dynamics within the patient's family have been suggested as a major factor,²⁹ this is unlikely to account for the differences in acute treatment response that were observed in our study. Another possibility is that patients from certain cultural settings have a better outcome because they have fewer negative symptoms, which are less responsive to antipsychotic drugs. Once again, our findings do not support this hypothesis - the Whites, who had the poorest outcome, did not have higher negative symptom scores. In fact, the baseline negative symptom scores of the Blacks were higher than, and those of the Coloureds similar to those of the Whites, while the response for negative symptoms tended to be better in both Blacks and Coloureds compared to Whites.

The differences in treatment response could be partly explained by the differences in baseline PANSS scores, which in turn may be due to age differences - younger patients have been reported to have higher positive scores and a better response to antipsychotic treatment.³⁰ On the other hand, another study reported that high scores on both negative and positive

subscales at index admission were significantly correlated with a *poor* outcome 5 years later.³¹ Even after controlling for age in our study, the Black and Coloured patients had significantly higher baseline positive scores and better response to treatment than the Whites. Our findings therefore support previous work suggesting that there are real differences in responses to antipsychotics between ethnic groups.^{7-11,12,16,20,21}

In addition to age differences, there are other factors that could explain the higher baseline symptom scores for the Coloured and Black patients. For example, the illness may express itself differently across cultures, being less severe in some. We do not consider this likely, however, as most studies report the core symptoms of schizophrenia to be similar across cultures,³²⁻³⁷ although a lower prevalence of first-rank or core symptoms has been found in developing countries,³⁸ in subjects less proficient in English,³⁹ and in minority groups,⁴⁰ while a higher prevalence of visual hallucinations has been reported in Kenyans.⁴¹ Also, in a large sample of indigenous Africans the factor structure for the symptoms of schizophrenia was found to be very similar to that previously described in Caucasian subjects.⁴²

A more likely explanation for the differences in baseline scores is that there was a longer delay in help-seeking in the Black and Coloured subjects. Generally, treatment facilities are less accessible, and the level of community awareness of mental health matters is lower for Blacks and Coloureds than it is for Whites.⁴³ This is not a problem that is specific to South Africa – for example, in the United States, African Americans have limited access to the mental health system, and a variety of socio-economic, cultural, attitudinal and biologic factors interact to preclude them from optimal care.⁴⁴ These patients are often treated differently – they are more likely to be hospitalised, involuntarily committed, placed in seclusion and given depot antipsychotics. These factors are thought to contribute to the reluctance of African Americans to utilise the mental health services.

There are a number of factors that could contribute to the observed differences in outcome between the ethnic groups, other than the already mentioned differences in baseline PANSS scores. For example, environmental factors such as differences in diet, nutritional status, body mass, and substance use and abuse may be important. These factors are known to affect the pharmacokinetics and pharmacodynamics of psychotropic drugs, and may differ considerably between ethnic groups.^{3,6} Apart from excluding substance abusers, none of these factors were investigated in this study. Finally, the possibility exists that genetically determined pharmacokinetic and pharmacodynamic differences exist between the ethnic groups. Further research will hopefully shed more light on this issue.

There are certain limitations to our study. First, there is a possibility of clinician bias, as the majority of investigators were White. Research has shown that the cultural and linguistic bias of the clinician has a significant influence upon the diagnosis and further management of the patient.⁴⁵ Clinicians, when dealing with patients from a different cultural background to their own, run the risk of unwittingly applying an ethnocentric bias to their evaluation and treatment of these patients. This has been demonstrated to lead to inaccurate assessment and inadequate treatment.^{10,46} It could be argued, for example, that the Black and Coloured groups contained some cases of 'atypical psychoses', or bouffee delirante, known to be common in developing countries⁴⁷ and to have a favourable prognosis.⁴⁸ However, we consider this unlikely to be a major factor in our study, as the use of standard diagnostic procedures and rating scales has been shown to largely eliminate the possibility of cultural bias.⁴⁹

Second, the study design did not make provision for examining the possible contributory effects of aspects such as diet, nutritional status, body mass and duration of untreated psychosis. Third, the fact that patients received different antipsychotic drugs should be borne in mind, although the possibility of a treatment bias is minimised by the fact that the trials were randomised. Details of medication were not available to us, as some of the studies had not been unblinded at the time of our analysis. Fourth, possible differences in chronicity and past treatment history could be important in explaining both baseline and outcome differences between the groups. Finally, it is not clear to what degree our findings can be generalised to other cultural settings.

This study confirms and extends previous work indicating ethnic differences in response to antipsychotic treatment. Substantial adjustments may be required in the prescribing habits of clinicians when dealing with patients of an ethnic group other than their own. Clinicians need to be alert to the many factors that may contribute directly and indirectly to cultural and ethnic variations in the response of patients to treatment. It may be that groups such as Blacks and Coloureds require lower doses of antipsychotics than Whites. It is of concern therefore that Black patients generally receive higher doses than Whites, considering that they not only respond better, but may be more at risk for developing side-effects such as tardive dyskinesia.⁵⁰ Future studies need to investigate factors such as body-mass, nutritional status and duration of symptoms before seeking help, and include assessments of blood levels of antipsychotics, as well as the genetic structure of the drug-metabolising enzymes in different ethnic groups. Although there are understandable sensitivities regarding research comparing different ethnic groups,⁵¹ further such studies are clearly indicated.² Not only do differences in efficacy and tolerability need to be defined, but so too do inequities in service provision and social circumstances.

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Table 1. Mean \pm SD baseline PANSS scores for the Black, Coloured and White subjects.

	Blacks (N=50)		Coloureds (N=63)		Whites (N=79)		F _{2,189}	P
	Mean	SD	Mean	SD	Mean	SD		
PANSS total	102.3	14.5	90.7	19.0	82.3	16.5	21.4	<0.0001
PANSS positive	24.4	5.5	23.1	5.5	18.6	6.8	16.9	=0.0001
PANSS negative	27.6	4.8	24.8	7.8	24.8	5.8	3.56	=0.034
General psychopathology	50.3	8.5	42.8	10.3	38.9	8.7	23.6	<0.0001
Composite score	-3.12	7.1	-1.7	9.1	-6.2	8.9	5.3	=0.006

Figure 1. Mean (and standard error) PANSS total scores for the 50 Black, 63 Coloured and 79 White subjects at baseline and after 6 weeks of treatment.

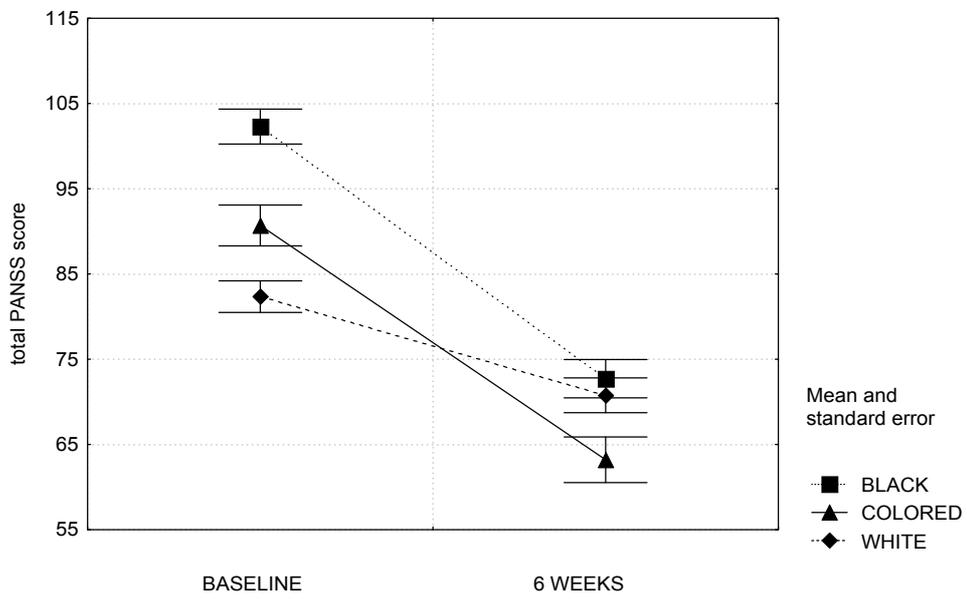


Figure 2. Mean (and standard error) PANSS positive subscale scores for the 50 Black, 63 Coloured and 79 White subjects at baseline and after 6 weeks of treatment.

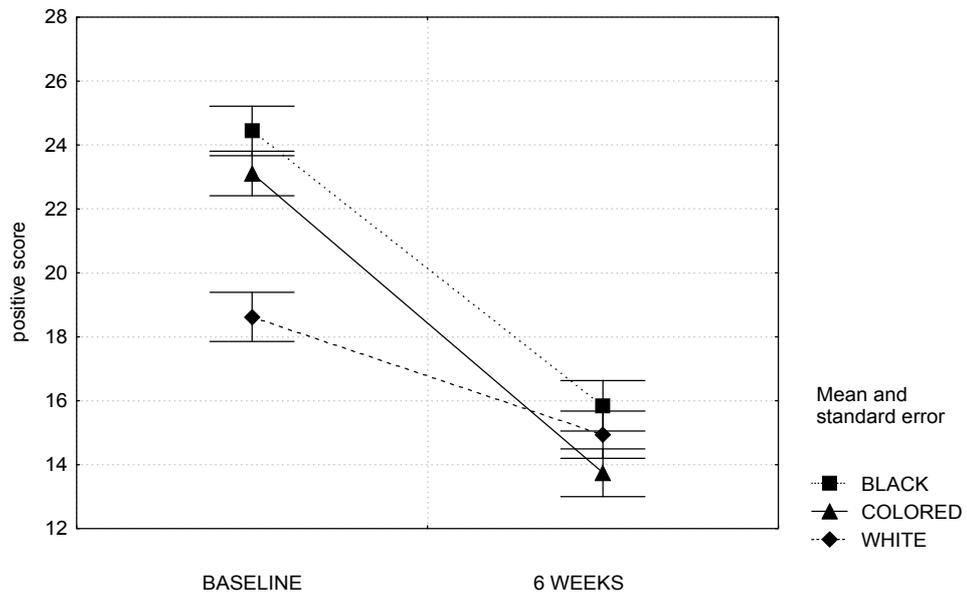


Figure 3. Mean (and standard error) PANSS negative subscale scores for the 50 Black, 63 Coloured and 79 White subjects at baseline and after 6 weeks of treatment.

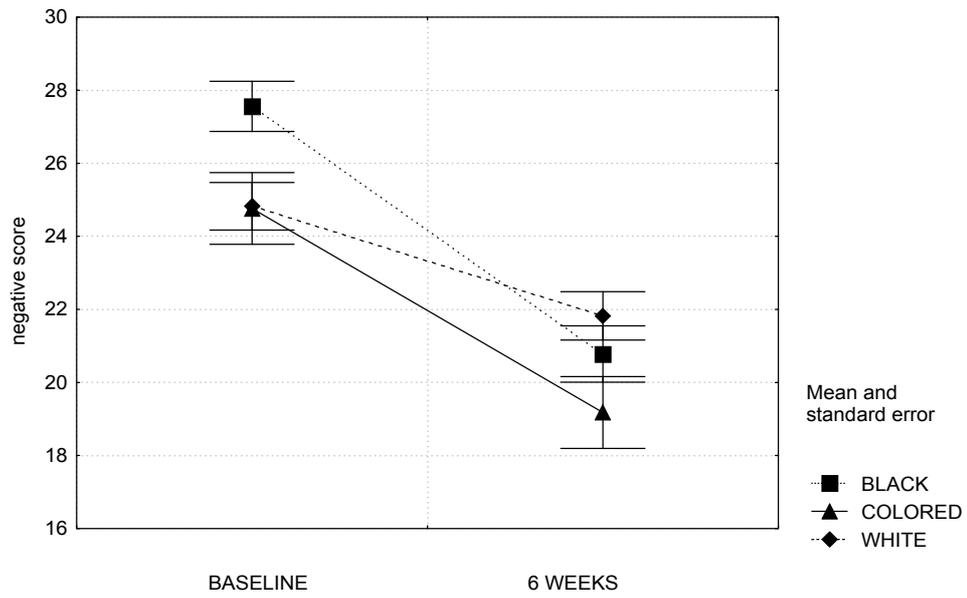
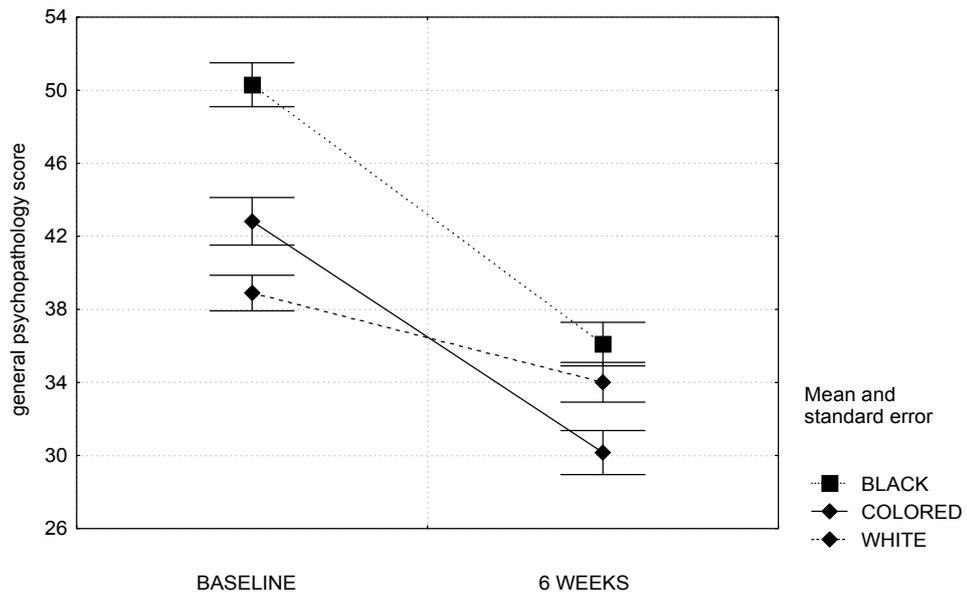


Figure 4. Mean (and standard error) PANSS general psychopathology subscale scores for the 50 Black, 63 Coloured and 79 White subjects at baseline and after 6 weeks of treatment.



3.a.ii Randomized, Placebo-Controlled Study of Ethyl-Eicosapentaenoic Acid as Supplemental Treatment in Schizophrenia

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Objective: The study investigated the efficacy and tolerability of ethyl-eicosapentaenoic acid (E-EPA) as add-on treatment in chronic, severe schizophrenia.

Method: A randomized, parallel-group, double-blind, placebo-controlled, fixed-dose, add-on study was conducted over 12 weeks. Forty patients with persistent symptoms after at least 6 months of stable antipsychotic treatment received E-EPA or placebo, in addition to their existing treatment.

Results: At 12 weeks, the E-EPA group had significantly greater reduction of Positive and Negative Syndrome Scale total scores and of dyskinesia scores than the placebo group.

Conclusions: EPA may be an effective and well-tolerated add-on treatment in schizophrenia.

Extrapyramidal symptoms and limited efficacy are serious limitations of conventional antipsychotics, while high acquisition costs have put the novel antipsychotics beyond the reach of patients in lower-income countries (1). Omega-3 polyunsaturated fatty acids may offer an affordable treatment alternative. Supportive findings include low levels of omega-3 polyunsaturated fatty acids in red blood cells (2) and the brain (3) in schizophrenia. Open-label supplemental studies have suggested a beneficial effect for omega-3 polyunsaturated fatty acids in schizophrenia. A pilot study found that eicosapentaenoic acid (EPA) was superior to docosahexaenoic acid and placebo when added to standard antipsychotic treatment (4), although another double-blind study of EPA versus placebo found no improvement of symptoms with EPA (5). In a dose-ranging study, ethyl-EPA (E-EPA) doses of 1, 2, and 4 g/day were no better than placebo, although subjects taking clozapine with E-EPA improved significantly, the effect being greatest with a 2 g/day dose of E-EPA (6). Recent reviews of the treatment of schizophrenia with omega-3 polyunsaturated fatty acids found results to be encouraging but preliminary (7), somewhat conflicting (8), and requiring independent replication (9).

Method

Forty subjects aged 18 to 55 years who met DSM-IV criteria for schizophrenia were recruited. All had received fixed doses of antipsychotics for at least 6 months and had a Positive and Negative Syndrome Scale (10) total score ≥ 50 . Exclusion criteria comprised substance abuse and significant medical conditions. The University of Stellenbosch ethics committee approved the study, and subjects provided informed, written consent.

This was a randomized, parallel-group, double-blind, placebo-controlled, add-on study conducted over 12 weeks. Patients were assessed at baseline and at weeks 3, 6, 9, and 12 by means of the Positive and Negative Syndrome Scale and the Extrapyramidal Symptom Rating Scale (11). Subjects were randomly assigned to receive either 3 g/day of E-EPA supplement in encapsulated form (three 500-mg capsules twice daily) (Laxdale Ltd., Stirling, Scotland) or placebo (3 g/day of medicinal liquid paraffin BP) in addition to the medication that they had been receiving.

The primary outcome measure was the percentage change in Positive and Negative Syndrome Scale total score between baseline and 12 weeks. Secondary efficacy measures were the changes in the Positive and Negative Syndrome Scale positive, negative, and general psychopathology subscale scores. Extrapyramidal symptoms were assessed by the changes in total Extrapyramidal Symptom Rating Scale scores and in the scale's subscores for dyskinesia, dystonia, akathisia, and parkinsonism. A dietician reviewed the dietary intake of each subject at baseline and throughout the study. EPA intake was calculated according to standard food supplementation tables provided by the South African Medical Research Council.

Comparisons were performed with Student's t test. An intent-to-treat design was used, with the last observation carried forward for any subject who did not complete the 12-

week study. An additional analysis was performed with analysis of covariance (ANCOVA) to control for the effects of dietary EPA, medication, duration of illness, and gender. A p value of ≤ 0.05 was considered statistically significant. All tests were two-tailed.

Results

Baseline demographic and clinical variables were similar for the two groups. The age and illness duration were 46.2 years (SD=10.6) and 23.1 years (SD=8.5) for the E-EPA group, and 43.6 years (SD=13.9) and 22.2 years (SD=12.4) for the placebo group. Antipsychotic doses (chlorpromazine equivalents) were 1011 mg/day (SD=532) for the E-EPA group and 931 mg/day (SD=652) for the placebo group. No additional medication was prescribed throughout the trial, except for occasional analgesics for headache and lorazepam for insomnia. There were no differences between groups regarding dietary intake of omega-3 polyunsaturated fatty acids. All subjects received a balanced diet before and throughout the trial. Dietary EPA intake was generally low, ranging from 0.56 g/week to 1.13 g/week. Antipsychotic medication remained unchanged for all subjects throughout the trial. Nine subjects in each group were receiving clozapine, and the rest were receiving conventional antipsychotics. One subject from the E-EPA group was withdrawn from the trial after taking an overdose of medication. No other serious adverse events were recorded.

For the primary outcome measure the difference between the groups was statistically significant in favor of the E-EPA group (mean=12.6 [SD=14.0] versus 3.1 [SD=13.3]) ($t=2.2$, $df=38$, $p=0.03$), and this difference remained significant after controlling for effects of dietary EPA, medication, duration of illness, and gender (Figure 1). The reduction tended to be greater in the E-EPA patients taking conventional antipsychotics than in those taking clozapine (mean=17.4, SD=12.1, versus mean=6.8, SD=14.6) ($t=1.8$, $df=18$, $p=0.09$). For the Positive and Negative Syndrome Scale subscales, the only significant difference was in favor of E-EPA in the percentage change in the general psychopathology subscale score at endpoint ($t=2.08$, $df=38$, $p=0.04$). There were no group differences for the changes in Extrapyramidal Symptom Rating Scale parkinsonism, dystonia, or akathisia scores. However, the E-EPA group showed a significantly greater reduction in Extrapyramidal Symptom Rating Scale dyskinesia scores at 12 weeks ($t=2.82$, $df=38$, $p=0.008$). A further analysis of covariance using change in Positive and Negative Syndrome Scale total score as the dependent variable and change in dyskinesia score as a covariate was performed. The difference between the E-EPA and placebo groups was no longer significant ($F=3.08$, $df=1$, 39 , $p=0.09$), suggesting that reduction in Positive and Negative Syndrome Scale scores is associated with reduction in dyskinesia scores.

Discussion

This study shows a significant advantage for E-EPA over placebo in the primary outcome measure. The between-group difference had reached significance after 3 weeks of treatment, signifying an early onset of action. We regard these results as remarkable, considering the refractory nature of schizophrenia in the subjects. The reduction in dyskinesia scores for the E-EPA group was unanticipated, although an inverse relationship between tardive dyskinesia scores and blood levels of EPA has been reported (12). Given the chronic nature of the disorder in the subjects, most of these dyskinetic symptoms are likely to have been due to neuroleptic-induced tardive dyskinesia. The following factors limit the generalization of our findings. First, the study was conducted in a small group of subjects. Second, whether E-EPA is an effective antipsychotic on its own is not known. And third, the results of the analysis of covariance suggest that reduction in Positive and Negative Syndrome Scale scores may at least in part be related to reduction in dyskinesia scores.

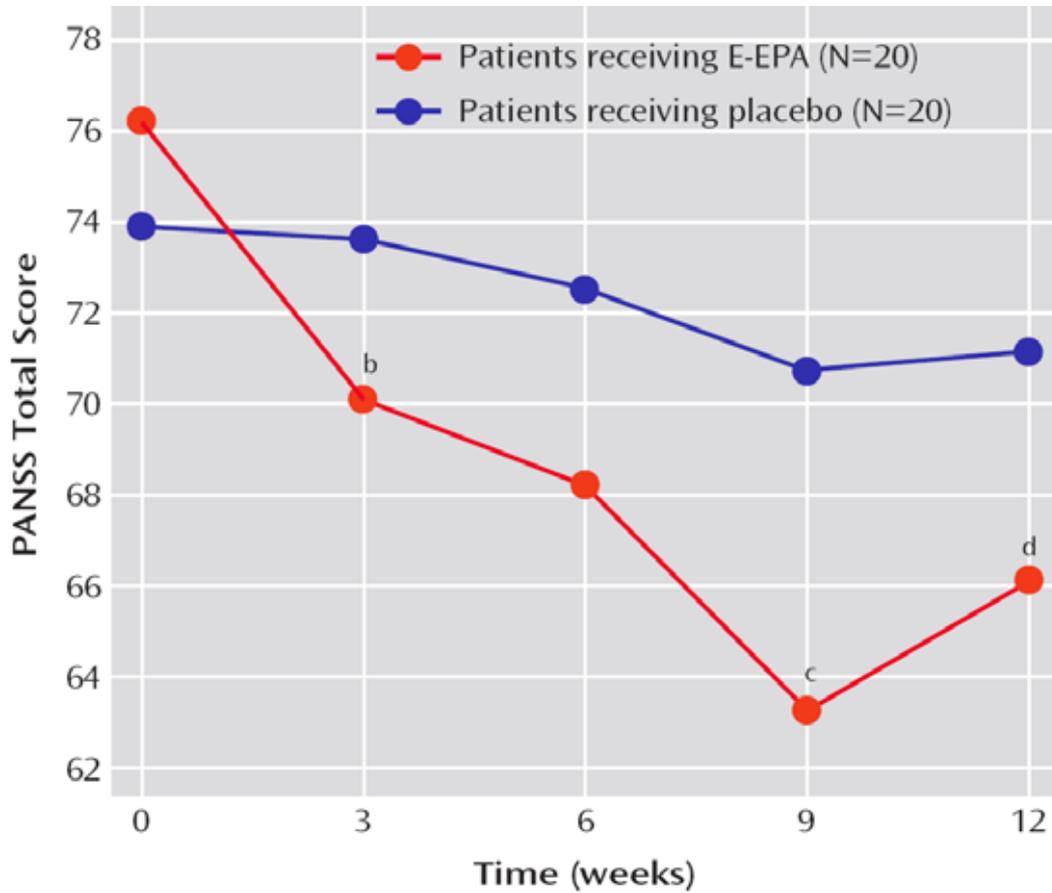
E-EPA may be an effective, safe, and well-tolerated add-on treatment in chronic schizophrenia. The extent of its antipsychotic activity remains to be determined. The beneficial effect observed on dyskinesia also requires further exploration. If efficacy in

psychosis and tardive dyskinesia is confirmed, it is likely to lead to revision of our understanding of the pathophysiology and treatment of these disorders.

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Figure 1. Mean Total Scores on the Positive and Negative Syndrome Scale of Patients Who Received Ethyl-Eicosapentaenoic Acid (E-EPA) or Placebo in a 12-Week Randomized, Parallel-Group, Double-Blind Study of Supplemental Treatment for Schizophrenia^a



^aLast observation carried forward.

^bSignificant difference between groups ($t=2,2$, $df=38$, $p \leq 0.05$).

^cSignificant difference between groups ($t=2,9$, $df=38$, $p \leq 0.05$).

^dSignificant difference between groups ($t=2,2$, $df=38$, $p \leq 0.05$).

3.a.iii Time course for antipsychotic treatment response in first-episode schizophrenia

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Abstract

Objective: Recent studies suggest an early onset of antipsychotic action, and early prediction of non-responders. We examined whether this was the case in first-episode schizophrenia by investigating the time to clinical response.

Method: The time to attaining a clinical response ($\geq 20\%$ improvement on PANSS total scores) was determined in 522 participants in a randomized, controlled trial comparing risperidone and haloperidol. The median treatment length was 206 days.

Results: A clinical response was achieved in 76% of subjects. Of these, 23.4%, 23.4%, 18.6% and 12.6%, was attained at weeks 1, 2, 3 and 4, respectively. However, 25% did not respond until after the fourth week, and 11% after the eighth week. Forty-five percent of patients responded on 1-2 mg, 27% on 3 mg, 17% on 4 mg and the remaining 11% on higher dosages. Response of at least 30%, 40% and 50% respectively were achieved by 62.5%, 44.5% and 27.3% of patients.

Conclusions: The time to response varied widely, suggesting that, in first-episode schizophrenia, longer treatment trials may be necessary.

Introduction

Early identification of non-responders to antipsychotic treatment could avoid unnecessary persistence with ineffectual agents, thereby diminishing the risk of adverse events. This in turn could reduce duration of hospitalization, level of care required, amounts of concomitant medication prescribed, and costs incurred. While most studies to date have examined putative response predictors prior to the initiation of treatment, symptom changes shortly after commencement of treatment may be a more reliable way of predicting response. A recent meta analysis has challenged the belief that the onset of action of antipsychotics is delayed, by providing evidence for a robust early onset (13.8% reduction in symptom scores after 1 week) (1). This suggests that response during the first week of treatment might provide an indication as to how patients are likely to respond later in the course of treatment. In keeping with earlier findings that early symptom changes could be a useful predictor of outcome (2), Correll et al. (3) investigated the predictive value of early symptom changes 1 week after initiation of treatment and found that early non-improvement ($< 20\%$ reduction BPRS total score at 1 week) predicted non-response at 4 weeks in 100% of cases, suggesting that treatment refractoriness may already be identifiable after 1 week.

Using data from a large multinational, randomized, double-blinded trial comparing risperidone and haloperidol, we determined the time to response in first-episode schizophrenia. We also examined as possible predictors of response previous antipsychotic exposure, duration of untreated psychosis, highest level of pre-morbid functioning age and sex.

Method

The study methodology has been published elsewhere (4). Patients with schizophrenia, schizophreniform disorder or schizoaffective disorder for ≤ 12 months were treated with either risperidone or haloperidol 1 mg/day, increased if necessary by 1 mg/day after 3 days, and weekly, to a maximum dose of 4 mg/day. In exceptional cases, i.e., for subjects showing insufficient response in whom not more than mild EPS were observed at 4 mg per day, the dose could then be increased further by 1 mg a week up to a maximum daily dose of 8 mg. The mean modal dose for risperidone was 3.3 mg/day, and for haloperidol 2.9 mg/day. The median treatment length was 206 days (maximum 1514). Thirty-one percent ($n=163$) had no previous exposure to antipsychotic medication. Clinical response was defined as $\geq 20\%$ reduction on the Positive and Negative Syndrome Scale (PANSS) total score.

Results

Of the 522 patients, 400 (76.6%) achieved at least 20% reduction in PANSS total score. However, time to response varied considerably (Figure 1), with 93 (23.4%) occurring during the first week of treatment, while at weeks 2, 3 and 4 the numbers were 93 (23.4%), 74 (18.6%) and 50 (12.6%), respectively. About one quarter ($n=112$) did not respond until after the fourth week and 53 (11.5%) after the eighth week. Dose at time of response was as follows: 1 mg, 15.5% ($n=62$), 2 mg, 29.8% ($n=119$), 3 mg, 27.3% ($n=109$), 4 mg, 16.8% ($n=67$) and more than 4 mg 11% ($n=43$).

Response of at least 30%, 40% and 50% respectively was achieved by 62.5%, 44.5% and 27.3% of patients. Response occurred on the PANSS positive, negative and psychopathology scales with the most improvement on the positive subscale (Table 1).

Based on Cox regression analysis, which controlled for baseline PANSS and study centre, patients with poor pre-morbid functioning (as measured using the Premorbid Adjustment Scale global assessment of highest functioning (5)) were less likely to respond ($OR=.89$; $CI=.83$ to $.95$; $p<.001$), as were those with previous antipsychotic exposure ($OR=.77$; $CI=.61$ to $.97$; $p<.03$). Age, sex and study medication were not significantly associated with response. For the neuroleptic naïve patients ($n=163$; 20 non-responders) a longer DUP (which was transformed with log transformation to make the distribution normal) was associated with decreased likelihood of response ($OR=.86$; $CI=.76$ to $.96$, $p=.01$), as was poorer pre-morbid functioning ($OR=.85$, $CI=.74$ to $.97$, $p=.01$).

Discussion

The majority of our subjects responded to antipsychotic treatment, in keeping with the previously reported favorable response in first-episode schizophrenia (6). Also, our findings provide further evidence that, at least in some patients, the onset of antipsychotic action is early – i.e. in the first week of treatment (1). However, the time course to response varied widely, with some responders only achieving 20% improvement after > 10 weeks of treatment with a median of almost 3 weeks.

Our findings therefore differ from those of a multi-episode sample (3) insofar as we did not find early non-response to be a reliable predictor of later non-response. Whereas Correll et al found that all patients who failed to achieve 20% improvement after 1 week of treatment failed to do so after 4 weeks of treatment, we found that 52% ($n=184/353$) of such patients did not respond by week 4. Moreover we found that of the non-responders at week 1 ($n=353$), 78.5% ($n=277$) went on to have a clinical response. Correll et al found that 35% of those who had responded by week 1 were also responders at week 4; we found that 77.4% ($n=72/93$) of such patients were responders at week 4.

If, according to practice guidelines (7), treatment trial periods of one month or even six weeks were applied to our subjects, many would incorrectly have been regarded as non-responders. Additional research is indicated, and if similar results emerge then practice guidelines recommending shorter durations of treatment (7) may need to be revised for patients with first-episode psychosis. A possible explanation for the discrepant findings is that in the Correll et al (3) study the treatment period was of short duration (4 weeks). Also, in our study a low-dosing strategy was adopted which could explain the slow response in some patients. We consider this unlikely however, as low doses of both risperidone (8) and haloperidol (9) have been shown to be at least as effective as high doses in first-episode

psychosis. Our finding that shorter DUP and better pre-morbid functioning was a predictor of response is in keeping with previous work (10, 11).

Strengths of this study include the large sample, the fact that this was a first-episode sample, the use of standardized assessment and diagnostic criteria, the ability to test treatment response in a typical and atypical antipsychotic and the long treatment period. The flexible dosing design was both an advantage in that it allowed mimicking clinical practice and also a limitation in that time to response for a specific dose could not be examined. Future studies should examine the relationship between early symptom reduction and later overall outcome.

Figure 1

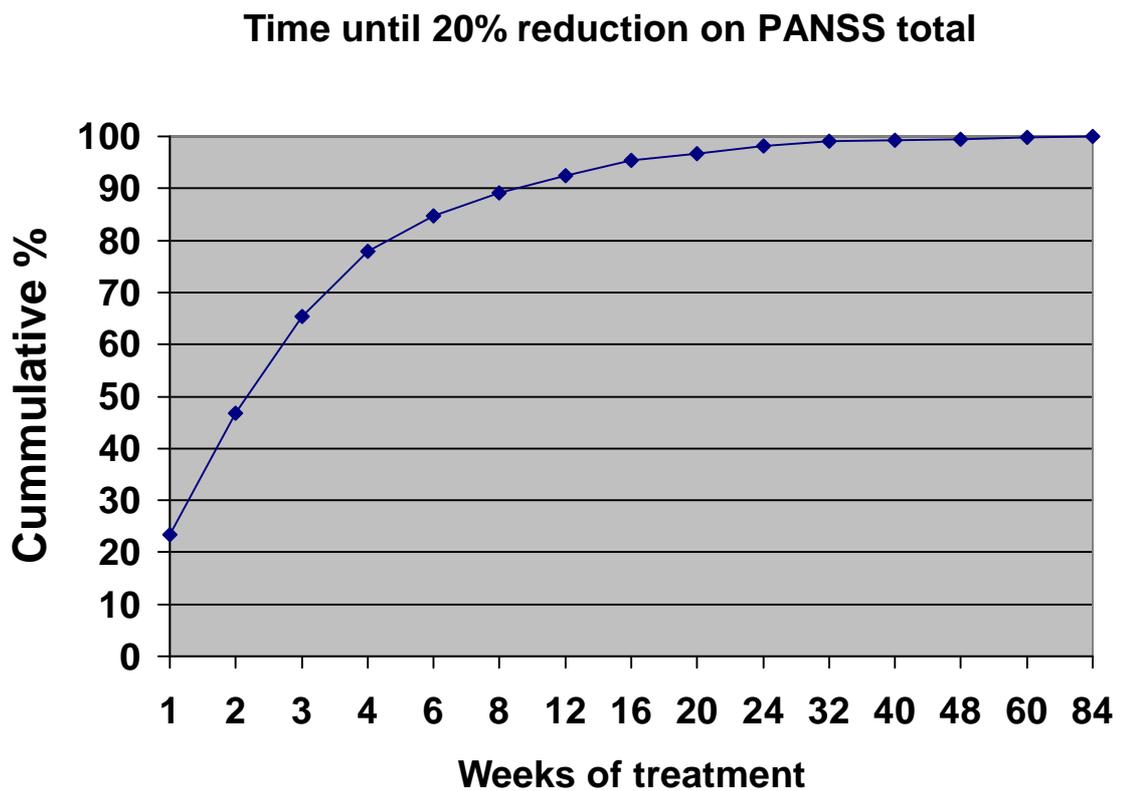


Table 1 Percent improvement from baseline for PANSS total and subscales (n=526)

	Positive	Negative	General Psychopathology	Total
60% or more	10.5% (n=149)	12.3% (N=65)	11.4% (N=61)	10.3% (n=54)
50% or more	48.1% (n=253)	26.8% (N=141)	28.7% (N=151)	27.3% (n=144)
40% or more	63.3% (n=333)	43.0% (N=226)	43.1% (N=233)	44.5% (n=234)
30% or more	73.8% (n=388)	59.1% (N=311)	61.6% (N=324)	62.5% (n=329)
20% or more	82.2% N=432)	72.5% (N=381)	76.2% N=401	76.2% (n=401)

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3.a.iv Remission in first episode psychosis: predictor variables and symptom improvement patterns.

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Abstract

Background: Previous attempts to identify clinically useful predictors of treatment outcome in schizophrenia have been hampered by methodological inconsistencies, including a lack of standardised outcome measures. Recently proposed operationally defined criteria for remission provide an opportunity to re-address this topic.

Method: We applied the remission criteria to a sample of 57 subjects with first-episode psychosis, treated according to a fixed protocol over two years. Various demographic, baseline clinical and early response variables were subjected to discriminant analysis for their ability to predict remission or non-remission. We also assessed the symptom improvement patterns over time and compared endpoint psychopathology in the remitters and non-remitters.

Results: A model incorporating neurological soft signs, 6 week treatment response, duration of untreated psychosis, pre-morbid functioning and PANSS excited factor baseline score was able to correctly predict 89% of the remitters and 86% of the non-remitters. Symptom reduction at 6-weeks, including core-psychotic symptoms, was similar in the two groups, where after the remitting group continued to improve while the non-remitting group failed to do so. Considerable overlap of endpoint symptoms was observed, and depressive symptom scores were similar in remitters and non-remitters

Discussion: A combination of demographic, baseline clinical and acute treatment response variables may accurately predict treatment outcome. Persistent non-core psychotic symptoms in subjects meeting proposed remission criteria require further investigation.

Introduction

Since the introduction of antipsychotic medication some fifty years ago, considerable attempts have been made to identify predictors of treatment outcome.¹ Reliable predictors of antipsychotic treatment outcome would be of great benefit, particularly by avoiding unnecessary persistence with ineffectual treatment before attempting alternative strategies. This in turn would reduce the risk of accruing morbidity, the development of side effects, the duration of hospitalization, the level of care required, the amounts of concomitant medication prescribed, and overall costs incurred.

Factors determining the response to antipsychotic treatment in schizophrenia are poorly understood, and results of studies thus far have been inconclusive and sometimes conflicting.² A poorer response has been associated, amongst other factors, with male gender, history of obstetric complications, more severe positive symptoms, the development of parkinsonism during antipsychotic treatment,³ extrapyramidal symptoms (EPS) prior to antipsychotic exposure,⁴ neurological soft signs,⁵ the development of tardive dyskinesia (TD), family history of schizophrenia⁶ and prolonged duration of untreated psychosis (DUP).⁷ However, associations as such do not necessarily imply predictive value, and none of these factors can be regarded as clinically useful in forecasting treatment outcome.² An alternative

approach has recently produced promising results: early treatment response appears to closely parallel later outcome,^{8,9} and recently evidence has emerged that a lack of early treatment symptom reduction may be an accurate predictor of later non-response.²

Part of the difficulty in interpreting the findings of studies to date is related to the divergent methodologies that were employed.¹⁰ Sample populations (e.g. first-episode, multi-episode), treatment durations and assessment instruments differ across studies. Another significant problem has been that the endpoint measures of outcome have varied widely. For example, clinical treatment trials often report a reduction in symptom severity from baseline to endpoint as the primary outcome measure, while other studies have attempted to define criteria for treatment response (e.g. 20% improvement in psychopathology scores),¹¹ relapse¹² or remission.¹³ Recently, in the hope of improving the assessment of treatment outcome, operational criteria defining remission in schizophrenia were proposed by a 'Remission in Schizophrenia Working Group'.¹⁴ These criteria define remission according to a threshold of severity of selected rating scale items rather than percentage improvements from a particular baseline. The items were selected on the basis of their representing 3 major symptom domains identified in factor analyses (negative, psychosis and disorganized factors) and the five criteria specified in DSM-IV for a diagnosis of schizophrenia. The proposed criteria define remission as absent, borderline or mild symptom intensity level where such symptoms do not influence an individual's behavior. An additional requirement is that these criteria must have been met for a duration of at least 6 months,

We applied these criteria in a post-hoc fashion to a sample of subjects with first-episode psychosis who were treated according to a fixed protocol over 24 months, and evaluated various potential predictors of outcome. The primary aim of our study was to identify any baseline and early treatment variables that could be useful to clinicians in predicting remission and non-remission. As a secondary aim, we explored the symptom improvement patterns over time and differences in endpoint psychopathology in remitters and non-remitters.

Methods:

Subjects

The sample comprised 57 participants in a 2-year prospective study of first episode psychosis in the Stikland Hospital catchment area in Cape Town, South Africa. The patient sample and study procedure have been described in detail elsewhere.¹⁵ Briefly, inclusion criteria comprised in- or outpatients aged 16 to 55 years, meeting DSM-IV¹⁶ diagnostic criteria for schizophreniform disorder, schizophrenia or schizo-affective disorder, who had been exposed to less than 4 weeks of antipsychotic treatment. Exclusion criteria were another DSM-IV axis I diagnosis including substance abuse or dependence, significant general medical condition and mental retardation. The study was approved by the Ethics Committee of the University of Stellenbosch and subjects and/or their guardians provided written, informed consent to participate in the trial.

Assessments

Participants were assessed by means of the Structured Clinical Interview for DSM-IV (SCID).¹⁷ Psychopathology was measured by means of the Positive and Negative Syndrome Scale (PANSS)¹⁸ and the Calgary Depression Scale for Schizophrenia (CDSS);¹⁹ and extrapyramidal symptoms (EPS) by means of the Abnormal Involuntary Movement Scale (AIMS),²⁰ the Barnes Akathisia Scale (BAS)²¹ and the Simpson-Angus Scale (SAS).²² For the purpose of this analysis we used baseline, 6 and 12 week, and then 3 monthly assessments.

Treatment

Subjects were treated according to a fixed protocol with low doses of haloperidol starting on 1mg/day, gradually increasing the dose for non-responders ($\leq 20\%$ reduction in PANSS total score) to a maximum of 10mg/day. The treatment was generally effective and well tolerated.¹⁵

Remission criteria

The symptom severity threshold comprises a score of 3 (mild) or less on each of the following PANSS items: Delusions (P1), conceptual disorganization (P2), hallucinatory behaviour (P3),

blunted affect (N1), social withdrawal (N4), lack of spontaneity (N6), mannerisms/posturing (G5) and unusual thought content (G9). The minimum time threshold for maintaining these symptom severity levels is 6 months.¹⁴

Symptom improvement patterns

PANSS total scores over time were compared for remitters and non-remitters by repeated measures analysis of variance (RANOVA). To examine whether any initial symptom reduction in the non-remitting group could be accounted for by improvement in non-core psychotic symptoms, we compared baseline to 6 week reductions in the PANSS symptoms used to define remission.¹⁴ Endpoint scores for PANSS total and factor scores, as well as CDSS scores were compared between the two groups.

Predictors of remission

The following variables were investigated as potential predictors of remission: Sex, age, diagnosis (schizophrenia vs schizophreniform/schizo-affective disorder), educational status (rated on a scale from 0-8), employment status, marital status (ever married), family history of schizophrenia, DUP (greater or less than 1yr), baseline PANSS scores (PANSS total scores and previously described PANSS factor scores²³), baseline CDSS scores, baseline neurological soft signs (total scores from the Neurological Evaluation Scale (NES)²⁴), the development of EPS other than tardive dyskinesia (TD) (a score of ≥ 1 on the BAS scale and ≥ 14 on the SAS at any stage during the study), and TD. Also, as a measure of acute symptom reduction we investigated the degree of clinical response at 6 weeks. (We chose 6 weeks as earlier time points did not show significant correlations with outcome.)

Statistical analyses

Due to the relatively small sample and the uncertainty regarding the predictive power of the individual variables, we adopted the following procedure to determine the predictive power of the selected variables: First, we split the data into a 'training' (n=25) and 'test' (n=16) set, only including the cases with no missing data (n=41). For the training set, we drew a random sample (n= 25) with a replacement (bootstrap) sample. We then applied the best subsets method to the bootstrap sample using discriminant analysis and support vector machines (SVM), and noted which variables were included in the "best model". Support Vector Machines are learning machines that can perform binary classification (pattern recognition) and real valued function approximation (regression estimation) tasks to solve classification and regression problems.²⁵ These steps were repeated until we were satisfied that clear patterns had emerged. The number of times each variable was included as a predictor determined its predictive power. Based on these findings, a subset of variables was selected and a final model constructed for the 25 'training' cases, and tested on the 16 'test' cases.

All statistical tests were two-tailed and a 5% ($p < 0.05$) significance level was set throughout. Results are expressed as the mean \pm standard deviation. Where appropriate, 95% confidence intervals are reported.

Results

The sample comprised 57 participants (51% women) aged 28 ± 8.5 yrs at study entry. Seventy-two percent were diagnosed with schizophrenia, 21% with schizophreniform disorder, and 7% with schizo-affective disorder. The mean DUP was 229 ± 358 days. Subjects were acutely ill at study entry, with a mean PANSS total score of 93.4 ± 16.6 . Twenty-eight (49%) completed the 24 months of treatment, the majority as out-patients. Of the 29 who discontinued, 23 were lost to follow-up, 3 were withdrawn due to poor response, 2 relocated and 1 committed suicide. While 40 (70%) met cross-sectional symptom reduction for remission at some point in the study, only 23 (40%) managed to achieve the full remission criteria when the 6-month duration was applied. Of these 23 subjects, nineteen (83%) maintained their remission status throughout the trial. For those attaining it, the mean time to remission was 10 ± 4.13 months. The remission and non-remission groups did not differ significantly regarding the endpoint dose of haloperidol (1.2 ± 0.8 vs 1.8 ± 1.3 , $p = 0.08$).

Symptom improvement patterns

Figure 1 depicts the PANSS total scores at each assessment point for the remitted and non-remitted groups separately. Group differences in PANSS total symptom reduction were highly significant ($p < 0.01$). Both groups showed significant early (baseline to 6 week) reductions (remitters $p < 0.0001$; non-remitters $p < 0.0001$), although the remission group reductions were significantly greater than the non-remission group ($p = 0.004$). However, whereas the remitting group continued to improve thereafter to endpoint ($p < 0.01$), the non-remitters failed to do so ($p = 0.55$). To assess whether these early symptom changes included improvement in 'core' psychotic symptoms rather than just non-specific treatment effects, we compared composite scores for the eight PANSS items included in the remission criteria,¹⁴ at 6 weeks. Significant reductions were observed in both the remitter ($p < 0.01$) and non-remitter groups ($p < 0.01$).

The endpoint PANSS scores for remitters and non-remitters are given in Table 1. PANSS total scores for the remitted and non-remitted groups were 40.7 ± 9.5 and 65.9 ± 20.7 ($p < 0.01$), respectively. However, there was considerable overlap between the groups, and several non-remitting subjects had lower PANSS total scores than some of the remitters. (Some subjects with a low PANSS total score who did not meet remission criteria had a score of > 3 on just one of the PANSS remission items. On the other hand, one subject managed to meet the remission criteria with a PANSS total score of 72.) There were highly significant endpoint differences between the remitter and non-remitter groups for the negative, disorganized and psychosis factor scores. This was of course expected, as the remission criteria were specifically selected to represent these three symptom domains. However, while the excited factor scores also differed significantly between the groups, the depressive factor scores did not.

Predictors of remission

Differences between the remitters and non-remitters for the potential predictors that we evaluated are given in Table 2. After inspection of the data we excluded TD as a variable, because there were too few cases. Guarding against over-fitting, the initial best subsets discriminant analysis identified the following predictors: NES total score; DUP less than 1 yr; marital status; educational status; early treatment response; and PANSS excited factor baseline score. The model was able to correctly predict 92% of the remitters and 85% of the non-remitters in the train set, and 89% of the remitters and 86% of the non-remitters in the test set. For the SVM verification model five predictors were identified (NES total score; early treatment response; DUP less than 1 yr; marital status; and PANSS excited factor baseline score), that were able to correctly predict 92% of the remitters and 85% of the non-remitters in the train set, and 89% of the remitters and 86% of the non-remitters in the test set.

Discussion

Application of the remission criteria¹⁴ to our sample of first-episode patients demonstrates once again that the overall outcome in schizophrenia is poor, despite a favourable initial treatment response.^{8,10} The fact that 70% of all of our subjects achieved the cross sectional symptom reduction criteria for remission at some time attests to the efficacy of antipsychotic treatment in first-episode schizophrenia in the acute setting.¹³ However considerably fewer than half managed to maintain these criteria for 6 months, and even fewer until the completion of the trial - highlighting the need for improved maintenance strategies in the early course of the illness.

The fact that both groups showed early (6 week) symptom improvement, including that of core psychotic symptoms, suggests that remitters and non-remitters are difficult to differentiate in the early phase of treatment. More specifically, early clinical response does not necessarily imply ongoing improvement and sustained remission. Conversely however, a lack of early response is highly predictive of non-remission. This is in keeping with the findings in a multi-episode sample, where 100% of subjects not responding after 1 week of treatment failed to respond after 4 weeks of treatment.² While early non-response may accurately predict later poorer outcome in both first-episode and multi-episode patients, there may be important differences between these patients insofar as some first-episode patients appear to take longer to respond to treatment.²⁶ This has implications for practice guidelines recommending

the duration of treatment trials, and suggests that clinicians need to persist longer with a particular treatment in the case of first-episode psychosis.

The differences in symptom profiles at endpoint between remitters and non-remitters are of interest. As expected, significant differences were found in PANSS total scores at endpoint. However, the considerable overlap between the remitters and non-remitters shows that patients who improve on core symptoms may still have other residual symptoms requiring attention. The significance of this finding needs to be investigated further. Particularly, the persistence of some depressive symptoms in remitted patients counts against the proposal that depression is one of the core symptoms of schizophrenia insofar as they do not respond to antipsychotic treatment.²⁷ Also, these 'post-psychotic' depressive symptoms are likely to require clinical intervention, considering their association with poor social and vocational functioning²⁸ and increased risk of relapse²⁹

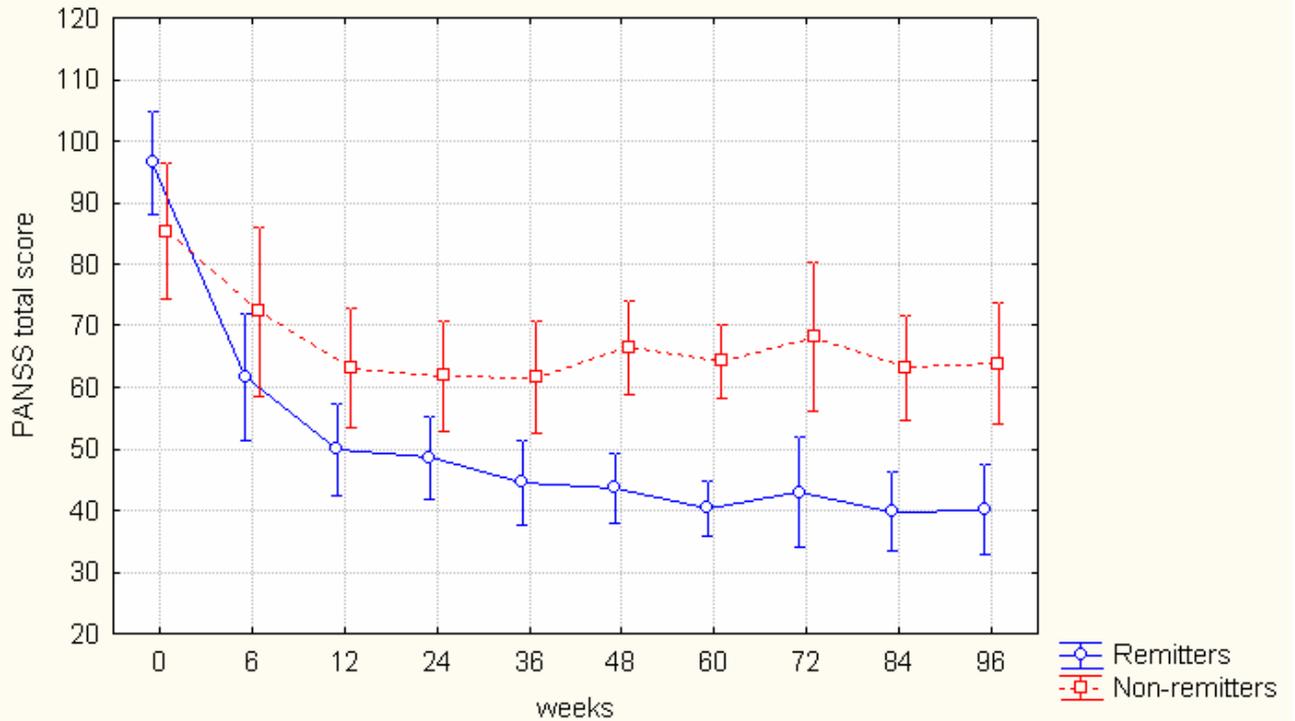
Our discriminate analysis findings suggest that a combination of certain baseline and early clinical response variables may be useful to clinicians in predicting outcome at an early stage of treatment. The predictor variables identified in our study were generally not unanticipated, as they have previously been linked with treatment outcome. The association between DUP and remission is consistent with many, although not all other studies showing a longer DUP to be associated with poorer outcome;³⁰⁻³³ neurological soft signs have been associated with poor treatment outcome;⁵ higher educational and positive marital status, as measures of good premorbid adjustment have been associated with a more favourable outcome;³⁴ and finally, early treatment response is well known to correlate strongly with later outcome.^{2,35} As was the case in a previous longitudinal study of patients with chronic schizophrenia, we failed to find significant associations between baseline psychopathology (other than the excitement/hostility factor) and outcome.⁸

In terms of their clinical usefulness, the predictor variables identified in our study are all easy to assess. In future, other variables not identified in this study may further refine our ability to predict treatment outcome. Strengths of this study are the uniform treatment protocol that was followed for all participants, the relatively long duration of follow-up and the fact that all subjects were assessed by the same investigator (PO). The study is limited by its post-hoc nature and the relatively small sample, compounded by the high attrition rate accompanying long-term studies such as this one. Also, no attempt was made to assess the role of compliance in our subjects. Given the high levels of non- and partial adherence to medication in first-episode samples,³⁶ persistent symptoms in the non-remitted subjects in our study could in part be explained on this basis. This is further supported by the finding that some previously "stable" non-remitted patients achieved symptom remission after receiving 'ensured' medication delivery, in the form of long-acting risperidone injection.³⁷ A further potential limitation is that this was a flexible dose study, and we did not investigate a possible role for dose of medication. However, the fact that both predictor models produced similar results, suggests that the accurate prediction of remission and non-remission based on the selected variables may be possible. Also, future studies should investigate the relationships between these operationally defined remission criteria and other measures of outcome.

In conclusion, this study provides further evidence that, in spite of a good initial response to antipsychotic medication, most patients do not maintain a state of sustained symptom improvement after a first episode of psychosis. Our findings also suggest that a combination of certain clinical and early treatment response variables may be useful in predicting later remission.

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Figure 1. Differences between remitters and non-remitters for the selected potential predictor variables.



Current effect: $F(9, 207)=7.7000, p=.00000$

Vertical bars denote 0.95 confidence intervals

Repeated measures analysis of variance. Only patients without missing values are included in this analysis.

Table 1. Mean±SD PANSS total and factor scores at 24 months for subjects who had achieved remission and those who had not.

Score at 24 months	remitters	non-remitters	p value
PANSS total	40.7±9.5	65.9±20.7	<0.01
Negative factor	9.1±3.4	15.4±6.0	<0.01
Disorganised factor	6.5±2.2	10.4±3.0	<0.01
Psychosis factor	5.1±1.9	10.0±4.6	<0.01
Excited factor	4.4±1.0	6.4±3.5	=0.02
Depression factor	4.5±2.3	4.5±2.2	=0.90

Table 2. Differences between remitters and non remitters for the selected potential predictor variables

Potential predictor	Remitters (n=19) ^a	Non-remitters (n=22) ^a	p value
Gender (male:female)	10:9	12:10	0.90
Race (black:white)	15:4	16:6	0.64
Employed (yes:no)	12:7	18:4	0.18
Ever married (yes:no)	8:11	5:17	0.18
Family history (yes:no)	7:12	7:15	0.74
DUP<1yr (yes:no)	18:1	14:8	0.01
EPS(yes:no)	7:12	9:13	0.79
TD(yes:no)	2:17	4:18	0.48
PANSS total % reduction at 6 wks	38±17	20±18	0.004
Age (yrs) ^b	27 (23-32)	32 (28-35)	0.14
PANSS total baseline ^b	97(89-104)	91(84-98)	0.26
PANSS positive factor ^b	17(16-18)	16(15-18)	0.32
PANSS negative factor ^b	14(11-17)	14(11-16)	0.97
PANSS disorganised factor ^b	13(12-16)	13(11-15)	0.47
PANSS excited factor ^b	11(10-13)	10(9-11)	0.26
CDSS baseline score ^b	3.5(1.9-5.1)	1.3(0-2.8)	0.05
NES total score ^b	4.6(2.9-6.4)	8.1(6.5-9.8)	<0.01
Educational level ^c	5.6(4.7-6.4)	5.6(4.8-6.4)	0.98
Diagnosis (schizophrenia: schizophreniform/schizo-affective disorder)	14:5	19:3	0.56

^a The sample size for the discriminant analysis model was 41

^b Values are given as mean (.95 confidence interval)

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3.a.v Remission in early psychosis: Rates, predictors, and clinical and functional outcome correlates

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Abstract

Background: Recently, the “Remission in Schizophrenia Working Group” proposed remission criteria consisting of a reduction to mild levels on key symptoms for at least 6 months.

Aims: This study applied these remission criteria to a large first-episode psychosis sample in order to (1) determine the rates of remission; (2) explore predictors of remission; and (3) test the external validity of these criteria.

Methods: We analyzed data from 462 subjects with a first-episode of psychosis who participated in a long-term, multinational, randomized, double-blinded trial of risperidone and haloperidol over 2 to 4 years.

Results: At some time point in the study 323 (70%) of the 462 subjects had a reduction to mild levels on the key symptoms as measured by the PANSS although only 109 (23.6%) maintained this level for at least 6 months thereby meeting remission criteria. The two strongest predictors of remission were shorter duration of untreated psychosis ($p=0.01$) and treatment response at 6 weeks ($p=0.001$). Compared to non-remitted patients, those in remission experienced greater improvement on all PANSS subscales ($p<.0001$), CGI-S ($p<.0001$), better quality of life ($p=0.006$), fewer relapses ($p<.0001$), displayed a more favorable attitude towards their medication ($p=.002$), had lower EPS levels according to the ESRS ($p<.0001$) and received lower doses of antipsychotic medication ($p=0.003$). The remission and non-remission groups did not differ significantly regarding composite cognitive scores, suicidality and body mass index.

Conclusions: The results suggest that the remission criteria, although based solely on core symptom improvement, can effectively identify patients who have a more favorable overall outcome.

Keywords: remission, schizophrenia, outcomes

Introduction

Notwithstanding the fact that subjects with a first-episode of schizophrenia generally respond well to antipsychotic treatment in the short term (Lieberman et al., 1993; Robinson et al., 1999), the overall outcome for this illness remains unsatisfactory. While some patients may experience a relatively circumscribed deterioration early in the illness, with stabilization thereafter, the majority of affected individuals do not. Recurrent relapses, often precipitated by partial or complete non-adherence to treatment, result in persistence of symptoms, accruing morbidity and enduring deficits in cognition and psychosocial function (Andreasen et al., 2005; Harrow and Jobe, 2005; Robinson et al., 2004). Estimates of outcome have varied considerably, ranging from very pessimistic in earlier studies to more optimistic in some recent studies (for a review see Jobe and Harrow (2005)). While these outcome differences may in part reflect the heterogeneity of the illness, they are also likely due to differences in

samples studied and methodologies employed. Efforts to accurately assess treatment outcome have been hampered by a multitude of methodological pitfalls, one of which has been a lack of standardized outcome measures. For example, many clinical trials report the degree of symptom reduction from baseline to endpoint as the primary efficacy measure. Others have defined criteria to assess rates of response (Schooler et al., 2005), relapse (Csernansky et al., 2002), remission (Lieberman, 1993) and recovery (Robinson et al., 2004). To further compound the problem, different cut-off scores and criteria have been employed across studies to assess these outcome measures.

In an attempt to standardize the definition for outcome in schizophrenia, a 'Remission in Schizophrenia Working Group' recently proposed operationally defined criteria for remission in schizophrenia (Andreasen et al., 2005). They defined remission as a state in which patients have experienced improvement to the extent that any remaining symptoms are of low intensity and no longer interfere significantly with behavior. These criteria define remission according to a threshold of severity for selected rating scale items representing the 'core features' of the illness. The items were selected to represent the 3 major symptom domains identified in factor analyses (negative, psychosis and disorganized factors) and the five criteria specified in DSM-IV for a diagnosis of schizophrenia. The proposed criteria define remission as absent, borderline or of mild symptom intensity level where such symptoms do not influence an individual's behavior. An additional requirement is that these criteria must have been met for a minimum duration of 6 months. The hope has been expressed that these criteria enhance the conduct and reporting of clinical investigations, and also reset expectations of treatment outcome to a higher level (van Os et al., 2006).

We applied the remission criteria to a sample of subjects with a early episode psychosis who participated in a long-term, multinational, randomized, double-blinded trial of risperidone and haloperidol. The sample was deemed very suitable for such an analysis because of its large size, the controlled nature of the study, utilization of standardized assessment tools, and the fact that subjects were followed over a long period from early in their illness. The aims of this post-hoc analysis were firstly, to determine the rates of remission after a first-episode of psychosis; secondly, to explore predictors of remission; and thirdly, to test the external validity of these criteria by comparing patients achieving remission with those who remained symptomatic, in terms of selected clinical, functional and quality of life outcome measures.

Methods

The study was conducted in 11 countries between November 1996 and January 2000. Patients were followed for between two and four years. Details of the study methodology and efficacy and safety results have been published elsewhere (Schooler et al., 2005).

Participants

The key inclusion criteria were age 16 to 45 years, having a DSM-IV diagnosis of schizophrenia, schizophreniform disorder or schizoaffective disorder for no more than 12 months, during which period they had no more than two psychiatric hospitalizations for psychosis, having persistent current psychotic symptoms requiring long-term antipsychotic treatment, and having had 12 weeks or less of cumulative lifetime exposure to antipsychotic medications. Exclusion criteria were meeting DSM-IV criteria for another Axis I diagnosis including substance dependence or abuse, requiring psychotropic medication other than an antipsychotic at enrolment, and having a serious or unstable medical illness. Approval was obtained from local Institutional Review Boards, and participants provided informed, written consent to participate in the study.

Five hundred and fifty nine patients from 11 countries were randomly assigned to receive either haloperidol or risperidone. For the purpose of this analysis we excluded 41 subjects, for the following reasons: Not receiving study medications (n=4); Good Clinical Practice violations (n=21); and missing baseline data (n=16). Additionally, 56 patients who at baseline had mild symptom levels on the key PANSS items used to define relapse were excluded, leaving a total sample of 462.

Two-hundred and sixteen (47%) subjects discontinued prematurely, for the following reasons: adverse events (n=30), insufficient response (n=41), ineligible to continue in the trial (n=4), lost to follow-up (n=36), non-compliant (n=13), withdrew consent (n=66), and other

reasons (n=26). As previously reported, the major efficacy findings in the original study were as follows: In both the risperidone and haloperidol treatment groups, the PANSS total and subscale scores and CGI scores improved significantly from baseline, with no significant differences between the treatment groups. Three-quarters of the patients achieved initial clinical improvement defined by more than 20% reduction in total PANSS score. Among those who achieved clinical improvement, 42% of the risperidone group and 55% of those in the haloperidol group experienced a relapse defined according to broad criteria (Csernansky et al., 2002) (Log rank=7.10, p=. 008) (Schooler et al., 2005).

Treatment

Subjects were randomly allocated to receive either risperidone or haloperidol after a 3 to 7 day drug washout period that was waived in extremely ill patients. A low-dosing strategy was followed, using equivalent doses of risperidone and haloperidol. Both treatment groups started with a once daily dose of 1 mg that was increased if necessary by 1 mg per day after 3 days, and thereafter by 1 mg per day each week, up to a maximum daily dose of 4 mg. In exceptional cases, the dose could be increased further by 1 mg a week up to a maximum daily dose of 8 mg. Thirty-one percent (n=163) of the participants had no previous exposure to antipsychotic medication. Participants were treated with trial medication for a mean of 381±426 days. The mean modal dose of risperidone was 3.3 mg and of haloperidol 2.9 mg. The median treatment duration was 206 days (maximum 1514).

Assessments

The investigators (N=49) and other designated raters underwent training for the assessment scales at investigator meetings prior to, and during the study. Psychopathology was assessed by means of the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) and Clinical Global Impressions (CGI) (Guy, 1976), which were completed weekly during the first four weeks and subsequently every four weeks (rating symptoms manifest at the time of the interview and for the previous week for the PANSS and ESRS). PANSS factors were derived according to a previous factor analysis conducted on this sample (Emsley et al., 2003). Quality of life (WQoL) was assessed using the Wisconsin QoL Index – Patient version (Becker et al., 1993). This self-administered questionnaire assesses nine separate domains that together encompass quality of life. We used the global score to compare remission and non-remission groups. Premorbid functioning was assessed with the Premorbid Adjustment Scale (PAS) (Cannon-Spoor et al., 1982) a 28 item rating scale that measures social isolation, peer relationships, functioning outside the family and school performance during four age periods (ages up to 11, 12-15, 16-18 and 19 and above), as well as social-sexual aspects of life starting at age 15 and a section of general items relating to various aspects of life. The PAS was completed on the basis of all available information, including patient interviews and collateral information. Using the scoring method developed by Cannon-Spoor et al (1982), average scores for each life stage were calculated by summing the item scores for each item in a section and dividing them by the possible score.

Patient attitudes towards treatment were evaluated by means of the self-report Drug Attitude Inventory (DAI) (Hogan and Awad, 2000). This is a 30-item inventory focusing on the subjective effects of antipsychotic medications in patients with schizophrenia. Neurocognitive performance was assessed by means of a composite score derived from a battery of neuropsychological tests (Wisconsin Card Sorting Test; Digit Symbol Test; California Verbal Learning Test or Ray Auditory Verbal Learning Test; Wechsler Memory Scale – Revised Visual Production and Verbal Fluency tests) (Harvey et al., 2005). Neurocognitive tests were performed at baseline, 3 and 6 months, and then at 6-monthly intervals. Extrapyramidal symptoms were evaluated by means of the Extrapyramidal Symptom Rating Scale (ESRS) (Chouinard and Margolese, 2005). The PANSS, CGI and ESRS were all rated at the same intervals, thus the exact evaluation point was used. The Wisconsin QoL and DAI were administered at week 1 (not the DAI), months 4, 8, 12 and then at 6-monthly intervals. The cognitive testing was done at baseline, after 3, 6 and 12 months and thereafter every 6 months following completion of the first year of the trial. Since 86% of patients achieving remission had done so by one year, the longest time between assessment of remission status and the other outcome measures was 2 months on Wisconsin QoL and DAI and 3 months on cognitive functioning.

Relapse was defined according to Csernansky et al (2002) criteria, which defines relapse as any one of the following occurring after clinical improvement, defined as 20% or greater decrease on PANSS total: (a) 25% or more increase in PANSS (or 10 points if the initial score is 40 or less); (b) CGI-C score of “much worse” or “very much worse”; (c)

deliberate self-injury; (d) emergence of clinically significant suicidal or homicidal ideation as a reported adverse effect; or (e) violent behavior resulting in significant injury to another person or significant property damage. Suicidality was assessed according to Adverse Event reporting.

Remission criteria

Remission consists of maintaining for at least 6 months a mild or lower level on 8 key PANSS items which are: delusions (P1), conceptual disorganization (P2), hallucinatory behavior (P3), blunted affect (N1), social withdrawal (N4), lack of spontaneity (N6), mannerisms/posturing (G5) and unusual thought content (G9) (Andreasen et al., 2005). Each PANSS item is rated on a scale of 1-7, with 1= absent, 2 = minimal or borderline and 3 = mild. For the remission group we included all participants who achieved remission at any stage in the trial, regardless of whether they were able to maintain this status for longer than 6 months until the study endpoint. For the non-remission group we included all subjects who never achieved remission despite having received antipsychotic treatment for an adequate treatment period which we defined as 9 months as it was the mean and median time to remission in the remission group.

Predictors of remission

The following variables were investigated for their potential as predictors of remission: Sex, age, age at onset of first symptoms, body mass index (BMI), previous antipsychotic treatment, duration of untreated psychosis (DUP), "good" vs. "poor" premorbid adjustment using Haas and Sweeney criteria (1992), trial medication treatment group (risperidone vs. haloperidol), mean dose of antipsychotic medication, and baseline PANSS factor scores (Emsley et al., 2003). DUP was defined as the time from the onset of overt hallucinations or delusions. The baseline interview had a special section in the case reporting form devoted to taking a detailed treatment and symptom history. Raters were trained in eliciting and recording this information. This section included an item noting the date of initiation of treatment with antipsychotic medication and an item noting estimated date of onset of first psychotic symptoms. These two items were used to compute DUP. Information was obtained using all available sources including patients, close family members, carers and psychiatric and medical records.

We also assessed the value of acute treatment response as a predictor of remission, as early lack of symptom reduction (after one week of treatment) has been shown to be highly predictive of later non-response (Correll et al., 2003). However, we decided to use a later assessment point (6 weeks) as a predictor variable, as the time to response has been found to vary widely in first-episode psychosis, with a substantial proportion of subjects being slow responders (Emsley et al., 2006). As defined in the study protocol and as reported in previous study publications (Schooler et al, 2005; Emsley et al, 2006), clinical response was defined as $\geq 20\%$ reduction in PANSS total scores.

Statistical analysis

All analyses were performed on an intent-to-treat basis. We created variables to indicate whether or not the 8 key PANSS remission items were rated as mild or lower at each measurement interval. An additional two variables were created, one indicating whether or not remission was attained as indicated by sustained mild or lower levels on the key PANSS items for 6 months, and the other indicating the time to first reduction to mild level on the 8 key PANSS items among patients who achieved remission. To examine the role of key variables as predictors of remission, Cox regression (a type of regression for survival analysis) was used. For those patients who met remission criteria, survival time was the first time symptom severity criteria were met, and for those not meeting remission criteria it was the end of the trial. The CHAID algorithm for recursive partitioning was used to examine the association of DUP and remission. Recursive partitioning in general and CHAID specifically construct trees, where each (non-terminal) node identifies a split condition, to yield optimum prediction (of continuous dependent or response variables) or classification (for categorical dependent or response variables). It has been previously used in schizophrenia research (Subotnik et al., 2005),

To test the external validity of the remission criteria patients achieving remission were compared with those who did not, in terms of selected clinical, functional and quality of life outcome measures using analysis of covariance (ANCOVA) and cross tabulations with Chi-square. For the purpose of this analysis we defined the remission group as those patients achieving remission, whether or not this was maintained until the end of the study. The remission group was compared to non-remitted participants who were in the trial for at least 9

months and never achieved remission. Nine months was chosen because it was the mean and median time to obtaining remission, in the remission group. This was to exclude those patients who did not achieve remission because they were not in the trial for a sufficient period of time. The measurement point used for the remission group was the first evaluation point that they achieved remission status, and for the non-remission group we used the last evaluation that was performed. Some of the scales were not assessed at all of the time points. For these, we took the one closest to the evaluation point for the non-remission group. For the remission group we did the same, with an additional requirement that the assessment had to be while they were in remission. All statistical tests were two-tailed. A significance level of 0.05 was used throughout.

Results

Remission rates

At some time during the study 323 (70%) of the 462 subjects had a reduction to mild or less on the key PANSS remission items. However, only 23.6% (n=109/462) were able to maintain this status for at least 6 months in order to meet the remission criteria, whereas 353 were not. Among those patients who met remission criteria (n=109), the mean time to first reaching remission symptom levels was $153 \pm$ SD 173 days. Of the 353 non-remission patients, 214 had at least one visit in which they met remission criteria. Of the 214, 38 were in remission for only 1 such visit and 58 for more than 1 visit, although not consecutively. Of the 176 who were in remission for at least 2 consecutive visits, the median time in remission was 1.5 months (69 had 1.5 months or less, 39 had 2 to 4 months and 10 had between 4 and 6 months).

Baseline characteristics of the remission and non-remission groups are provided in Table 1. There was a significant difference between the groups in terms of diagnostic distribution, with a higher proportion of schizophrenia in the remission group. Also, compared with the non-remission group, patients in remission had a shorter DUP; the PANSS negative factor score at baseline was 1.5 points lower; and they expressed greater medication satisfaction (DAI) at month 4.

Predictors of remission

Since there were differences in the length of stay in the trial between the diagnostic groups (with schizoaffective and schizophreniform patients spending less time in the trial), separate Cox regression survival analyses were conducted for patients with a diagnosis of schizophrenia on the one hand, and those with a diagnosis of schizoaffective/schizophreniform disorder on the other. The predictor variables examined and the results at the bivariate level are presented in Table 2. As can be seen the only variable to be associated with remission in both diagnostic groupings was DUP. This was followed by a stepwise (forward) analysis which found significant effects for DUP in both the schizophrenia (OR=.83 [.72; .95], Chi-square=7.02, p=.008) and the schizophreniform/schizoaffective group (OR=.66 [.45; .97], Chi-square=4.50, p=.03). The other significant predictors were, for the schizophrenia group, the negative symptom factor (OR=.95 [.92; .98], Chi-square=10.50, p=.001) and for the schizophreniform/schizoaffective group age at onset of first psychotic symptoms (OR=1.10 [1.03; 1.16], Chi-square=9.44, p=.002). There were no differences between the treatment groups regarding remission rates or time to remission.

To further explore the relationship between DUP and remission we performed recursive partitioning, a procedure designed to determine optimal cutting points. The most suitable DUP cutting point for the schizophrenia group was 391 days (21% of the patients had a DUP of at least this duration). Of the subjects with a DUP of \leq 391 days, 33% achieved remission as compared to only 18% of those with a DUP > 391 days. As premorbid adjustment and baseline symptom severity have both been proposed as possible confounders for the DUP effect (Marshall et al., 2005; Verdoux et al., 2001), we re-ran the Cox regression model adjusting for total PANSS scores at baseline and premorbid adjustment, age and sex. The significant effect for DUP was found to be independent of these two variables in both the schizophrenia group (p=0.01) and schizoaffective/schizophreniform group (p=0.02).

Another round of analyses was performed to test whether early clinical response (defined as \geq 20% reduction on PANSS at 6 weeks) could predict remission. In a Cox regression equation controlling for baseline PANSS scores, response at 6 weeks was found

to be a significant predictor of remission in both the schizophrenia groups (OR=1.72 [1.06; 2.77], Chi-Square=10.19, p=.001) and the schizo-affective/schizophreniform group (OR=5.25 [1.90; 14.52], Chi-Square=10.19, p=.001). Survival curves for the time to remission for the responders vs. non-responders at 6 weeks are depicted for the schizophrenia group (Figure 1a) and the schizoaffective/schizophreniform group (Figure 1b) respectively. Interestingly, a considerable number of non-responders at 6-weeks in the schizophrenia went on to achieve remission later, in contrast to the schizo-affective/schizophreniform group where almost all of the non-responders did not achieve remission.

Clinical and functional outcome correlates of remission and non-remission

Table 3 depicts the differences between subjects who achieved remission and those who did not, despite sufficiently long study drug exposure, for the selected clinical and functional outcome variables. As expected, the remission group showed greater reductions in PANSS total scores, as well as in all of the 5 PANSS factor domains and CGI. Patients in remission also reported much greater improvement in QoL, had fewer relapses (as per criteria used elsewhere (Csernansky et al., 2002)), displayed a more favorable attitude towards their medication, received lower doses of antipsychotic medication and had lower levels of extrapyramidal symptoms. The only variables that did not show a significant difference between the groups were suicidality, the composite neurocognitive score, BMI and treatment group. Figure 2 portrays the time to relapse for patients achieving remission compared with those who did not. Differences were highly significant (Chi-sq 29; df=1; p<0.0001). After 90, 180, 270, 360, and 450 days respectively, the cumulative proportion of patients relapsing for the remission group was 16%, 18%, 21%, 26% and 30% and for the non-remission group 37%, 50%, 60%, 67% and 72%.

Discussion

The fact that the majority (70%) of the participants in this study managed to achieve a rating of mild or less on the 8 key PANSS remission items representing the core symptoms of schizophrenia at some stage in the trial, confirms the efficacy of antipsychotic medication in first-episode psychosis in the short term (Lieberman et al., 1993; Robinson et al., 1999). The mean time to first reduction on these items of about 5 months is consistent with our previous finding that some first-episode patients take a considerable period of time to respond to treatment (Emsley et al., 2006), in contrast to the rapid onset of action that has been reported in multi-episode subjects (Agid et al., 2003; Kapur et al., 2005; Leucht et al., 2005). But despite the favorable initial response, only one in three of our subjects who achieved symptom reduction were able to maintain a relatively asymptomatic state for at least 6 months to meet remission criteria. While this, and other randomized controlled trials, may not accurately reflect a "real world" setting, (Wahlbeck et al., 2001), our results seem to once again highlight the shortcomings of oral antipsychotic medication, emphasizing the need for improved maintenance strategies after a first-episode of schizophrenia. One likely important variable is non- or inadequate adherence to medication, which has been reported in almost 59% of patients 12 months after a first psychotic episode (Coldham et al, 2002). In a similar vein the "CATIE" study, reported rates of treatment discontinuation over 18 months ranging from 64% to 82%, and the authors concluded that, although effective in symptom reduction, antipsychotic drugs have substantial limitations in their overall effectiveness in patients with chronic schizophrenia (Lieberman et al., 2005; Stroup et al., 2006)

The low remission rate reported in our sample would at first glance appear to differ considerably from rates reported in other studies such as Malla et al (2006) (82.2%) and Lieberman et al (2003) (80%). However, in the Malla et al (2006) study remission was defined as the absence of psychotic symptoms lasting at least 1 month, and the Lieberman et al (2003) study remission was defined as a 50% reduction in total BPRS score and no score > mild on the 5 BPRS psychosis items, with no temporal requirement. These studies are therefore consistent with our own findings of high rates of acute symptom improvement. Another recent study reported a somewhat better outcome in their first-episode sample, with 47.2% achieving remission within 5 years (Robinson et al, 2004). Remission in this study required a symptom reduction level of mild or less on positive and disorganized symptoms, moderate or less on selected negative symptoms, and a duration of 2 years. However, only a quarter of the subjects achieved sustained social/vocational recovery, and only 13.7% met criteria for full recovery.

The most significant predictors of remission in this study were a shorter DUP and an early (6 wk) response to treatment. The finding of female sex being associated with better

outcome is in keeping with previous work (Angermeyer et al., 1990; Robinson et al., 1999; Seeman, 1986), as is an association between negative symptoms and poorer outcome (The-Scottish-Schizophrenia-Research-Group, 1987). However, baseline levels of psychopathology were not associated with outcome in other studies (Breier et al., 1991; Robinson et al., 1999), although depressive symptoms have been (Emsley et al., 1999; Oosthuizen et al., 2002). Our DUP results add to an already substantial literature supporting a relationship between DUP and treatment outcome (Marshall et al., 2005; Perkins et al., 2005). Our results also support the view that DUP is an independent predictor variable, not confounded by premorbid adjustment level or baseline symptom severity (Marshall et al., 2005). This is of considerable importance, as DUP is one of few prognostic indicators that are potentially modifiable. Finally, early treatment response is well known to correlate strongly with later outcome (Correll et al., 2003; Stern et al., 1993) and symptom levels after acute treatment have been proposed as a critical predictor of outcome (Breier et al., 1991). Our results suggest that this relationship is stronger in patients with a diagnosis of schizo-affective or schizophreniform disorder, while some patients with schizophrenia who achieve remission seem to respond more slowly. It could be that combining these two variables (DUP and early treatment response) may increase their predictive power to a level where they could be useful clinical tools in the early identification of patients who are non-responsive to first-line antipsychotic treatment. Future studies could explore such a possibility.

Our findings contribute to the validation of the remission criteria proposed by the Remission in Schizophrenia Working Group (Andreasen et al., 2005). Although based on core symptom reduction only, the criteria appear to effectively identify patients who do well on several other outcome measures. These patients report a better quality of life, display a more favorable attitude towards their medication, have lower levels of “non-core” symptoms (excitement/hostility and depression/anxiety), require a lower dose of antipsychotic medication, and experience fewer extrapyramidal symptoms and fewer relapses.

Our failure to demonstrate significant differences in cognitive performances between the remission and non-remission groups was surprising, considering a previously reported association between cognitive function and treatment outcome (Addington and Addington, 1993). One possible explanation is that, due to the high discontinuation rate, the trial did not have sufficient power to detect differences between the groups. However, an alternative explanation is that cognitive deficits are independent of the core symptoms of psychosis, and reflect a more enduring trait-like status (Lieh-Mak and Lee, 1997). This possibility was proposed by Auslander and Jeste (2004) when they similarly failed to demonstrate significant differences in cognitive performance between older patients with sustained remission compared with symptomatic controls, although Kopelowicz and co-workers reported differences between recovered schizophrenics and matched controls (Kopelowicz et al., 2005).

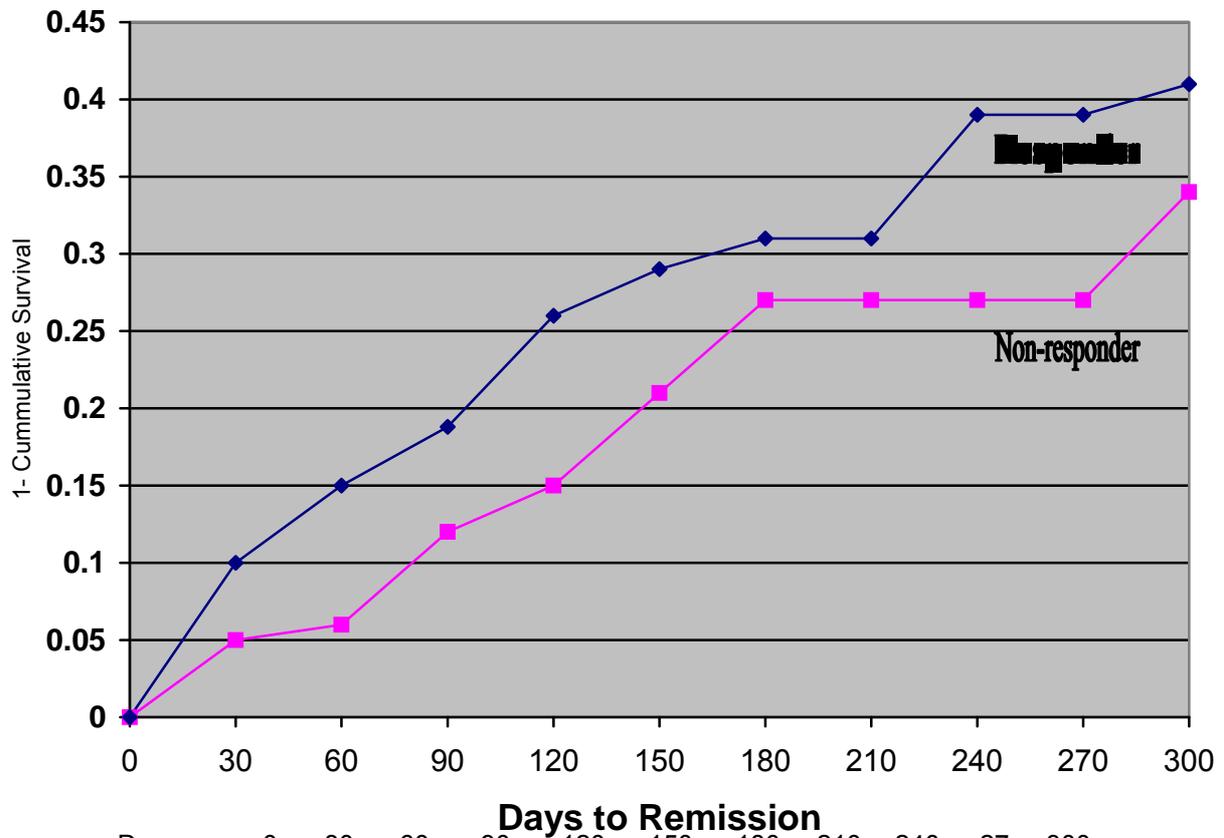
The lower mean daily dose of antipsychotic medication in patients in remission does not necessarily mean that lower antipsychotic doses are more effective than higher doses. More likely, it may reflect increases in doses in patients who failed to respond sufficiently. While the lower ESRS scores in patients in remission are consistent with the lower antipsychotic dose that they received, the similar increases in BMI between the remission and non-remission groups are not. The latter finding could be explained by the fact that the subjects in remission tended to stay in the trial longer, thereby being exposed to more antipsychotic treatment days. Another probable contributory factor is that the non-remitting patients were likely to have been less adherent to antipsychotic medication, thereby having less exposure to the weight-gain effects of antipsychotics. This would not be surprising, considering that 59% of patients are either non-adherent or inadequately adherent 12 months after a first-episode of psychosis (Coldham et al., 2002), and psychotic symptoms are likely to emerge in the majority (Gitlin et al., 2001).

There are several aspects of this study that limit the generalisability of our findings. One difficulty was in choosing the most suitable endpoints to compare the remission and non-remission groups because those who achieved remission did so at different times during the study. This resulted in different treatment durations for the remission and non-remission groups, which could have influenced some of the group comparisons of outcomes. Also, it could be expected that patients who remained in remission would continue to show improvement in outcome measures beyond the 6 months. This may have biased against the remission group achieving an even better outcome, and more treatment side-effects. Further, the involvement of many investigators posed challenges for standardizing the rating

instruments. To minimize these problems, training courses were conducted at the start of, and during the study. (While inter-rater reliability assessments were not conducted, investigators were required to attain a high level of agreement with a videotaped interview.) Also, there may be difficulties in comparing patients across countries due to service provision and cultural differences. Another limitation was the reduced sample sizes at later assessment points in the study due to the high dropout rate that occurs in long-term trials such as this one (Wahlbeck et al., 2001). It could also be argued that, by excluding patients who met cross-sectional remission criteria at baseline, we omitted patients with the most favorable prognosis. This would not explain the poor outcome that we observed however, as the majority of patients were able to achieve cross sectional reduction – the problem was in the *maintenance* thereof.

In conclusion, this study provides further evidence for a favorable acute effect for antipsychotics in treating early episode psychosis, but highlights the failure of the medication to maintain this improved status. DUP and early treatment response are two promising predictors of outcome. Finally, those patients who achieved remission according to the proposed operational criteria (Andreasen et al., 2005) also displayed a better overall outcome in terms of various functional and quality of life measures.

Figure 1a. One minus survival curve for time to remission for patients achieving a clinical response at 6 weeks vs. those who did not, for patients with a diagnosis of schizophrenia



		Days to Remission										
Day		0	30	60	90	120	150	180	210	240	270	300
NO. AT RISK												
Responder		123	119	106	88	79	70	58	55	51	45	39
Non-responder		124	163	129	102	75	22	61	31	1	0	0
NO. WITH RELAPSE												
Responder		0	6	9	14	17	31	27	27	27	27	31
Non-responder		0	44	63	79	90	94	97	104	112	112	112

Figure 1b. One minus survival curve for time to remission for patients achieving a clinical response at 6 weeks vs. those who did not, for patients with a diagnosis of schizoaffective or schizophreniform disorder

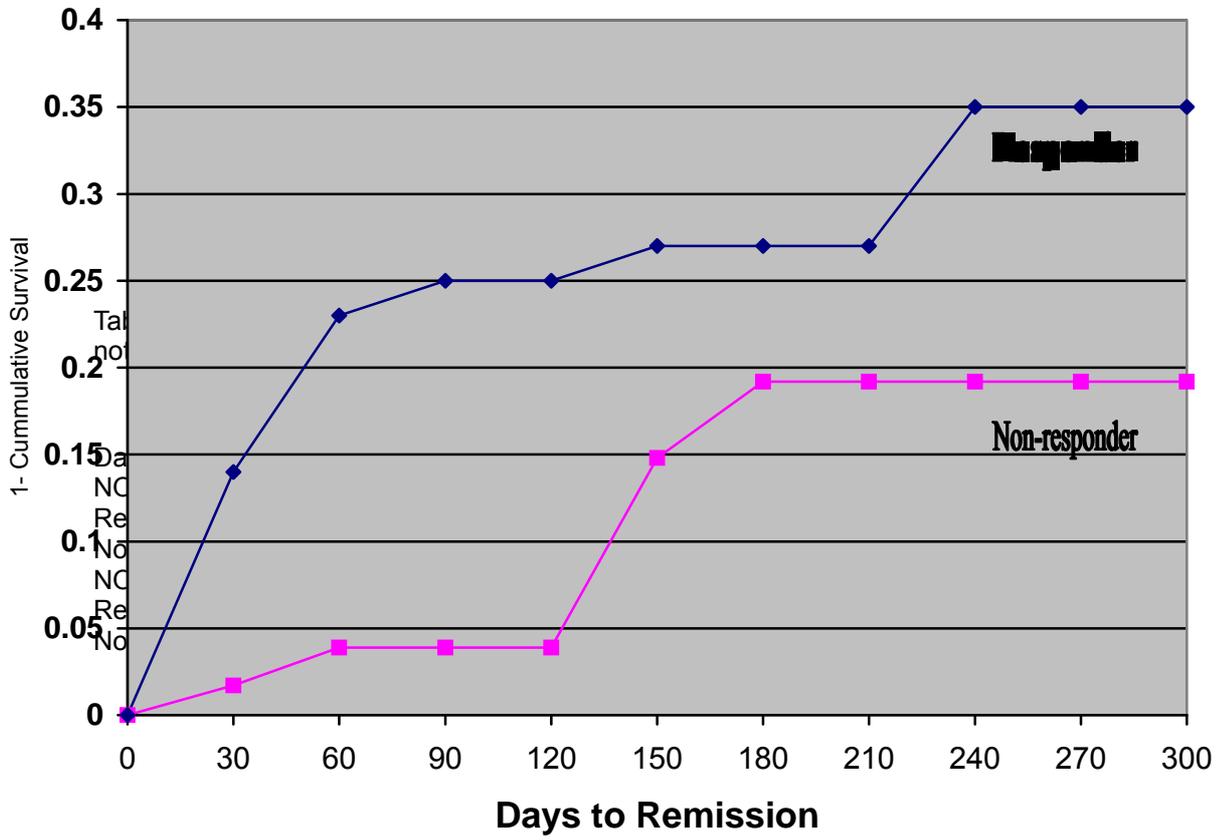


Table 2. Results of the Cox regression bivariate analysis of potential predictor variables of remission, for the diagnostic groups of schizo-affective/schizophreniform disorder and schizophrenia.

Characteristic	Remission Group (n=109)	Non-remission Group (n=353)	
Male sex (n, %)	n=74, 67.9%	n=259, 73.4%	$X^2=1.24$, df=1, p=.26
Race or ethnic group (n, %)			
White	N=85, 78%	n=253, 71.7%	$X^2 =5.5$, df=3, p=.14
Black	n=53, 15.0%	n=7, 6.4%	
Hispanic	N=4, 3.7%	n=11, 3.1%	
Other	N=9, 8.3%	n=30, 8.5%	
Mean age (yr)	25.5 sd 6.14 n=109	25.2 sd 6.88n=353	T=.34, df=460, p=.73
DSM-IV diagnosis (n, %)			$X^2 =11.4$, df=2, p=.003
Schizophrenia	n=85, 78.0%	n=215, 60.9%	
Schizoaffective disorder	N=3, 2.8%	n=30, 8.5%	
Schizophreniform disorder	n=21, 19.3%	n=108, 30.6%	
Antipsychotic naïve (n, %)	n=34, 31.2%	n=122, 34.7%	$X^2 =.45$, df=1, p=.50
Duration of untreated psychosis	Mean: 272.5 sd 576.0	Mean: 535.0 sd 1246	T=3.03, df=393.4,
PANSS Total score (mean, SD)	82.6 sd 16.6 n=109	85.4 sd 16.9 n=353	T=1.53, df=460, p=.13
PANSS positive factor (mean, SD)	26.6 sd 6.4 n=109	26.1 sd 6.32 n=353	T=.74, df=460, p=.46
PANSS negative factor (mean, SD)	19.9 sd 6.5 n=109	21.5 sd 7.0 n=353	T=2.03, df=460, p=.04
PANSS disorganization (mean, SD)	18.0 sd 5.3 n=109	19.1 sd 5.7 n=353	T=1.73, df=460, p=.08
PANSS excitement (mean, SD)	7.5 sd 3.3 n=109	7.8 sd 3.4 n=353	T=0.88, df=460, p=.38
PANSS depression (mean, SD)	10.5 sd 3.5 n=109	10.9 sd 3.7 n=353	T=0.99, df=460, p=.32
CGI-S score (mean, SD)	4.57 sd .89 n=109	4.59 sd .87 n=353	T=.18, df=460, p=.86
Wisconsin QoL score (mean, SD)	.48 sd .96 n=64	.41 sd .84 n=202	T=.56, df=264, p=.57
Premorbid adjustment scale scores (mean, SD)	.36 sd .14 n=109	.38 sd .15 n=349	T=1.17, df=456, p=.24
DAI score (mean, SD) (Month 4)	4.19 sd 4.47 (n=94)	2.92 sd 4.66 (n=132)	T=2.05, df=224, p=.04
Composite neuro-cognitive z-score (mean, SD)	-.08 sd .61 n=106	-.01 sd .77 n=335	T=0.18, df=460, p=.86
ESRS total score (mean, SD)	3.20 sd 4.22 n=109	3.40 sd 4.63 n=351	T=.39, df=458, p=.70
BMI (mean, SD)	23.6 sd 4.3 n=108	23.4 sd 5.2 n=346	

	Schizoaffective-Schizophreniform (n=162)		Schizophrenia (n=300)	
	Chi-Square	P	Chi-Square	P
Age	6.06	0.01	1.34	0.25
Age of onset	9.58	0.00	0.00	0.96
Sex	0.20	0.66	5.81	0.02
BMI	0.01	0.93	1.89	0.17
Previous antipsychotic exposure	0.20	0.66	0.94	0.33
Duration of untreated psychosis	3.90	0.05	6.24	0.01

(logged)				
Mean dose	3.99	0.05	0.92	0.34
Treatment group	0.17	0.68	0.18	0.67
Premorbid functioning	1.74	0.19	3.03	0.08
Positive symptom factor	0.46	0.50	0.07	0.79
Negative symptom factor	1.98	0.16	9.92	0.00
Disorganized thoughts factor	0.94	0.33	5.52	0.02
Excitement/ hostility factor	0.11	0.74	0.06	0.80
Depression/anxiety factor	0.85	0.36	0.48	0.49

Table 3. Comparison of clinical, functional and quality of life measures for the patients who achieved remission vs. those who did not and who had at least 9 months of treatment

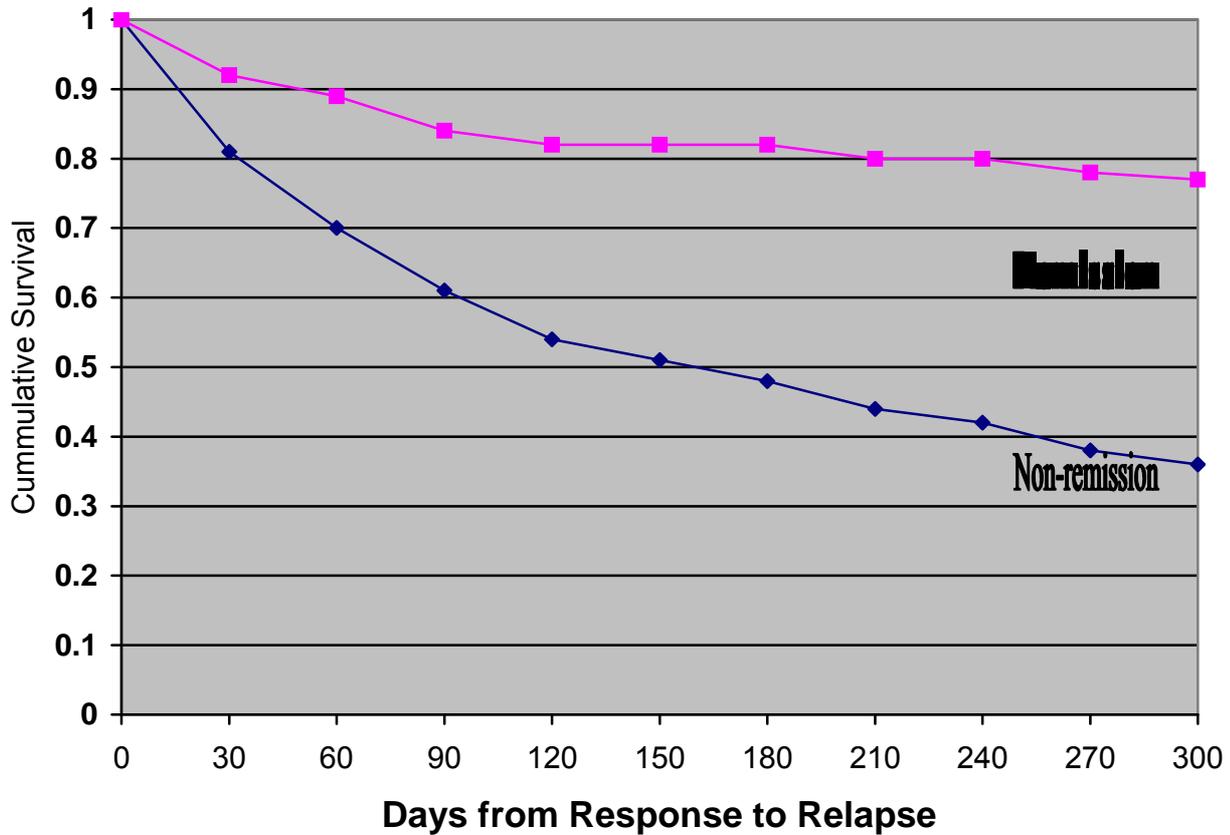
	Remission group (at time of first meeting remission criteria)	Non-remission group (at study endpoint)	P value
Wisconsin Quality of Life scale, change from baseline ¹	0.72 (0.11) n=60	0.30 (0.10) N=57	P=0.006
Drug attitude inventory, change from baseline ¹	4.84 (.38) n=103	3.51 (.45) N=90	P=0.02
Composite neuro-cognitive z-score, change from baseline ¹	.02 se .06 n=103	.04 se .06 N=92	P=0.81
Antipsychotic dose after 12 months of treatment (mg/d) ¹	2.99 (.17) n=106	3.81 (.21) N=93	p=0.003
PANSS total score, change from baseline ¹	-41.0 (1.39) n=106	-22.8 (1.49) n=93	p<.0001
PANSS positive factor score change from baseline	-14.7 (.49) n=106	-10.3 (.53) N=93	p<.0001
PANSS negative factor score change from baseline	-9.46 (γ .56)n=106	-3.56 (.56) N=93	p<.0001
PANSS disorganization factor score change from baseline	-9.05 (.39) n=106	-4.87 (.41) n=93	p<.0001
PANSS excitement/hostility factor score change from baseline	-3.02 (.20) n=106	-1.90 (.21) N=93	p<.0001
PANSS depression/anxiety factor score change from baseline	-4.44 (.27) n=106	-2.45 (.29) N=93	p<.0001
CGI-S score, change from baseline ¹	-2.49 (.10) n=106	-1.52 (.11) N=93	<0.0001
ESRS total score change from baseline ¹	-.97 (.45) n=106	1.62 (.48) N=93	P<.0001
Relapse rates (%) ²	34.0% n=36/106	63.2% n=55/87	0.0001
Body mass index change from baseline (Kg/M ²) ¹	3.21 (.33) n=105	3.00 (.35) n=91	p=.66
Suicidality (%) ³	6.6% n=7/106	8.6% n=8/93	0.59

¹ Mean (standard error) when covariates included adjusted mean presented.

² According to the criteria of Csernansky et al (8), only patients achieving clinical response (20% decrease on PANSS).

³ Serious suicidal ideation or attempts, reported as adverse events.

Figure 2. Survival curve for time to relapse from time of clinical response for patients achieving remission vs. those who did not.



Day	0	30	60	90	120	150	180	210	240	270	300
NO. AT RISK											
Remission	197	101	96	89	87	86	85	83	80	79	75
Non-remission	240	163	129	102	75	59	61	31	1	0	0
NO. WITH RELAPSE											
Remission	0	55	66	70	72	76	78	80	80	80	82
Non-remission	0	44	63	79	90	94	97	104	112	112	112

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3.a.vi Differential effect of quetiapine on depressive symptoms in patients with partially responsive schizophrenia

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Abstract

While atypical antipsychotics appear to be effective in reducing depressive symptoms in the acute phase of schizophrenia, little is known about their efficacy in patients with ongoing symptoms. The present study assessed whether quetiapine (Seroquel[®]) is more effective than haloperidol in treating depressive symptoms in patients with persistent positive symptoms, and investigated whether this effect is independent of, or secondary to, reductions in other symptoms such as positive, negative or extrapyramidal symptoms (EPS). Patients with schizophrenia and a history of partial refractoriness to conventional antipsychotics who had not responded to 4 weeks' fluphenazine treatment (20 mg/day) were randomised to receive either quetiapine (600 mg/day) or haloperidol (20 mg/day) for a further 8 weeks. Change in the PANSS depression factor score from baseline to endpoint was calculated and path analyses were performed on data from 269 patients. Quetiapine produced a greater reduction in depressive scores than haloperidol (-1.60 vs -0.54; $p=0.006$). The path analyses indicated that this was a direct effect on depressive symptoms. These findings extend the evidence for an antidepressant effect for the novel antipsychotics in schizophrenia, and suggest that this is not limited to acutely psychotic patients.

Key Words: Quetiapine, haloperidol, schizophrenia, depression, clinical efficacy

Introduction

Symptoms of depression are common in schizophrenia, the prevalence having been reported at between 7% and 70%, depending on the samples studied and criteria applied (Barnes *et al.*, 1989; Siris, 1991). They are often not easy to recognise, as they may mimic negative symptoms (Tollefson *et al.*, 1998a), neuroleptic-induced akinesia (van Putten and May, 1978) or akathisia (van Putten and May, 1975). There are numerous factors that could produce depressive symptoms in schizophrenia, such as a psychological response to the illness and its accompanying adverse life events (Birchwood *et al.*, 1993), substance abuse (Tollefson *et al.*, 1998a), co-morbid major depressive disorder or anxiety disorders, and neuroleptic-induced dysphoria (Harrow *et al.*, 1994). It is also possible that depressive symptoms represent a core feature of the schizophrenic illness itself (Johnson, 1981; Koreen *et al.*, 1993). The majority of depressive symptoms appear to occur concurrently with the acute psychotic symptoms, and resolve as the psychosis remits (Koreen *et al.*, 1993). Although not clear-cut, the presence of depressive symptoms in the acute phase of the illness may be associated with a favourable outcome (Kay and Lindenmayer, 1987; Siris, 1991). However, there are patients with schizophrenia who experience persistent depressive symptoms that are not responsive to conventional antipsychotic treatment alone. A depressive syndrome was found in 12.9% of patients with chronic schizophrenia, and these symptoms persisted beyond 3 months in 60% of the subjects. (Barnes *et al.*, 1989). Persistent depressive symptoms may be particularly important, considering their association with poor social and vocational functioning (Mandel *et al.*, 1982; McGlashan and Carpenter, 1976), increased risk of relapse (Birchwood *et al.*, 1993) and suicide (Roy *et al.*, 1983). Therefore, when present in the chronic course of schizophrenia, depressive symptoms appear to be negative prognostic indicators (Mandel *et al.*, 1982; McGlashan and Carpenter, 1976).

Recently, there has been renewed interest in depression in schizophrenia and it is now recognised that these symptoms may be an important target for treatment. Owing to their novel pharmacological profiles, and particularly their serotonergic effects, the atypical antipsychotics could be valuable in treating these symptoms. Indeed, considerable supportive evidence exists. Clozapine decreases suicidality in treatment-refractory schizophrenia (Meltzer and Okayli, 1995; Walker *et al.*, 1997), and exerts mood-stabilising thymoleptic properties in treatment-refractory schizophrenia, schizo-affective disorder and psychotic mood disorder (McElroy *et al.*, 1991; Suppes *et al.*, 1992; Zarate *et al.*, 1995; Calabrese *et al.*, 1996). There is also evidence of an effect on depressive symptoms in schizophrenia for risperidone (Marder *et al.*, 1997), olanzapine (Tollefson *et al.*, 1998a; Tollefson *et al.*, 1998b), and quetiapine (Arvanitis *et al.*, 1997). While these results are encouraging, they were conducted in samples with acute exacerbations of schizophrenia, ie those patients in whom the depressive symptoms would be expected to respond to antipsychotic treatment (Koreen *et al.*, 1993). It is also important from a clinical point of view to assess the efficacy of the atypical antipsychotics in treating depressive symptoms other than those associated with acute psychotic exacerbations. An important group of patients are the partial responders, in whom positive symptoms persist after conventional antipsychotic treatment (Breier *et al.*, 1994). These patients represent the majority of schizophrenic patients that a practising psychiatrist is likely to treat (Weiden *et al.*, 1996) and a group at risk for persistent depressive symptoms (Barnes *et al.*, 1989). We recently reported the results of a multinational controlled trial in which the efficacy and tolerability of quetiapine (Seroquel®) and haloperidol were compared in such a group of patients (Emsley *et al.*, 2000). The present study examined the efficacy of quetiapine compared with haloperidol in reducing depressive symptoms in this sample, and assessed whether any beneficial effects observed were related to the improvement in positive symptoms, negative symptoms or extrapyramidal symptoms (EPS).

Methods

Patients and study design

This was a multicentre, double-blind, randomised trial comparing the use of quetiapine and haloperidol in patients with no more than a partial response to conventional antipsychotic treatment. A detailed description of the study design, patient selection criteria, and efficacy and safety measures has been reported elsewhere (Emsley *et al.*, 2000), and so will only be briefly described here. Patients meeting DSM-IV (American Psychiatric Association, 1994) diagnostic criteria for schizophrenia and who had a history of only partial response to conventional antipsychotics (defined as persistent positive symptoms while previously taking therapeutic doses of antipsychotics) were subjected to a 4-week active run-in treatment phase with fluphenazine (20 mg/day). Those patients showing either no response, or only a partial response to the fluphenazine treatment (defined as <30% reduction in the Positive and Negative Syndrome Scale (PANSS) total score), were randomised to receive either quetiapine (600 mg/day) or haloperidol (20 mg/day). Doses were titrated over a 7-day period, and then fixed for the next 7 weeks. Key exclusion criteria included severe resistance to conventional antipsychotics, known nonresponders to clozapine, and an acute psychotic exacerbation within the past 3 months.

Clinical outcome

Depressive symptoms were measured by means of the depressive factor identified by Kay (Kay, 1991) in his original factor analysis of the PANSS and used subsequently in other studies (Marder *et al.*, 1997; Emsley *et al.*, 1999). The PANSS depressive factor has been found to correlate strongly with other scales specifically designed to measure depressive symptoms (El Yazagi *et al.*, 2002). This factor comprises the composite score for the PANSS items of somatic concern (G1), anxiety (G2), guilt feelings (G3), and depression (G6). All analyses were performed on the intent-to-treat (ITT) population using the last value carried forward (LVCF). Scores were calculated for the patient's baseline assessments (Week 4) and their final assessments either at withdrawal or Week 12 (endpoint). The change in the composite PANSS depression factor score from the patient's baseline to their final or endpoint score was calculated. These changes from baseline were used in analyses of covariance (ANCOVA) of the difference between the two treatments, with the covariate being baseline factor score. Response rates, defined as the proportion of patients with a reduction

of $\geq 20\%$, $\geq 30\%$, $\geq 40\%$ and $\geq 50\%$ in the depression factor score, were considered by logistic regression, including pooled centre as covariate (LVCF on ITT population).

In order to assess the treatment effect on depressive symptoms in those patients with more prominent symptoms, all of the analyses were repeated on patients with a baseline PANSS depression factor score of ≥ 8 (ie an average score of ≥ 2 for each of the four items, with a score of 2 indicating the definite presence of that symptom).

Path analyses

Path analysis (Retherford, 1993) as an analysis of psychiatric data was popularised by Moller and co-workers (1995) to estimate to what degree the effect of an antipsychotic on a specific symptom domain (in this case depressive symptoms) is mediated by its effects on other symptoms (positive symptoms, negative symptoms or extrapyramidal symptoms [EPS]). In comparison with linear or multiple regression, path analysis allows the response variable to be affected both directly by the predictor variable and indirectly through one or more intervening variables, and allows the analysis of possible causal relationships. In this case it can be estimated whether there is a 'direct effect' of treatment on depressive symptoms. Path analyses were performed on the depression factor in order to explore whether the differential effects of quetiapine and haloperidol on depressive symptoms could be attributed to differential effects on other symptoms. Change from baseline in the depression factor score was the response variable and change from baseline in the PANSS positive subscale score, negative subscale score and Simpson–Angus Scale score were the intervening variables. These variables were intended to represent positive symptoms, negative symptoms and EPS, respectively.

Figure 1 provides a simple diagrammatic representation of the path analysis. Baseline scores were also included in the 'Path Model', but are omitted from the diagram for clarity. The path co-efficients were calculated by simultaneous linear regressions of the individual paths. Hence the total effect of treatment on depressive symptoms ($[P1 \times P5] + [P2 \times P6] + [P3 \times P7] + P4$) was calculated. The direct effect (P4), and the contributions from the indirect paths, were compared by calculating the percentage of the total effect accounted for by each individual path. Only those patients whose final PANSS and final Simpson–Angus scores were measured during the same week were analysed. The analyses were designed so that positive coefficients implied a better result for quetiapine, in terms of a larger difference from baseline compared with haloperidol.

Path analysis is a statistical approach based on multiple regression analysis developed to differentiate between the direct and indirect effects of antipsychotic drugs on specific symptoms. It has often been used to assess the effect of antipsychotic medication on negative symptoms (eg. Kopelowicz *et al.*, 2000), and depressive symptoms (Tollefson *et al.*, 1998a; Tollefson and Anderson, 1999). In brief, the analysis was based on the assumptions of weak causal order and causal closure. The first of these two assumptions tells us that, given any two variables such as x and y , it is known or assumed that x may affect y but that y cannot affect x . The second tells us that the covariance between the two variables x and y is solely the result of the direct causal relationship of one on the other or to other variables that are included in the model. If either a variable or a connection between variables is missing from the model, then the model itself is incorrect and inadequate and the required assumptions have been broken. It has been pointed out that the path analysis method is limited by how completely the model identifies relevant variables and relationships between them. The validity of this technique rests on the assumption that all relevant 'causes' have been included (Kopelowicz *et al.*, 2000),

Results

A total of 365 patients were recruited into the fluphenazine run-in phase. Of these, 288 (78.9%) were randomised to treatment with either quetiapine ($n=143$) or haloperidol ($n=145$). Seventy-seven patients were not randomised for the following reasons: condition deterioration ($n=9$); lost to follow-up ($n=4$); adverse events ($n=14$); protocol noncompliance ($n=10$); informed consent withdrawn ($n=16$); and other reasons ($n=24$; predominantly due to a good efficacy response during the fluphenazine run-in). Seven of the 288 randomised patients who did not have post-baseline efficacy data were excluded, as were a further seven whose final PANSS and Simpson–Angus Scale scores were not carried out in the same week. A further 5 patients who were randomised to receive quetiapine were excluded because they did not satisfy the USA label requirements of achieving a maintenance dose of at least 150 mg/day. Hence, the ITT population ($n=269$) comprised 132 patients on quetiapine and 137 on

haloperidol. Eighty-four percent of the ITT population completed the trial. Demographic and baseline characteristics for all patients in the two treatment groups and those with a baseline Kay's depressive factor score ≥ 8 are provided in Tables 1 and 2.

The depression factor score, from baseline to endpoint, was reduced in both quetiapine (-1.60) and haloperidol (-0.54) treated groups, and the difference between the two treatments (1.05; confidence interval 0.31 to 1.79) attained statistical significance in favour of quetiapine ($p=0.006$).

A summary of response rates, defined as the proportion of patients with a reduction of $\geq 20\%$, $\geq 30\%$, $\geq 40\%$ and $\geq 50\%$ in the depression factor score (LVCF on ITT population), is provided in Table 3. There were significantly more responders in the quetiapine group when both 20% and 30% improvement were used to define response.

Path analysis of the total patient group gave a total effect size of 1.1 and a direct effect size of 0.8 and revealed that the direct 'path' from treatment to depressive symptoms was significantly in favour of quetiapine compared with haloperidol ($p=0.016$) and accounted for 79% (0.8/1.1) of the total effect size (Table 4; Figure 2).

Repeating the analysis in 94 quetiapine-treated patients and 86 patients receiving haloperidol who had more prominent symptoms (baseline PANSS depression factor score of ≥ 8) revealed a mean change from baseline to endpoint for the quetiapine group of -2.24 compared with -1.27 for the haloperidol group. Therefore, as expected, greater reductions were seen in the more symptomatic patients. The difference between the two treatments approached statistical significance ($p=0.057$). Path analysis of this group of patients gave a total effect size of 1.0 and a direct effect size of 1.0 and revealed that the direct 'path' from treatment to effect on depression was significantly in favour of quetiapine compared with haloperidol ($p=0.029$) and accounted for 99.5% of the total effect size (Table 5; Figure 3).

For both the analyses of the whole patient group, and the patients who had more prominent symptoms, the path co-efficients relating to the indirect paths exhibit a similar pattern. Firstly, the path from treatment to EPS was statistically significant ($P<0.001$, in favour of quetiapine), whereas the path from EPS to depressive symptoms was NOT statistically significant. Hence the indirect (or compound) path from treatment to depressive symptoms via EPS only accounted for approximately 10% of the total effect. Secondly, neither of the paths from treatment to positive or negative symptoms were statistically significant, although both of the paths from either positive or negative to depressive symptoms were highly statistically significant. Hence the compound paths from treatment to depressive symptoms via either negative or positive symptoms only accounted for less than 10% of the total effect.

Thus, there is a differential treatment effect on EPS, however EPS did not affect depressive symptoms; positive and negative symptoms did affect depressive symptoms, but there was no differential effect of treatment on either positive or negative symptoms. Hence, the compound (indirect) paths had no effect on depressive symptoms and all the differential treatment effect on depressive symptoms is concluded to be direct.

Discussion

The results of this study suggest that quetiapine is more effective than haloperidol in reducing depressive symptoms in patients with refractory schizophrenia. Although the magnitude of the improvement in depressive symptoms is modest, we believe that it is of considerable significance bearing in mind the refractory nature of the sample and the fact that all patients had received antipsychotic treatment immediately prior to entry into the randomised phase of the trial. Consequently, it will be important to determine over the longer term whether by reducing depressive symptoms more effectively, quetiapine might ameliorate some of the sequelae of chronic depression in schizophrenia, namely impaired social and vocational functioning (Mandel *et al.*, 1982; McGlashan and Carpenter., 1976), the risk of relapse (Birchwood *et al.*, 1993) and suicide (Roy *et al.*, 1983). Also, because of its beneficial effect on depressive symptoms, quetiapine may be more acceptable to patients than conventional antipsychotics. Indeed, alongside its favourable side-effect profile, this effect may play a role in the enhanced patient satisfaction that has previously been reported with this drug (Hellewell *et al.*, 1999).

The results of the path analyses indicate that the superior efficacy of quetiapine in treating the depressive symptoms is not secondary to differential treatment effects on positive or negative symptoms, or the development of EPS, and suggest a direct effect of the agent on depressive symptoms. While both agents were associated with improvement in depressive symptoms,

only quetiapine exhibited a significant direct effect distinct from positive or negative symptom change. It has been suggested that this difference may be related to the wider pharmacological binding profiles of the atypical antipsychotics compared to haloperidol (Tollefson *et al.*, 1988a). Changes in positive and negative symptoms were associated with changes in the depressive factor score, but as there were no statistically significant treatment differences in changes of positive or negative symptoms, this mechanism does not explain the differential antidepressant effect. These findings are supported by other studies. In a post-hoc analysis of data from two acute treatment trials, quetiapine, but not haloperidol, was superior to placebo in improving Brief Psychiatric Rating Scale (BPRS) mood cluster scores. Depressive symptoms associated with schizophrenia were improved in significantly more of quetiapine-treated patients than either haloperidol or placebo groups (Arvanitis *et al.*, 1997). In a 4-month comparative study of quetiapine and risperidone among patients with schizophrenia and related psychoses (30% had a diagnosis of depression/bipolar disorder), quetiapine proved superior to risperidone in reducing depressive symptoms in both schizophrenia and related mood disorder patients (Goldstein *et al.*, 2000). Depressive symptoms were common in our sample, with 67% of patients having prominent symptoms, as indicated by a score of ≥ 8 on the PANSS depression factor. The mean \pm SD baseline depressive factor scores (11.29 ± 2.96 and 11.86 ± 3.02 in the quetiapine and haloperidol groups, respectively) are higher than those previously reported in acutely psychotic multi-episodic schizophrenia (7.4 ± 2.84), even when compared with patients experiencing their first episode of schizophrenia (8.5 ± 3.32) (Emsley *et al.*, 1999), a group in whom depressive symptoms have been found to be particularly common (Johnson, 1981; House *et al.*, 1987; Koreen *et al.*, 1993; Emsley *et al.*, 1999; Lancon *et al.*, 2001). There are several possible explanations for the prominence of depressive symptoms in our sample: they could have occurred concurrently with positive symptoms within the context of the acute psychotic episode (Koreen *et al.*, 1993) and, because of the refractoriness of the sample, the depressive symptoms have persisted together with the positive symptoms. This would be in keeping with previous observations of a significant association between positive symptoms and depressive symptoms (Barnes *et al.*, 1989; Norman and Malla., 1994; Lysaker *et al.*, 1995; Emsley *et al.*, 1999). Alternatively, they could represent a psychological response (demoralisation) to an apparently uncontrollable life event, namely the illness and its attendant disabilities (Birchwood *et al.*, 1993; Rooke and Birchwood, 1998). In fact, in the stress–diathesis context, depressive symptoms may themselves constitute a stressor that triggers a psychotic episode (Siris, 1993). Another possibility is that they could be a consequence of the antipsychotic treatment, although the existence of so-called neuroleptic-induced dysphoria is controversial (Koreen *et al.*, 1993; Siris, 2000). Finally, the depressive symptoms in our patients could also be explained on the basis of ‘post-psychotic depression’ (which probably includes some of the above possibilities). The ICD-10 (World Health Organization, 1992) definition of post-psychotic depression requires that, along with general criteria for schizophrenia during the previous 12 months, the patient must still exhibit persistent hallucinations, thought disorder or negative symptoms not due to depression or antipsychotic medication. Clearly, the majority of patients in the present study would meet these criteria. However, recent work indicates that depressive symptoms may also emerge irrespective of positive symptoms. In a 12-month prospective study of 105 patients with schizophrenia, two patterns of depressive symptoms were identified: those following the same course as positive symptoms during psychotic episodes; and those emerging *de novo* without a change in positive symptoms (Birchwood *et al.*, 2000). The depressive symptoms in our sample of refractory schizophrenic patients most likely represent a combination of the above mentioned factors.

Limitations of this study include the lack of a specific scale for the assessment of depressive symptoms, the high dose of haloperidol used, and the previously mentioned possible drawbacks of path analysis.

In conclusion, this study indicates that depressive symptoms are common in patients with schizophrenia with persistent positive symptoms. Our findings extend the evidence for an antidepressant effect for the novel antipsychotics such as quetiapine in schizophrenia, and suggest that this effect is not limited to the reduction of depressive symptoms in acutely psychotic patients.

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Table 1. Demographic and baseline characteristics (mean [SD]) for all patients receiving either quetiapine 600 mg/day or haloperidol 20 mg/day

	Treatment	
	Quetiapine	Haloperidol
n	132	137
Sex: Male	93	97
Female	39	40
Age (years)	37.5 (10.4)	38.8 (11.4)
PANSS total score	88.32 (18.01)	87.78 (21.16)
PANSS positive score	21.69 (4.54)	21.96 (5.53)
PANSS negative score	24.05 (6.32)	23.18 (6.44)
PANSS depression factor	9.66 (3.64)	9.64 (3.81)
Simpson–Angus Scale score	15.56 (5.32)	15.03 (4.81)

Table 2. Demographic and baseline characteristics (mean [SD]) for all patients with a baseline Kay's depressive factor score ≥ 8 receiving either quetiapine 600 mg/day or haloperidol 20 mg/day

	Treatment	
	Quetiapine	Haloperidol
n	94	86
Sex: Male	67	58
Female	27	28
Age (years)	37.1 (10.6)	38.3 (11.5)
PANSS total score	90.71 (18.48)	94.16 (21.97)
PANSS positive score	21.99 (4.86)	23.34 (5.95)
PANSS negative score	23.91 (6.41)	23.97 (6.43)
PANSS depression factor	11.29 (2.96)	11.86 (3.02)
Simpson–Angus Scale score	15.84 (4.92)	15.32 (4.63)

Table 3. Response rates, defined as the proportion of patients with a reduction of $\geq 20\%$, $\geq 30\%$, $\geq 40\%$ and $\geq 50\%$ in the depression factor score (last value carried forward [LVCF] on intent-to-treat [ITT] population) for all patients receiving either quetiapine 600 mg/day or haloperidol 20 mg/day

PANSS depression factor response rates	Quetiapine			Haloperidol			p-value
	Total number assessed	Responders		Total number assessed	Responders		
		n	%		n	%	
$\geq 20\%$ reduction	132	56	42.4	137	41	29.9	0.023
$\geq 30\%$ reduction	132	45	34.1	137	27	19.7	0.004
$\geq 40\%$ reduction	132	25	19.7	137	17	12.4	0.072
$\geq 50\%$ reduction	132	17	12.9	137	9	6.6	0.051

PANSS depressive factor ≥ 8 at baseline							
	Total number assessed	Responders		Total number assessed	Responders		p-value
		n	%		n	%	
$\geq 20\%$ reduction	94	43	45.7	86	30	34.9	0.138
$\geq 30\%$ reduction	94	36	38.3	86	22	25.6	0.067
$\geq 40\%$ reduction	94	24	25.5	86	15	17.4	0.186
$\geq 50\%$ reduction	94	17	18.1	86	9	10.5	0.143

PANSS: Positive and Negative Syndrome Scale

Table 4. Effect sizes for change from baseline to endpoint in Kay's depressive factor, for quetiapine compared with haloperidol and the contribution of direct and indirect effects (n=269)

	Effect				
	Total	Direct	Positive	Negative	EPS
Effect sizes	1.106	0.803	0.057	0.090	0.066
Percentage effect sizes	100.00	79.02	5.62	8.90	6.47
p-value for direct effect (quetiapine vs haloperidol)		p=0.016			

EPS: extrapyramidal symptoms

Table 5. Effect sizes for change from baseline to endpoint in Kay's depressive factor for quetiapine compared with haloperidol and the contribution of direct and indirect effects in patients with baseline PANSS depression factor score of ≥ 8 (n=180)

	Effect				
	Total	Direct	Positive	Negative	EPS
Effect sizes	0.995	0.990	0.085	0.031	0.121
Percentage effect sizes	100.00	99.61	-8.52	-3.10	12.12
p-value for direct effect (quetiapine vs haloperidol)		p=0.029			

EPS: extrapyramidal symptoms; PANSS: Positive and Negative Syndrome Scale.

Figure 1. Diagrammatic representation of the path analysis.

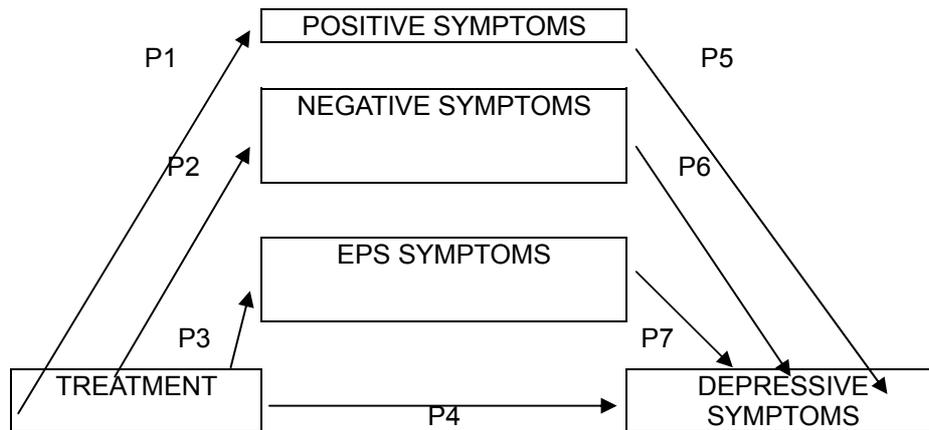


Figure 2. Diagrammatic representation of the path analysis containing path coefficients and p-values (in parentheses) for the complete dataset (n=269).

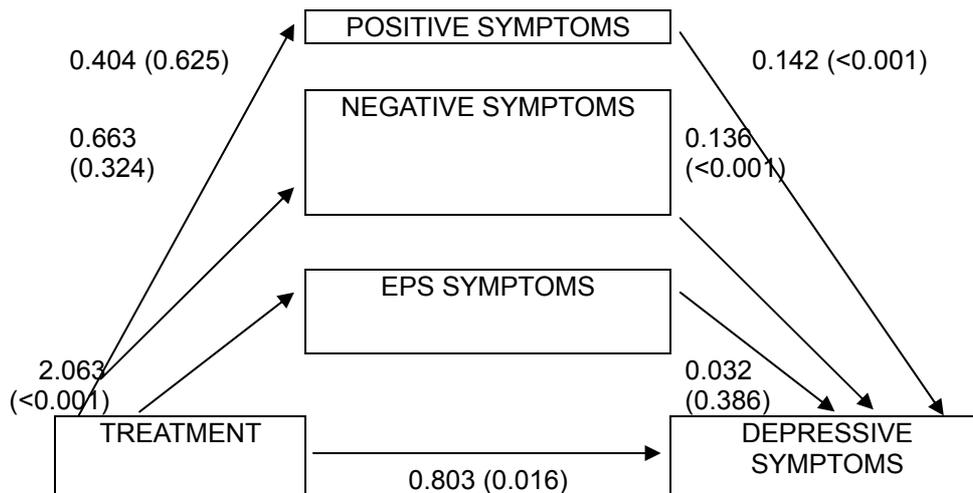
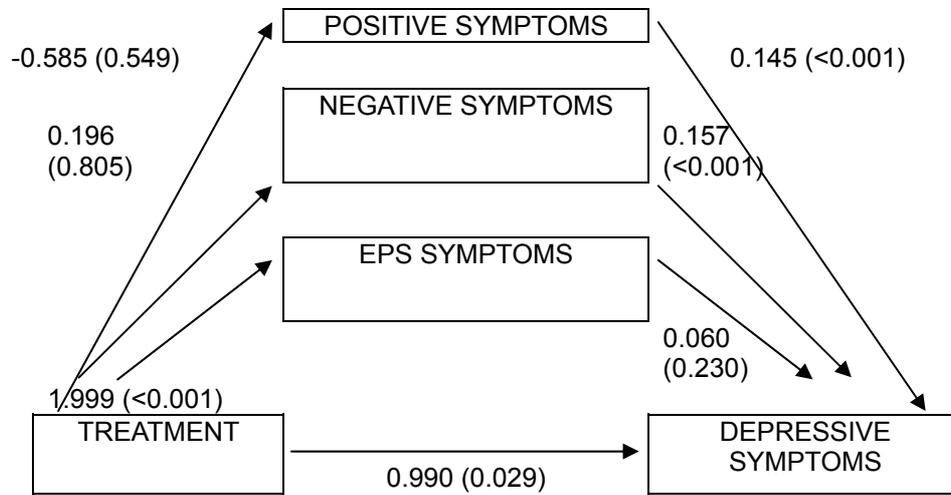


Figure 3. Diagrammatic representation of the path analysis containing path coefficients and p-values (in parentheses) for the symptomatic at baseline dataset (n=180).



3.a.vi Clinical Potential of Omega-3-Fatty Acids in the Treatment of Schizophrenia.

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Abstract

It has been hypothesised that abnormalities of phospholipid metabolism are present in schizophrenia, and that the omega-3 fatty acids, and eicosapentaenoic acid (EPA) in particular may have a role in treating this illness. Considerable pre-clinical and clinical evidence provides support for this proposal. An epidemiological study reported a better outcome for schizophrenia in countries whose diet was rich in unsaturated fatty acids. Evidence of abnormalities of essential fatty acids (EFAs) has been found in erythrocyte membranes and cultured skin fibroblasts, and abnormal retinal function and niacin skin flush tests have been reported in patients with schizophrenia. Case reports and an open-label clinical trial reported efficacy for EPA in schizophrenia. Four randomised controlled trials using EPA versus placebo as supplemental medication have now been reported. Two of these trials showed significant benefit for EPA, while the other two were negative on the primary efficacy measure. One study also reported a beneficial effect on dyskinesia. In the only published trial in which EPA versus placebo was used as monotherapy in schizophrenia, some evidence was found to suggest antipsychotic activity. Taken together, there is considerable evidence to suggest abnormalities of EFAs in cell membranes, and there is preliminary evidence that EPA is effective as supplemental treatment in schizophrenia.

While the introduction of conventional antipsychotic agents almost 50 years ago heralded a major advance in the treatment of schizophrenia and other psychotic disorders, these compounds have serious limitations in terms of both efficacy and tolerability. Patients treated with these agents often have persistent psychotic symptoms, suffer frequent relapses, develop prominent functional impairment and experience distressing and disabling side-effects.^[1] With regard to efficacy of conventional antipsychotics, approximately 70% of patients show substantial symptom reduction in the short-term. However, in the longer term the majority of patients experience persistent positive and/or negative symptoms. The most important side-effects are extrapyramidal symptoms (EPS), particularly tardive dyskinesia (TD).

The development of the novel antipsychotic drugs has effectively addressed some of these problems. Accumulating evidence indicates significant advantages over their predecessors. In particular, it has been shown that the newer drugs are less likely to induce acute EPS.^[2] Other reported advantages include improved efficacy in treatment-refractory patients,^[3] negative symptoms,^[4] depressive symptoms,^[5] reduced levels of suicidality,^[6] less neurocognitive impairment,^[7] better subjective quality of life,^[8] reduced incidence of TD^[9] and improved overall outcome.^[10] But even these newer agents have troublesome side effects such as leukopenia (with clozapine), weight gain^[11], increase in serum triglycerides, and the development of insulin resistance and diabetes mellitus. Clearly therefore, there is still a lot of

room for improvement in the treatment of schizophrenia. In addition, the high acquisition costs of these new compounds has put them beyond the reach of many patients worldwide.^[12] The search for alternative treatments for psychosis therefore remains a high priority. One such candidate is omega-3 polyunsaturated fatty acids (PUFA's). There is now considerable evidence to suggest that the omega-3 polyunsaturated fatty acids may offer an affordable and effective alternative in the treatment of psychosis.

1. The membrane phospholipid hypothesis

A disorder of membrane phospholipid metabolism has been proposed as the biochemical basis for the neurodevelopmental hypothesis of schizophrenia,⁵ and provides a rationale for intervention studies using these compounds. In addition to their structural role in membranes (e.g. in the formation and remodelling of dendrites and synapses), phospholipids are involved in various biochemical reactions. One of these is the phospholipase A₂ (PLA₂) cycle which involves the release of arachidonic acid (AA) and other highly unsaturated fatty acids from phospholipids for cell signaling and prostaglandin synthesis. Specifically, it is postulated that in schizophrenia there is an accelerated rate of loss of unsaturated fatty acids. When present to a mild degree, this increased rate of loss will be compensated for by increased incorporation, but there will be a change in membrane composition if there are deficiencies in the enzymes involved in phospholipid synthesis, the elongases, desaturases, and acyltransferases, in addition to a reduced dietary intake of EFA's.^[13] The phospholipase A₂ (PLA₂) cycle is one of the intra-neuronal signal transduction systems that link the receptors of neurotransmitters such as dopamine, serotonin and glutamate. This cycle involves the release of arachidonic acid (AA) and other highly unsaturated fatty acids from neuronal membrane phospholipids. It has been proposed that there may be abnormalities in phospholipid-AA signalling in schizophrenia.^[14] Horrobin^[15] summarised various research findings and noted the existence of clinical, biochemical and genetic evidence to suggest that schizophrenia is caused by a disorder of membrane phospholipid metabolism. He proposed that this involves excessive loss of highly unsaturated fatty acids from membranes, owing to enhanced activity of PLA₂. He postulated that this abnormality results in changes in the properties of membranes throughout the body, with such physical abnormalities as reduced vasodilator responses to niacin and histamine and altered immunological functions. The most serious consequences however, are produced in the brain. Horrobin has further proposed his membrane phospholipid hypothesis as a biochemical substrate for the well-known neurodevelopmental hypothesis of schizophrenia.^[16] In essence, the neurodevelopmental hypothesis states that genetic and environmental factors interact to influence the ways in which nerve cells are laid down, differentiated, selectively culled by apoptosis and remodelled by expansion and contraction of dendrites and synaptic connections. These changes begin in utero, are affected by events around birth, and become fully expressed in early adulthood.^[17]

Pregnancy and perinatal events which have been found to be related to later schizophrenia can be explained by their effects on the availability of normally-structured phospholipids.^[13] Starvation during pregnancy increases the risk of schizophrenia: strong evidence for the impact of maternal food deprivation, especially EFA deficiency, on later schizophrenia comes from the study of Sinclair^[18] of the Dutch famine of 1944-45. Low head circumference is also a risk factor for schizophrenia. The supply of AA to the developing foetus is a determinant of brain growth. The consistent increase in the risk of schizophrenia in association with obstetric complications, particularly pre-maturity and perinatal hypoxia, causing mobilization of EFAs from brain phospholipids, which would exacerbate any tendency towards low AA and DHA levels in neuronal membranes. Stress during pregnancy is associated with a small, but significant, increased risk of schizophrenia in the offspring. Stress leads to elevation of cortisol and catecholamines, both of which are known to reduce the rate of formation of AA and DHA from dietary precursors. Stress could therefore lead to reduced availability of brain-specific EFAs for the foetus.^[13]

Preterm infants receiving DHA supplementation or breast milk (which is high in n-3 FAs, especially DHA) have scored better on intelligence and development scales than infants fed on formula feeds, which are deficient in these PUFAs.^[19] The effect of severe pre-eclampsia on maternal and cord erythrocyte membrane EFA profiles were investigated by Kirsten et al.^[20] It was found that the cord blood DHA levels of infants of pre-eclamptic women are lower

than those of the infants of normotensive women, suggesting that infants born to pre-eclamptic women need dietary DHA to replenish DHA stores. Generally, preterm formulas and parenteral lipid emulsions do not contain AA and DHA.

Neuronal membranes are made up largely of phospholipids.^[21] Brain phospholipids are uniquely rich in highly unsaturated fatty acids with three to six double bonds, falling into the general class of essential fatty acids (EFAs). These EFAs cannot be manufactured *de novo* in the mammalian body.^[22] In schizophrenia, the basic abnormality in phospholipids creates a vulnerable state, which may be exacerbated by nutritional deficiencies. Horrobin has pointed out that the hypothesis could be tested in the form of relatively simple and safe treatment modalities.^[15] Other workers have proposed that supplemental omega-3 fatty acids exert their action via their role in correcting oxidative stress that causes cellular injury through peroxidation of membrane phospholipids.^[23]

Interestingly, similar alterations in EFAs have also been postulated in depressive and neurodegenerative disorders. Lower n-3 EFA (particularly DHA) levels were found in erythrocyte membranes of depressed patients compared to control subjects. There were also significant negative correlations between the Beck Depression Inventory scores and n-3 red blood cell membrane fatty acid levels.^[24]

Lower levels of EPUFAs have also been reported in patients with neurodegenerative disorders such as multisystem neurodegeneration, multiple sclerosis and Huntington's disease.^[25] In a subsequent clinical trial of EPA in Huntington's significant clinical improvement was shown.^[26]

2. Epidemiological evidence

There is some evidence that diet may have a role in the pathogenesis and course of schizophrenia. In an analysis of data from an outcome study conducted in eight different countries, it was found that differences in dietary intake correlated significantly with the course and outcome of schizophrenia. Better outcome was reported in countries whose diet was rich in unsaturated fatty acids from vegetable and marine sources, compared to countries with high intake of saturated fatty acids from land animals and birds.^[27]

3. Evidence of abnormalities of essential fatty acids in patients with schizophrenia

On the basis of a generalised disorder of membrane phospholipid metabolism, Horrobin postulated that changes in the properties of membranes throughout the body would be apparent.^[15] A number of studies have in fact reported such changes.

3.1 Erythrocytes:

One study measured the fatty acid composition of red blood cell membranes from 23 medicated patients with schizophrenia and a healthy control group. Substantial depletions of fatty acids from the omega-6 and omega-3 series, particularly arachidonic and docosahexanoic acid, were found. An inverse relationship between depleted omega-6 fatty acids and plasma levels of thiobarbituric acid reactive substances suggested that the depletion was caused by increased breakdown of the fatty acids, rather than by impaired incorporation of fatty acids into membranes. Arachidonic and docosahexanoic acids appear to show a bimodal distribution. The authors postulated that their findings might represent an abnormality in cell membrane fatty acid composition in schizophrenia, which is of aetiological importance.^[28] Similar abnormalities in levels of EFAs in blood cells have also been noted in association with the presence of tardive dyskinesia (TD). The relationships between psychiatric symptoms, dyskinesia and relative levels of the omega-3 and omega-6 fatty acids were examined in red blood cell membranes and plasma in a sample of 72 subjects with schizophrenia or schizoaffective disorder. Subjects were followed up over a period of 4.5 years to determine whether changes in symptoms were related to changes in EFA levels. It was hypothesised that subjects with schizophrenia would show lowered levels of omega-6 and omega-3 series fatty acids, compared with healthy controls, and that this abnormality

would be greater in the patients with TD and prominent negative rather than positive symptoms. However, the only consistent findings were that the patient sample had lower levels of linoleic acid and higher levels of dihomo-gamma-linolenic acid compared with the healthy controls. The authors noted that there was considerable variability in patients' EFA profile.^[29]

The long chain polyunsaturated EFA derivatives, particularly AA and docosahexaenoic acid (DHA), are highly concentrated in the brain. However, red blood cell levels may be a peripheral marker of central EFA status. Red blood cell levels of fatty acids are influenced by diet, medications, and other factors. A study by Mahadik et al (1994) examined cell plasma membrane compositions of AA and DHA in cultured skin fibroblasts from 12 patients with schizophrenia, 8 of whom were drug-naïve and in a first episode of psychosis, 6 bipolar patients, and 8 healthy control subjects. They found DHA as well as total omega-3 EFA contents to be significantly lower in cell lines from the patients with schizophrenia than in cell lines from the bipolar patients and healthy controls, with no difference between the latter two groups. AA levels did not differ across the groups. They concluded that their findings could be explained on the basis of deficient delta-4 desaturase activity in schizophrenia.^[30] In another study, significantly reduced DHA and docosapentaenoic acid (DPA) concentrations were found in erythrocyte membranes from patients with schizophrenia compared with a carefully matched control group. Polyunsaturated fatty acid concentrations were measured in the erythrocyte membranes of 19 medicated young patients with schizophrenia and compared with matched healthy controls. Symptoms were rated by means of the Positive and Negative Symptom Scale (PANSS) and Montgomery-Asberg Depression Rating Scale. Significant differences in erythrocyte fatty acid composition were found. The most prominent finding was that fatty acids of the omega-3 series were significantly decreased. The differences could not be explained on the basis of nutritional or hormonal status, medication or substance use. No consistent pattern emerged from the different fatty acid abnormalities and the clinical symptom scores.^[31]

In a recent study, Yao *et al*^[32] investigated the correlations between the concentrations of EPUFAs in erythrocyte membranes and *in vivo* brain phospholipid metabolites, using ³¹P Magnetic Resonance Spectroscopy, in first episode, neuroleptic-naïve schizophrenic subjects. The results support the association between decreased EPUFAs in erythrocyte as well as neuronal membranes.

3.2 The niacin flush test:

The niacin skin flush test has been investigated as a possible marker for schizophrenia. This test, which involves prostaglandin-induced vasodilatation, has been proposed as a method of exploring essential fatty acid metabolism, and may serve to define a subgroup of patients with schizophrenia. This test is based on the effect of topically applied aqueous methyl nicotinate (AMN) on the production of prostaglandin D2 (PGD2) from skin macrophages and the resultant cutaneous capillary vasodilatation. Skin flushing after oral administration of nicotinic acid is due to the same reaction described above. It has been shown to be normal in subjects with mood disorders and neurosis. Furthermore, the ingestion of cyclo-oxygenase inhibitors such as aspirin, may result in false-positive findings, i.e. failure of vasodilatation.

The effect of topically applied niacin was investigated in patients with schizophrenia with prominent negative symptoms. The investigators examined the clinical accompaniments of the niacin response. Patients failing to flush with niacin had significantly lower levels of AA and DHA. Conversion from non-flushing to flushing during the 6-month supplementation period was predicted by an increase in AA levels in red blood cell membranes, irrespective of the nature of supplementation. While negative or positive symptoms did not predict flushing, more prominent affective symptoms were significantly associated with a positive flush response.^[33] In another study the sample comprised 38 patients with schizophrenia and 22 healthy controls. Four concentrations of AMN were applied topically to the skin of the forearm in all subjects, and any resulting vasodilatation was rated as redness after 5 min. At all concentrations of AMN, the patients with schizophrenia were significantly different from the

controls. The greatest degree of differentiation was when 83% of patients with schizophrenia, but only 23% of controls, had a zero or minimal response to AMN. The results of this study are consistent with the concept of reduced membrane AA levels in schizophrenia. The authors suggested that this test might contribute to the reliable diagnosis of schizophrenia.^[34]

3.3 Cultured skin fibroblasts:

Utilization of radiolabeled linoleic (omega-6) and alpha-linolenic (omega-3) acids was studied in cultured skin fibroblasts from patients with first-episode psychosis, chronic schizophrenia and healthy controls. Uptake and incorporation of both of the EFAs was similar in fibroblasts from all 3 groups. However, the utilization of EPA into DHA was significantly lower in first-episode psychotic patients versus the healthy controls. These results suggest that the level of delta 6- as well as delta 5-desaturase is normal, while the levels of delta 4-desaturase may be lower in fibroblasts of patients with schizophrenia.^[35]

3.4 Retinal function:

Retinal function has also been investigated as a possible marker for cell membrane omega-3 fatty acid depletion in schizophrenia. The omega-3 fatty acids, particularly DHA, are found in high concentrations in the photoreceptor cells of the retina and abnormalities of light sensitivity have been reported in patients with schizophrenia. Animal studies have demonstrated that reduced EFA levels are associated with changes in the electrophysiological response of the retina to light, as measured by the electroretinogram (ERG). The ERG of 9 largely unmedicated patients with schizophrenia and 9 age and sex matched control subjects was measured. Subjects with schizophrenia had significantly reduced a-wave amplitudes on the ERG when compared with healthy controls. The a-wave amplitude was independent of the dose of antipsychotic agents being taken. The a-wave of the ERG is thought to reflect activity of the photoreceptor cells. These findings lend support to the hypothesis that patients with schizophrenia have abnormalities of photoreceptor function, as a consequence of reduced levels of omega-3 fatty acids in the cell membrane.^[36]

3.5 Post mortem studies

In a study of post-mortem caudate cell membrane composition of schizophrenic patients vs controls, significantly lower amounts of phosphatidylcholine, phosphatidylethanolamine and total PUFAs were found in the schizophrenic brain samples, while the reduced PUFAs were largely attributable to decreases in AA, suggesting that deficits identified in peripheral tissues such as erythrocytes, may also be present in the brains of schizophrenic patients.^[37]

4. Case reports

In a single case report a 30-year-old male with severe, refractory DSM-IV schizophrenia with prominent positive symptoms, was treated for 6 months with a fatty acid supplement. For 2 years prior to the study his clinical profile had remained unchanged, and he had not received antipsychotic medication during this period. Treatment with 30 ml/day of emulsion rich in EPA was initiated, and the patient was assessed at monthly intervals, by means of the Schedules for the Assessment of Positive Symptoms and Negative Symptoms. A marked reduction in his symptoms was observed at 2 months, and further improvement followed. At 6-months few symptoms remained. These findings suggest that treatment with certain fatty acids may have significant benefits in the management of schizophrenia.^[38]

Another case report involved a 30-year-old woman with chronic schizophrenia, who experienced an episode of acute exacerbation of psychotic symptoms during pregnancy. The subject was treated with omega-3 fatty acids as monotherapy. Dramatic improvements in both positive and negative symptoms were reported, accompanied by a significant increase of omega-3 fatty acids in erythrocyte membranes.^[39]

5. Clinical trials

5.1 Open label:

In an extension to a study reported above, in which substantial depletions of fatty acids were found in red cell membranes,^[28] dietary analysis revealed no deficiency of fatty acid intake in the patients with schizophrenia, although greater intake of omega-3 fatty acids was associated with less severe symptomatology. Patients were then given dietary

supplementation with 10 g per day of concentrated fish oil for six weeks, which resulted in significant improvement in psychotic symptoms. This clinical improvement was associated with an increased level of omega-3 fatty acids in the red cell membranes.^[40]

5.2 Randomised controlled trials:

Four randomised, placebo controlled EPA supplementary studies in schizophrenia have been reported in the literature. The first was designed to distinguish between the possible effects of two different omega-3 fatty acids: EPA and DHA. Forty-five outpatients with schizophrenia with persistent symptoms while on stable antipsychotic medication were randomised to treatment with EPA, DHA or placebo for 3 months in addition to their normal antipsychotic medication. Symptoms were assessed by means of the PANSS. Subjects receiving EPA showed significantly greater total PANSS score reduction than both the DHA and placebo groups. Furthermore, a greater response rate (>25% PANSS total reduction) was also found in the EPA group. Within the EPA group, there was a significant association between the change in positive PANSS scores and baseline omega-3 fatty acid levels. Baseline EPA emerged as a significant predictor of improvement in clinical scores.^[41]

A recent, multi-site, randomised, placebo-controlled trial of ethyl-EPA supplementation for residual symptoms and cognitive impairment in schizophrenia reported negative findings. The sample comprised 87 outpatients meeting DSM criteria for schizophrenia or schizoaffective disorder, with persistent symptoms despite antipsychotic treatment. Subjects had to have had no change in medication in the 30 days prior to the trial, and the presence of significant residual symptoms (defined as either one or more positive and/or negative symptom scores > 4 or total PANSS scores > 45 with a score of 3 or more on at least 3 positive or negative items on the PANSS scale). Participants were randomly assigned to receive either ethyl-EPA 3 g/day (N=43) or placebo (N=44) in a 16-week, double-blind design, in addition to their standard antipsychotic treatment. Subjects were assessed at baseline and at weeks 1, 2, 4, 8, 12, and 16, and cognitive testing was performed at baseline and at week 16. No significant differences were found between the groups in positive or negative symptoms, mood, cognition, or global impression ratings. Results were similar for the intention-to-treat (N=87) and completer (N=75) analyses. The mean reduction in PANSS total scores from baseline to endpoint was 5 for the ethyl-EPA group and 6 for the placebo group. The AA/EPA ratio change (used to index pre- and post- treatment fatty acid composition in red blood cells) from baseline to endpoint was not significantly associated with any efficacy variable.^[42]

Another multi-centre, but this time dose-ranging study of the effects of ethyl-eicosapentaenoate as supplemental medication in patients with persistent schizophrenic symptoms was recently conducted. The sample comprised 115 patients with DSM-IV-defined schizophrenia. Thirty-one were on clozapine, 48 on new atypical drugs and 36 on conventional antipsychotics. Patients were randomised to receive, in addition to their other antipsychotic medication, the following: ethyl-EPA 1mg/day, 2mg/day, 4mg/day or placebo. The study was conducted over 12 weeks. The primary efficacy measure was change from baseline to 12 weeks on the PANSS total score and its sub-scales. No treatment-related side effects or adverse biochemical or haematological effects were reported. Patients on 2 and 4 g/day EPA showed significant reductions in triglyceride levels, which had been elevated by clozapine. All groups improved significantly from baseline but there were no significant differences between groups. Specifically, no difference was found between EPA and placebo in terms of the primary efficacy outcome measure. There was a large mean reduction in total PANSS scores in the placebo group (-16.6). In patients on EPA 2 g/day there were improvements on the PANSS and its sub-scales, but there was no difference between active treatment and placebo. However, patients on clozapine showed little placebo response, but a statistically significant reduction of symptoms if they received EPA. This effect was greatest at 2 g/day. A positive relationship was reported between improvement on rating scales and rise in red blood cell AA concentration.^[43] In this study, EPA produced a dose-related increase in red cell EPA concentrations, but a plateau was reached at 2 g per day. DHA showed little change in the 1 g/day group, rose to a small extent in the 2 g/day group, but fell overall in the 4 g/day group. AA levels rose in the 1 and 2g/day groups, but fell in the 4 g/day group.^[44]

A further randomized, placebo-controlled study of ethyl-EPA as supplemental treatment was conducted in 40 patients with persistent symptoms of schizophrenia despite at least 6 months of stable conventional antipsychotic medication. The patients were randomised 1:1 to receive either EPA 3 g/day or placebo, as a supplement to their existing treatment. This was a fixed-dose, double-blinded study over 12 weeks. In this study the EPA group had a significantly greater reduction of the Positive and Negative Syndrome Scale (PANSS) total scores, as well as PANSS negative subscale scores at 12 weeks. An early onset of action was suggested by significant differences being evident at 3 weeks. A significantly greater reduction in Extrapyramidal Symptom Rating Scale (ESRS) dyskinesia scores for the EPA group was also observed at 12 weeks. The authors concluded that these results suggest that EPA may be an effective, safe and well tolerated supplemental treatment in schizophrenia, with an additional benefit of improving tardive dyskinesia. They further point out that EPA offers the prospect of an effective, well-tolerated and affordable treatment for schizophrenia – a matter of great relevance particularly to lower income countries, where the high acquisition costs of the novel antipsychotics put them beyond the reach of most patients.^[45]

Thus, of the four published randomised controlled trials comparing EPA to placebo as supplemental treatment, two were positive and two were negative on the primary efficacy measure. It is not clear why these studies reported such different results, given the fact that the designs were similar in many ways. Samples comprised chronic patients with persistent symptoms, and EPA doses were similar. Possible explanations for the differences are:

(1) Background fatty acid intake may be substantially different between the populations studied. Fatty acids compete with one another for uptake, so that a diet rich in fatty acids may result in less uptake of EPA. Erythrocyte levels of EFAs in the samples suggest that this could explain the different outcome in the Fenton et al^[42] and the Emsley et al studies^[45]

(2) The study by Fenton et al^[42] had a moderate placebo response rate, and the dose ranging study^[43] had a high placebo response rate. This could have affected the assay sensitivity of these studies.

(3) It needs to be kept in mind that negative studies are frequently reported in schizophrenia. A recent article reported that 25% of studies comparing novel antipsychotics with placebo failed to differentiate between the active compound and placebo.^[46]

In the only published trial in which EPA was used as monotherapy, antipsychotic drugs were allowed if this was thought to be clinically imperative. By the end of the study, all 12 patients on placebo, but only eight of 14 patients on EPA, were taking antipsychotic drugs. The EPA subjects also had significantly lower scores on the PANSS. The authors concluded that EPA may represent a new treatment approach to schizophrenia.^[41]

6. Reviews

A review article evaluated all potentially relevant English-language articles that were identified from the medical and psychiatric literature with the aid of computer searches, using key words such as lipids, phospholipids, prostaglandins and schizophrenia. All studies that included human subjects were reviewed. The authors reported that the most consistent clinical findings included red blood cell fatty acid membrane abnormalities, NMR spectroscopy evidence of increased phospholipid turnover and a therapeutic effect of omega-3 fatty acid supplementation of neuroleptic treatment in some schizophrenia patients. They pointed out that greater attention to factors that influence tissue EFA levels, such as diet, tobacco and alcohol, are required to reconcile inconsistent findings. They concluded that treatment studies, although promising, required independent replication.^[47]

Another review based on a Medline search was conducted in September 1999. At that stage the authors could find only four studies that used fatty acids as an adjunctive therapy in schizophrenia. They felt that the data on schizophrenia were conflicting, but that omega-3 and omega-6 fatty acids had been proved effective. Most of the evidence suggested that the main effect is an improvement in negative symptoms.^[48] The author of another review article felt that substantial evidence existed supporting a potential role of omega-3 fatty acids in schizophrenia, although treatment data are needed. He furthermore suggested that omega-3 fatty acids may prove to be a safe and efficacious treatment for psychiatric disorders in pregnancy and in breastfeeding.^[49]

A Cochrane Database Systematic Review was published in 2000, evaluating the evidence for the use of polyunsaturated fatty acids for schizophrenia. The meta-analysis was conducted to specifically review the effects of supplementing standard antipsychotic treatment in schizophrenia with polyunsaturated fatty acids, EFAs and non-EFAs, and to also evaluate the effects of EFA's as a sole, antipsychotic treatment. Relevant randomised trials were identified and the authors selected all randomised clinical trials of polyunsaturated fatty acid supplementation to standard treatment or as primary intervention for schizophrenia (however defined) versus standard care. They found that four relatively small trials (total n=204) showed low levels of loss to follow up and adverse effects for subjects taking EFAs. The results suggest a positive effect of EPA over placebo. However, the authors caution that the data is limited so that the results are difficult to interpret with confidence. There were no clear effects of primrose oil (omega-6) EFA supplementation. They concluded that the data are all preliminary, but that results look encouraging. EPA does not seem harmful, may be acceptable to people with schizophrenia and have moderately positive effect. They also pointed out that, considering that EPA may be an acceptable intervention, large, long simple studies reporting clinically meaningful data should be undertaken.^[50]

7. Conclusions

A lot of the research conducted in this field to date could be criticised for its methodological limitations. Samples were generally small, and some studies were unblinded. However, it needs to be kept in mind that funding available for studies like these is not comparable to studies conducted by large pharmaceutical companies. Taken together, there is now considerable evidence indicating abnormalities of EFAs in cell membranes of subjects with schizophrenia. There is also preliminary evidence for EPA specifically, as an effective supplementary treatment in schizophrenia (although there are some negative findings), with potentially additional benefits in TD. Further studies currently underway will hopefully shed more light on the subject. In particular, EPA still has to be tested properly as a stand-alone antipsychotic agent in schizophrenia. Most clinical studies are short term and nothing is known about the possible consequences of longer term supplementation like the induction of unwanted effects in the different PUFA series and their derivatives (eicosanoids.) Future studies should pay more attention to aspects such as body mass index, detailed and validated dietary questionnaires and substance abuse. Laboratory analyses should include cholesterol and triglyceride profiles, vitamins B12, B6 and folic acid, homocysteine and the hormones cortisol, dehydroepiandrosterone-sulphate, testosterone and prolactin. "Fish flavour" should also be added to the capsules for a real double-blind placebo-controlled study.

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Table. Randomised controlled trials of EPA vs. placebo as supplementation in schizophrenia.

Authors	Sample size	Dose of EPA	Duration	Outcome
Peet et al, 2001	45 (including DHA arm)	2 g/day	12 weeks	EPA significantly better than placebo and DHA
Fenton et al, 2001	87	3g/day	116 weeks	No difference
Peet & Horrobin, 2002	115	1, 2 and 4g/day	12 weeks	No difference
Emsley et al, 2002	40	3g/day	12 weeks	EPA significantly better

3.b.1 A Single-Blind, Randomised Trial Comparing Quetiapine and Haloperidol in the Treatment of Tardive Dyskinesia

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ABSTRACT

Background: While the atypical antipsychotics should ultimately reduce its prevalence, tardive dyskinesia (TD) is likely to remain a significant clinical problem for a long time to come. No strategy has clearly emerged as the treatment of choice for TD. Atypical antipsychotics have reduced propensities for producing acute extrapyramidal symptoms and possibly TD, and may be effective in treating patients with established TD.

Method: This 12-month, randomised, investigator-blinded study compared the efficacy of quetiapine ('Seroquel'; n=22) with haloperidol (n=23) in treating patients with schizophrenia or schizoaffective disorder and established TD. Dyskinesia was assessed using the Extrapyramidal Symptom Rating Scale (ESRS) dyskinesia subscale scores and the Clinical Global Impression (CGI) dyskinesia scores. Other EPS, weight, serum prolactin and glycosylated haemoglobin were also assessed.

Results: Mean endpoint doses were 400 mg/day quetiapine and 8.5 mg/day haloperidol. Compared with haloperidol, the quetiapine group showed significantly greater improvements in ESRS dyskinesia (6 and 9 months [$p < 0.01$]) and CGI dyskinesia (from 6 months onwards), and with repeated measures analysis ($p = 0.002$). Response rate ($\geq 50\%$ symptom reduction) was greater with quetiapine than haloperidol (64% and 37% at 6 months; 55% and 28% at 12 months). Other EPS decreased significantly with quetiapine. Endpoint serum prolactin levels reduced with quetiapine but increased with haloperidol ($p = 0.005$). No significant changes in weight or glucose metabolism were recorded in either group.

Conclusion: Quetiapine effectively reduces the severity of TD and is well tolerated in patients with established TD.

INTRODUCTION

While the new generation of atypical antipsychotics may ultimately reduce its prevalence, tardive dyskinesia (TD) is likely to remain a significant clinical problem for a long time to come. TD is a common complication of conventional antipsychotic treatment, and worldwide clinicians continue to use these agents extensively for the treatment of psychosis. Five percent of patients on conventional antipsychotics develop TD each year for the first eight years, with an average reported prevalence rate of approximately 20% depending upon the

patient populations studied.¹ Even the use of very low-doses of conventional antipsychotics does not protect against the development of TD.² The condition is under-recognised in clinical settings.³ Although in many cases the disorder is mild and non-distressing, TD symptoms contribute to social and vocational impairment, as well as to the further stigmatisation of psychotic illness. Some patients develop more severe symptoms, which are extremely distressing and disabling, and may even be life-threatening.⁴

Treatment of TD is problematic, and no strategy has emerged that is clearly the treatment of choice.⁵ Although antipsychotic drug withdrawal is a course of action that needs to be considered, this may result in an exacerbation of the TD symptoms in the short term,^{6,7} as well as an increased risk of psychotic relapse.⁵ Also, there are no controlled trials assessing the effect of dose reduction and intermittent dosing strategies, such as drug holidays.⁸ Paradoxically, ongoing treatment with a conventional antipsychotic may suppress, and even improve symptoms,⁹ particularly in the short-term.¹⁰ With the exception of clozapine,^{11,12,13} and possibly branched-chain amino acids,¹⁴ little evidence exists to indicate efficacy for any treatment modality for TD. There is no good evidence to support the use of benzodiazepines,¹⁵ cholinergic agents,¹⁶ vitamin E,¹⁷ melatonin,¹⁸ gamma-aminobutyric acid,¹⁷ calcium channel blockers,¹⁹ or various miscellaneous treatments such as endorphins, essential fatty acids, ganglioside, insulin, lithium, naloxone, oestrogen, periactin, phenylalanine, piracetam, stepholidine, tryptophan, and electro-convulsive therapy.²⁰

While earlier clozapine studies suggested modest efficacy after extended periods of treatment,^{11,12} a more recent study¹³ indicated efficacy after a relatively brief period of treatment (5 to 6 weeks), and at a relatively low dose. However, the moderate improvements in TD need to be weighed against the higher reported morbidity and poorer tolerability of clozapine.¹² There are indications that the newer atypical antipsychotic agents, with a reduced propensity to produce acute extrapyramidal symptoms (EPS) are also less likely to cause TD. This raises the possibility that they may also have an antidyskinetic effect in patients with established TD. However, while a reduction in dyskinesia scores has been reported in patients with chronic schizophrenia treated with risperidone compared to placebo,²¹ efficacy has yet to be demonstrated in samples of patients with TD.⁵ Quetiapine is a novel antipsychotic that, like clozapine, has a reported incidence of acute EPS across the dose range that is no different to that of placebo.²² Quetiapine appears to be associated with a low risk of tardive dyskinesia in adult²³ and elderly²⁴ patients. Its low striatal D2 receptor binding profile,²⁵ rapid release from D2 receptors,²⁶ possible neuroprotective action²⁷ and its lack of antimuscarinic activity (reported to exacerbate TD),²⁸ theoretically make it a particularly good candidate for the treatment of TD.

This study aimed to evaluate the efficacy of quetiapine compared with haloperidol in treating schizophrenic patients with established TD in a controlled design over a 12-month period. Previous TD treatment trials have often been limited by very small samples, brief durations and lack of blinding procedure. The present study was designed with these potential pitfalls in mind.

METHOD

Patients:

In- and out-patients from Stikland and Tygerberg Academic Hospitals, as well as surrounding community clinics in Greater Cape Town were screened for the presence of TD. Males and females aged 18 - 65 years were considered for inclusion if they met DSM IV criteria and Schooler and Kane criteria²⁹ for the diagnosis of TD. The latter criteria comprise: a) a history of at least three months cumulative antipsychotic exposure, b) the presence of at least moderate abnormal, involuntary movements in one or more body areas or at least mild movements in two or more body areas and c) an absence of other conditions that might produce abnormal involuntary movements. Additionally, patients were required to have a diagnosis of schizophrenia or schizo-affective disorder. Exclusion criteria were: neurological disease, any general medical condition that may cause movement disorders; psychiatric disorder not stabilised; and patients currently receiving clozapine. The study protocol and

patient information and consent procedures were approved by the University of Stellenbosch Ethics Committee, and all subjects provided written, informed consent to participate. The study complied with International Conference on Harmonization Guidelines for Good Clinical Practice.³⁰

Study design:

This was an investigator-blinded, parallel-group comparison of flexible doses of quetiapine and haloperidol in patients with TD. After an initial screening visit, subjects were tapered from all psychotropic medication over a 2 week period (although a shorter period was allowed if there was concern regarding the clinical status of the patient during this period). Subjects were then randomised to receive either quetiapine or haloperidol for a 50-week treatment period. The dose of medication was titrated over seven days to the starting dose (haloperidol: 5mg/day for 4 days, 10mg/day for 3 days; quetiapine, 100mg/day for 2 days, 200mg/day for 2 days, 300mg/day for 2 days and 400mg/day for 1 day). At the end of the titration period all patients were receiving either quetiapine 400mg/day or haloperidol 10mg/day. Thereafter, flexible dose adjustment was allowed at the discretion of the investigator, according to the status of psychiatric and motor symptoms, up to a maximum dose of haloperidol 20mg/day and quetiapine 800mg/day. Haloperidol was adjusted in 2.5mg increments and quetiapine in 100mg increments. Medication compliance was assessed by 'pill counts' at each visit.

The following concomitant medication was allowed: benzodiazepines for agitation or insomnia; and anticholinergic agents in the event of treatment emergent or worsening EPS. Medications that were not allowed were other antipsychotics, or other medication known to improve or exacerbate movement disorders.

Assessments were conducted at two-weekly intervals for the first 6 weeks, and thereafter 4 weekly, until the completion of the trial (50 weeks of treatment). Patients were assessed by means of the following scales: Extrapyramidal Symptom Rating Scale (ESRS),³¹ Clinical Global Impression (CGI) for dyskinesia; and Positive and Negative Syndrome Rating Scale (PANSS).³² The investigators were experienced psychiatrists who participated in training sessions. The inter-rater-reliability testing concordance coefficients were above 0.8 for the ESRS and PANSS. Blood samples for serum prolactin and glycosylated haemoglobin (HbA1c) were collected at screening and every three months. Subjects were weighed at screening and 3 monthly.

Primary analysis:

The primary outcome of interest was the change in dyskinesia scores over time. Severity of dyskinesia was assessed by the ESRS dyskinesia subscale scores (items 49-55) and the CGI dyskinesia scores. Treatment groups were compared at 3, 6, 9 and 12 months. The percentage change in scores from baseline to endpoints at 6 and 12 months was calculated. The percentage of responders was also calculated at 6 and 12 months (response being defined as $\geq 50\%$ reduction in ESRS dyskinesia subscale and CGI dyskinesia scores).

Secondary analysis:

The effect of the treatments on psychotic symptoms was assessed by means of the PANSS. Other EPS (parkinsonism, including an item for akathisia, and dystonia) were assessed by means of the ESRS total score minus the ESRS dyskinesia subscale score. Mean group values for weight, body mass index (BMI), serum prolactin and glycosylated haemoglobin were compared at three monthly intervals.

Statistical analyses:

The sample size was not based on formal statistical criteria. We initially conducted an observed cases (OC) analysis for between-group comparisons. For assessing the treatment effects over time and dealing with the problem of missing values due to subject withdrawals we performed two analyses on the intent to treat population. We employed a repeated measures mixed effects modeling approach for the primary efficacy measures (change in dyskinesia scores) and a last observation carried forward (LOCF) approach for the secondary measures.³³ For the repeated measures mixed effects model, plots of dyskinesia scores versus time indicated some dependence between the two variables, and that this could adequately be represented by a straight line. So the model we fitted assigned a slope and an

intercept to every subject; they are, therefore the random effects. The variation between times within subjects was modeled via an "unstructured" option. Student's t-test was used to compare the treatment groups with respect to continuous variables. Significance tests were performed at a two-sided alpha level of 0.05. Results are expressed as mean±SD.

RESULTS

Forty-seven subjects were entered into the study between 5 April 2000 and 13 March 2002. Two were excluded (one withdrew before reaching the target treatment dose, and one had unrelated medical illness). Thus, the analysis was conducted on 22 subjects in the quetiapine group and 23 in the haloperidol group. Baseline demographic and clinical details were similar for the two treatment groups (Table 1). Ten quetiapine-treated subjects failed to complete the trial, for the following reasons: worsening of psychosis (n=7); non-compliance (n=1); withdrawal of consent (n=1); and pregnancy (n=1). In the haloperidol group eight subjects did not complete the trial, due to worsening of psychosis (n=4); non-compliance (n=1); withdrawal of consent (n=1); severe, persistent dystonia (n=1); and disallowed concomitant treatment (n=1). For the OC analysis the sample sizes for quetiapine and haloperidol were, respectively, 19 and 21 at 3 months; 15 and 16 at 6 months; 13 and 16 at 9 months and 12 and 15 at 12 months. The mean±SD endpoint doses were 400±147.7mg/day for quetiapine and 8.5±5.6mg/day for haloperidol.

Effect of treatment on TD:

For both treatment groups there was a significant reduction in ESRS dyskinesia subscale scores from baseline to endpoint ($p > 0.0001$). For the OC analysis, quetiapine-treated patients showed significantly greater improvement than haloperidol-treated subjects at 6 ($p = 0.01$) and 9 ($p = 0.004$) months, but not at 12 months ($p = 0.1$). For the CGI-dyskinesia scores the quetiapine patients did significantly better than those treated with haloperidol at 6 ($p = 0.03$), 9 ($p = 0.001$) and 12 months ($p = 0.03$). In the repeated measures, mixed effects model analysis, both treatments produced significant dyskinesia reductions as reflected by the baseline to endpoint total change scores. There were statistically significant differences between treatments in the rates of change in the CGI dyskinesia score (but not the ESRS dyskinesia subscale scores). The model demonstrated that CGI dyskinesia scores declined significantly more in subjects taking quetiapine than in those taking haloperidol ($F = 10.52$, $df = 1:43$, $P = 0.002$) (Figure 1). The response rates ($\geq 50\%$ CGI dyskinesia reduction) for quetiapine and haloperidol respectively, were 64% and 37% at 6 months and 55% and 28% at 12 months.

Effect of treatment on psychosis:

Baseline PANSS scores were low in each treatment group, as patients were required to be clinically stable to be eligible for the study. There were no differences at any stage between the two treatment groups for the PANSS total scores, as well as for the PANSS positive, negative and general psychopathology subscale scores (Table 2).

Tolerability:

EPS:

The quetiapine-treated subjects showed a significantly greater reduction of EPS other than dyskinesia at 3, 6 and 9 months ($p = 0.01$; $p = 0.01$ and $p = 0.002$, respectively), but not at 12 months ($p = 0.3$). Fourteen (60%) subjects in the haloperidol group required ongoing or newly prescribed anticholinergic medication compared to 6 (27%) subjects in the quetiapine group.

Weight and glucose metabolism:

The mean body weights did not change significantly throughout the study, and did not differ significantly between groups (Table 3). Glycaemic control as evaluated by glycosylated hemoglobin (HbA1c) also did not change throughout the study for the quetiapine (baseline=6.4±1.1%; endpoint=6.1±2.4%) and haloperidol-treated patients (baseline=7.0±2.4%; endpoint=5.5±1.2%), and there were no between-group differences.

Serum prolactin:

For the haloperidol-treated patients the mean±SD serum prolactin levels increased from 15.2±9.2 ng/ml at baseline to 25.5±14.9 ng/ml at endpoint, while for the quetiapine group they decreased from 25.4±23.3 ng/ml at baseline to 9.1±10.2 ng/ml at endpoint. Endpoint values differed significantly between the groups ($p=0.005$).

DISCUSSION

The results of this study confirm previous case-reports^{34,35,36} suggesting that quetiapine is an effective treatment for TD. While both treatments were associated with improvement in dyskinesia, the quetiapine-treated patients did significantly better. The beneficial effect for quetiapine was substantial, and sustained, as exemplified by the finding that 55% of the subjects achieved ≥50% reduction in dyskinesia at the end of the trial, with their mean CGI dyskinesia scores declining from 4 (moderate) at baseline, to 2 (borderline) at endpoint.

Our findings confirm that paradoxically, antipsychotics (including conventional antipsychotics) are effective in reducing the severity of TD.³⁷ While previous work indicated an antidyskinetic effect in short-term studies, the long-term outcome of continuous antipsychotic treatment in patients with TD was unknown.⁵ The present study indicates that this effect is enduring. Furthermore, we found no indication of worsening of TD, even in the haloperidol-treated subjects, thus supporting the observation that TD does not seem to progress with ongoing antipsychotic treatment.⁵

The underlying mechanism of the beneficial effect on dyskinesia is not clear. The fact that substantial improvement was apparent even after 12 weeks of treatment suggests either an early masking or suppressant effect on TD. However, the sustained improvement in the quetiapine-treated subjects supports a direct antidyskinetic effect with this agent. Although not directly confirmed in our trial, the results of another study suggest that this may well be the case for atypical antipsychotics. Withdrawal of clozapine after 12 months of treatment was not associated with an exacerbation of TD symptoms, whereas withdrawal of haloperidol was.³⁸

These results are also of interest in that they provide data on the long-term use of quetiapine under blinded conditions. Psychotic symptoms were comparable in both groups at baseline and throughout the treatment period. This was not unexpected despite a previously reported superior response rate for quetiapine over haloperidol,³⁹ as a requirement for selection was a stable psychiatric condition, and the baseline PANSS scores were low. Quetiapine-treated patients had fewer other EPS (parkinsonism, akathisia and dystonia), and were prescribed less anticholinergic medication. Whereas serum prolactin levels increased in the haloperidol group, they decreased in the quetiapine group. Differences between the groups were highly significant, in keeping with findings in previous short-term studies.²² Neither treatment group showed any tendency toward persistent weight gain, and glycaemic control was also maintained in both groups.

It deserves to be noted that 10 (45%) of the quetiapine-treated subjects were withdrawn from the trial, and 8 (34%) from the haloperidol group. While the dropout rates did not differ significantly between the groups, and were in line with what could be expected from a controlled study over 12 months,⁴⁰ the relatively low doses of quetiapine used may also be partially responsible for this. The most common reason for withdrawal in the quetiapine group was worsening of psychosis (31%). The low doses prescribed probably reflect the fact that investigators were primarily concerned with motor symptoms, and were reluctant to use higher doses of antipsychotics in subjects with TD. Future studies should further address this issue.

The following factors limit the generalization of our findings. First, the sample size was relatively small, thereby increasing the chances of type II errors. (A substantially larger sample in a TD study would be difficult to obtain from a single site however, as recruiting these subjects proved to be difficult - it having taken us 2 years to complete enrollment for this study.) This problem was compounded by the high withdrawal rate associated with trials of long duration such as this. Second, the dose of quetiapine was lower than that generally recommended in clinical practice. While the use of higher doses may possibly have reduced

the number of dropouts due to worsening of psychosis, it is not clear what the effect would have been on dyskinesia symptoms. Finally, our study did not investigate whether the improvement in dyskinesia was maintained after discontinuation of quetiapine.

CONCLUSION

The best treatment for TD is prevention. In this regard, the use of atypical antipsychotics as first-line medications is likely to reduce the incidence of TD. Patients with established TD who are taking conventional antipsychotics are candidates to be switched to an atypical antipsychotic.⁴¹ While clozapine has been reported to be moderately effective, its use in the treatment of TD is limited by the risk of agranulocytosis⁴¹ and poor tolerability.¹² To date, no other controlled studies exist evaluating the efficacy of other atypical antipsychotics in the treatment of TD. Quetiapine appears to be effective and well tolerated in TD, and seems to be a good treatment option for these patients.

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Table 1. Baseline demographic and clinical details of the two treatment groups (mean±SD).

	Quetiapine (n=22)	Haloperidol (n=23)
Male : female	14:8	15:8
Age	49.2±14.5 yrs	50.1±8.6 yrs
ESRS Dyskinesia scores	10.8±5.0	13.8±5.7
CGI Dyskinesia scores	4.0±0.9	4.0±0.9
ESRS total scores	35.0±12.8	37.2±15.8
Duration of psychosis	15.9±11.7 yrs	17.4±10.6 yrs
Antipsychotic dose prior to randomization (Chlorpromazine equivalents)	393.6±420 mg/day	234.5±142 mg/day

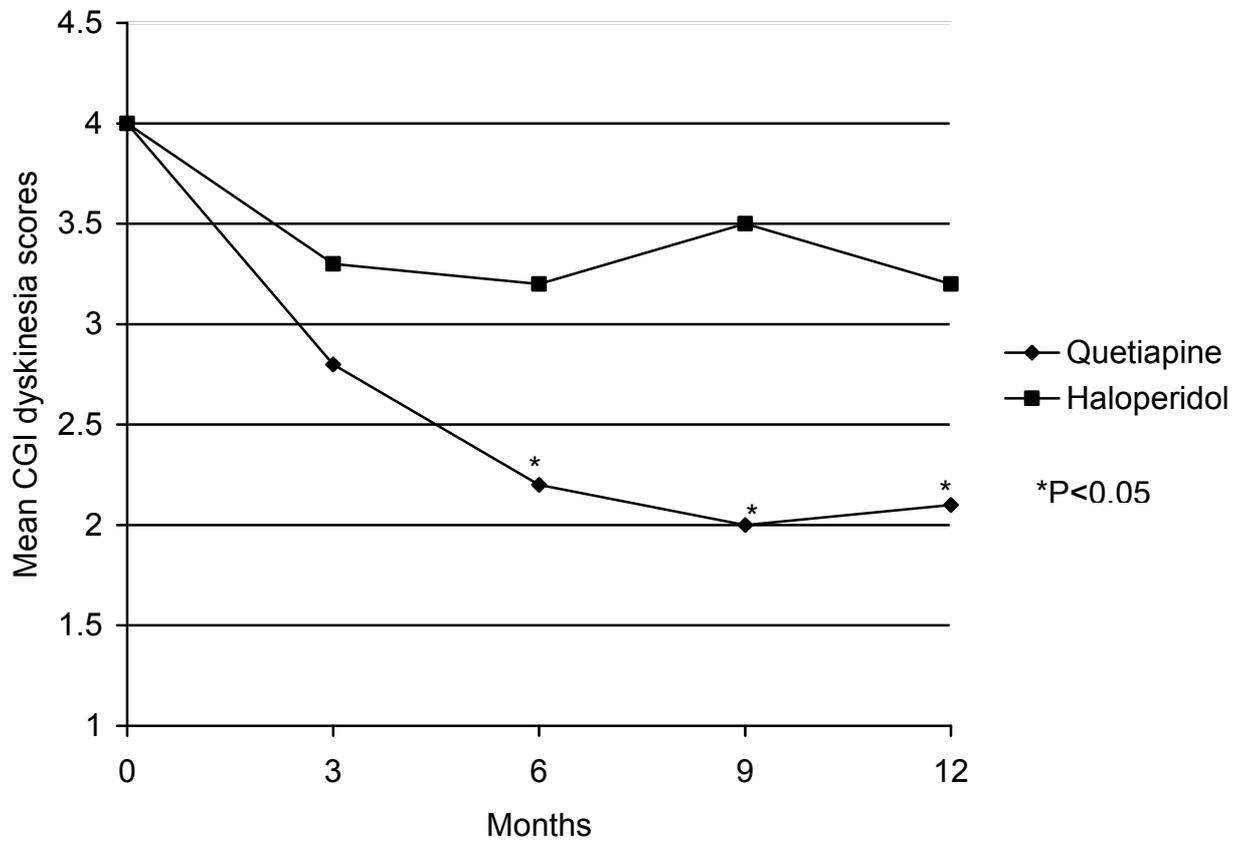
Table 2. Baseline and 12 month PANSS scores (mean±SD) for the two treatment groups.

	Quetiapine		Haloperidol	
	Baseline	Endpoint	Baseline	Endpoint
PANSS total	55.5±12.9	49.2±11.5	57.0±14.1	51.5±15.4
PANSS positive	10.8±4.4	8.0±2.1	10.7±5.4	9.3±3.9
PANSS negative	19.4±5.5	20.0±6.1	20.6±5.9	18.8±5.1
PANSS general psychopathology	25.5±5.9	21.1±5.2	25.6±6.1	23.3±7.7

Table 3. Mean±SD body weight (Kg) for the two treatment groups.

	Quetiapine	Haloperidol
Baseline	71.9±21.3	66.6±11.7
3 months	77±22.5	66.5±11.2
6 months	71.0±25.8	66.8±11.0
9 months	71.7±22.3	66.0±10.6
12 months	71.2±2	66.9±11.1

Figure 1. Mean CGI-dystonia scores over 12 months for the two treatment groups.



3.b.ii The effects of eicosapentaenoic acid in tardive dyskinesia: a randomised, placebo-controlled trial

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Objective: Worldwide, conventional antipsychotic medication continues to be used extensively, and tardive dyskinesia (TD) remains a serious complication. The primary objective of the present study was to compare the efficacy of EPA versus placebo in reducing symptoms of TD.

Method: This was a 12-week, double-blinded, randomised, study of ethyl-EPA 2g/d versus placebo as supplemental medication, in patients with schizophrenia or schizoaffective disorder, with established TD.

Results: Eighty-four subjects were randomised, of whom 77 were included in the analysis. Both the EPA and placebo groups displayed significant baseline to endpoint improvements in Extrapyramidal Symptom Rating Scale dyskinesia scores, but there were no significant between-group differences ($p=0.4$). Response rates ($\geq 30\%$ improvement in TD symptoms) also did not differ significantly between EPA treated subjects (45%) and placebo treated subjects (32%) ($p=0.6$). However, a post-hoc linear mixed model repeated measures analysis of variance indicated an effect for treatment group and duration of TD. The EPA treated patients had significantly greater mean reductions in dyskinesia scores initially, although this was not sustained beyond 6 weeks.

Conclusions: This trial failed to demonstrate an antidyskinetic effect for ethyl-EPA 2 g/d on the primary efficacy measure. However, a modest and transient benefit is suggested in patients with more recent onset of TD. The lack of clear-cut efficacy could be explained on the basis of the dose of EPA being too low, the study being underpowered, TD being too chronic in the majority of cases, differences in dietary fatty acid intake, or that EPA lacks an antidyskinetic action.

1. Introduction

Results from available long-term studies indicate that new-generation antipsychotics have a reduced risk for inducing tardive dyskinesia (TD), compared to conventional antipsychotics (Correll et al., 2004; Margolese et al., 2005). While the increasing use of new generation antipsychotics should therefore ultimately reduce its prevalence, TD remains a significant clinical problem. TD is a frequent complication of conventional antipsychotic treatment (Kane et al., 1988), and worldwide these agents continue to be used extensively to treat psychotic disorders. This occurs largely in lower income countries due to the high acquisition costs of the newer agents (Emsley et al., 1999).

TD is usually persistent, and refractory to treatment. With the exception of clozapine (Lieberman et al., 1991; Tamminga et al., 1994; Spivak et al., 1997), quetiapine (Emsley et al., 2004) and possibly branched-chain amino acids (Richardson et al., 2003) and a presynaptic monoamine depleting agent tetrabenazine (Ondo et al., 1999), little evidence exists to indicate efficacy for any other treatment modality for TD. No adequate studies exist to support the use of benzodiazepines (Umbrich and Soares, 2003), cholinergic agents (Tammenmaa et al., 2002), vitamin E (Soares and McGrath., 2001a), melatonin (Nelson et al., 2003), gamma-aminobutyric acid (Soares et al., 2001), calcium channel blockers (Soares and McGrath, 2001b), non-neuroleptic catecholaminergic agents (El-Sayeh et al., 2006) or various miscellaneous treatments such as endorphins, essential fatty acids, ganglioside, insulin,

lithium, naloxone, oestrogen, cyproheptadine, phenylalanine, piracetam, stepholidine, tryptophan, electro-convulsive therapy (McGrath and Soares, 2000a) and acupuncture (Rathbone and Xia, 2005). Withdrawal of the offending antipsychotic drug is usually not feasible, as this may result in an exacerbation of the TD symptoms (Gardos et al., 1984; Dixon et al., 1993), and dramatically increases the risk of precipitating a psychotic relapse (Egan et al., 1997). The effect of dose reduction and intermittent dosing strategies, such as drug holidays has not been adequately assessed in controlled trials (McGrath and Soares, 2000b). Paradoxically, ongoing treatment with a conventional antipsychotic may suppress, and even improve symptoms (Jeste et al., 1979; Emsley et al., 2004), particularly in the short-term (American Psychiatric Association Task force on Tardive Dyskinesia, 1992).

Clearly, there remains an unmet need for an effective and affordable treatment for TD. One possible candidate is eicosapentaenoic acid (EPA), an omega-3 polyunsaturated fatty acid obtained from marine and plant sources (Stensby, 1969). It has been hypothesised that a disorder of neuronal membrane phospholipid metabolism is present in schizophrenia (Horrobin, 1998), and that the omega-3 fatty acids, and EPA in particular, may have a role in treating this illness. Reports of abnormalities of essential fatty acids in erythrocyte membranes and cultured skin fibroblasts in patients with schizophrenia, as well as case reports, open-label clinical trials and some but not all, of randomised controlled trials using EPA as supplemental medication lend support to this hypothesis (for review see (Emsley et al., 2003)).

In addition to its possible antipsychotic effect, there is reason to believe that EPA may have a role in the treatment of TD. In a study of 20 hospitalised subjects with chronic schizophrenia, a significant inverse correlation between dietary EPA and severity of TD has been reported. Subsequent open-label treatment of these subjects with a standard EPA-rich marine oil for 6 weeks resulted in significant improvement in TD (Peet et al., 1996). In a controlled study of essential fatty acid (EFA) supplementation in psychiatric patients with TD, evidence of EFA deficiency was found, and a marginally significant antidyskinetic effect of EFA supplementation was reported (Vaddadi et al., 1989). In a study assessing the relationships between psychiatric status, TD and levels of essential fatty acids in red blood cell membranes and plasma, 72 patients with schizophrenia or schizoaffective disorder were followed up over 4 to 5 years. It was found that patients with TD had lower levels of linoleic acid and higher levels of dihomo-gamma-linolenic acid (but not reduced levels of omega-3 fatty acids) (Vaddadi et al., 1996).

We previously reported a 12-week randomised, double-blind study with ethyl-EPA 3g/day versus placebo as add-on to standard antipsychotic treatment, in forty subjects with chronic, refractory schizophrenia. While there were no differences between the groups regarding changes in the Extrapyramidal Symptom Rating Scale (ESRS) parkinsonism, dystonia or akathisia scores, the ethyl-EPA group showed a significantly greater reduction in dyskinesia scores ($p=0.008$). This study also reported a significant advantage for the ethyl-EPA group in terms of overall psychosis symptom reduction (PANSS total). An analysis of covariance indicated an interaction between PANSS total score reduction and ESRS dyskinesia score reduction, suggesting a common mechanism for antidyskinetic and antipsychotic actions (Emsley et al., 2002).

The present study was undertaken to assess the antidyskinetic effect of EPA in patients with established TD.

2. Methods:

2.1 Objectives:

The primary objective was to compare the efficacy of EPA versus placebo as supplementary medication in reducing symptoms of TD. Secondary objectives were to compare the efficacy of EPA versus placebo as supplementary medication in reducing symptoms of psychosis in these subjects. Safety and tolerability assessments were also performed, but will be reported in a separate publication.

2.2 Study setting and design:

This was a double-blinded, randomised, parallel-group comparison of EPA and placebo in the treatment of established TD in patients with schizophrenia or schizoaffective disorder. It was a single-site study, and patients were recruited from Stikland Academic Hospital and its surrounding community psychiatric services in the greater Cape Town area of South Africa. Participants were recruited between 4 April 2003 and 31 December 2004. There was a pre-trial screen, following which subjects were entered into the randomised treatment phase for 12 weeks.

2.3 Participants:

Eligible patients were male or female; aged 18 to 60 yrs; meeting Diagnostic and Statistical Manual of Mental Diseases, Fourth Edition (DSM-IV) (American Psychiatric Association, 1994) criteria for TD, as well as for schizophrenia or schizoaffective disorder; with a CGI severity of TD score ≥ 3 ; and who had received a fixed dose of antipsychotic medication for at least 6 weeks prior to trial entry. Patients were excluded if their psychiatric disorder was not stable; they had significant neurological disorder other than TD; significant other medical illness; substance abuse; were pregnant or breast-feeding; or were currently receiving clozapine.

The study complied with ICH Guidelines for Good Clinical Practice (International Conference on Harmonization, 1996). The trial was approved by the Institutional Review Board of the University of Stellenbosch, and the Medicines Control Council of South Africa (national regulatory authority). Written informed consent was obtained from the participants at the screening visit.

2.4 Assessments:

All patients were screened to assess their eligibility for the trial. The screening visit included the following: Demographic details, psychiatric history, medical history, physical examination, vital signs and laboratory tests. The duration of TD was assessed by interrogation of the participants and family members where possible, as well as by scrutinizing the clinical files. Patients were assessed at baseline and at 3-weekly intervals by means of the Extrapyramidal Symptom Rating Scale (ESRS) (Chouinard and Margolese, 2005), Clinical Global Impressions for TD, and the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987).

2.5 Trial treatment:

Subjects were randomly assigned to receive either an encapsulated ethyl-EPA supplement 2 g/day (2X500 mg capsules twice daily) (Amarin Neuroscience Ltd.), or an identical capsule containing placebo (medicinal liquid paraffin BP 2 g/day), in addition to the medication that they had been receiving, for the duration of the study. Ethyl-EPA is a highly purified derivative of fish-oil. The Food and Drug Administration of the United States of America has affirmed the status of fish-oil as generally recognised as safe with EPA doses up to 3 g/day (Department of Health and Human Services, 1997). Trial supplies were packed by an independent contract clinical trials supplies company (DHP), who prepared the placebo and active packs for the entire trial and assigned the randomisation numbers to the packs. The randomisation code was broken after completion of the trial.

2.6 Concomitant treatment:

In addition to the trial medication and the ongoing, fixed antipsychotic medication, the following concomitant medication was allowed: Anticholinergic medication for treatment-emergent extrapyramidal symptoms (EPS); anxiolytic or hypnotic medication for treatment-emergent insomnia or anxiety; any medication for physical conditions that were present prior to the commencement of the trial, or that arose during the course of the trial.

2.7 Outcome measures:

The primary outcome measure was the change in ESRS dyskinesia subscale scores from baseline to week 12. Secondary outcome measures for an antidyskinetic effect were: The proportion of TD responders (defined as an improvement in ESRS dyskinesia subscale score $\geq 30\%$); and change in TD CGI scores from baseline to 12 weeks. Additional secondary outcome measures were change from baseline to week 12 for ESRS parkinsonism, akathisia

and dystonia subscale scores. Finally, for an effect of EPA on psychosis we examined change from baseline to week 12 in PANSS total scores, positive, negative and general psychopathology subscale scores; and the proportion of responders (defined as an improvement in PANSS total scores $\geq 20\%$).

2.8 Statistical analysis:

The primary intent of this study was to evaluate the ability of ethyl-EPA versus placebo to reduce TD symptoms after 12 weeks of treatment. The principal null hypothesis was therefore that ethyl-EPA would not differ from placebo on the primary efficacy measure. For sample size determination we obtained an estimate of the variability of the change in ESRS dyskinesia scores after 12 weeks of treatment with ethyl-EPA and placebo as add-on to their previous antipsychotic medication from the previous trial conducted at our centre (Emsley et al., 2002), which gave 2.13 as the standard deviation (unpublished). We calculated that, with a significance level of 5% and 90% power, 32 patients per randomised group would be sufficient to detect a 1.75 point difference in change in ESRS dyskinesia scores (the difference obtained in our previous study) from baseline to endpoint. Allowing for an estimated withdrawal rate of 30%, we decided to recruit 42 patients per treatment group.

Comparisons between the treatment groups were performed by intention-to-treat (all subjects who were treated and with at least one post-baseline assessment), with last observation carried forward. Analysis of variance and the Chi-square test were used for comparing univariate differences between numeric and categorical variables respectively. We used analysis of covariance for the assessment of changes from baseline to endpoint for ESRS dyskinesia, parkinsonism, dystonia and akathisia subscale scores and TD CGI scores, including the baseline ESRS subscale score, treatment received, age and duration of TD as factors. For PANSS changes from baseline to endpoint, we included baseline PANSS total score, treatment received, age and duration of schizophrenia as factors. Comparison of the time to response for the two groups was calculated by means of Kaplan-Meier survival curves. Controlling for covariates was done by Cox proportional hazard regression.

For assessing the treatment effects over time we adopted the linear mixed model approach, modelling the time trends in dyskinesia scores by straight lines. Treatment group was a class variable, while age and duration of TD were numerical variables. All of the tests were interpreted at 5%, 2-tailed significance level.

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6 Results:

3.1 Characteristics of the two treatment groups:

Out of a total of 125 patients who were pre-screened, 84 were recruited and randomised to double blind supplemental treatment with either ethyl-EPA or placebo. The data on 7 patients (3 on ethyl-EPA and 4 on placebo) were excluded from analysis because they failed to complete at least one post-randomisation visit. Data from the remaining 77 patients were included in the final analysis. The demographic characteristics and baseline PANSS scores in the two treatment groups were similar, but baseline ESRS dystonia subscale and TD CGI scores differed significantly (Table 1). Most patients had been ill for more than a decade and had TD for more than 5 years. All had been treated with conventional antipsychotics at study entry. None had received new generation antipsychotics in the preceding 6 weeks. The number of subjects who discontinued medication prematurely in the ethyl-EPA group was 8 (19%) (consent withdrawal n=4; non-compliance n=3; protocol violation n=1), and in the placebo group 14 (33%) (consent withdrawal n=9; non-compliance n=3; adverse events n=2 [congestive cardiac failure; nose-bleed]) (Chi-square=2.2, df=1, p=0.1).

3.2 Effect of treatment on dyskinesia:

There was a significant reduction from baseline to endpoint in ESRS dyskinesia scores for the ethyl-EPA treatment group (p=0.0001), as well as for the placebo group (p=0.004). However, there were no between-group treatment differences for the primary efficacy measure. Analysis of covariance found that changes in dyskinesia scores were not

significantly influenced by age, duration of TD, baseline dyskinesia scores or treatment group ($F[1, 60]=0.003$, $p=0.95$). Dyskinesia response rates did not differ significantly between the treatment groups (ethyl-EPA group $n=17$ [45%]; placebo group $n=12$ [32%], $p=0.3$), and the time to TD response was similar (ethyl-EPA group 7.7 ± 3.5 wks; placebo group 8.1 ± 3.4 wks, $p=0.6$).

Details of the fitting of a linear mixed model allowing for random between-subject effects are provided in Table 2. Several of the coefficients were significantly different from zero, and an effect for duration of TD as well as treatment group is suggested. In the linear mixed model repeated measures ANOVA, both EPA (Figure 1 (a)) and placebo (Figure 1 (b)) produced significant dyskinesia score reductions. In view of the fact that there were several significant interactions between coefficients (Table 2), we compared the expected means of the two treatment groups at the same values of duration of TD. Figure 2 shows a plot of the estimated mean differences with two-sided 90% and 95% confidence bands. The EPA treated patients had significantly greater mean reductions in dyskinesia scores up to approximately 6 weeks, but this was not sustained.

Table 2 about here
Figures 1a and 1b about here
Figure 2 about here

3.3 Effect of treatment on other EPS

There were no differences between the EPA and placebo groups respectively, for baseline to endpoint change in the ESRS parkinsonism subscale (-0.8 ± 3.2 vs. -1.1 ± 3.3 [$F_{91, 67}=0.1$, $p=0.7$], dystonia subscale (0.05 ± 0.5 vs. 0.4 ± 0.5 [$F_{91, 67}=0.1$, $p=0.7$], and akathisia score (-0.1 ± 0.4 vs. -0.06 ± 0.7 [$F(1, 67)=0.1$, $p=0.7$]).

3.4 Effect of treatment on psychosis:

There were no significant differences in the change in PANSS total scores from baseline to endpoint between the ethyl-EPA and placebo treatment groups. The analysis of covariance found that changes in PANSS total scores were not significantly influenced by age, duration of schizophrenia, baseline PANSS total scores or treatment group ($F[1, 62]=0.005$, $p=0.9$). The response rates ($\geq 20\%$ PANSS total score) were 1 (2.5%) for the EPA group and 2 (5%) for the placebo group (Chi-square 0.5, $df=1$, $p=0.5$). In a post-hoc analysis to assess the effect on psychosis symptoms in the more symptomatic subjects (PANSS total score ≥ 60), again changes in PANSS total scores were not significantly influenced by age, duration of schizophrenia, baseline PANSS total scores or treatment group ($F[1, 25]=0.008$, $p=0.9$).

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10 Discussion

This study failed to demonstrate a beneficial effect for ethyl-EPA 2 g/day on TD on the primary efficacy measure. However, the linear mixed model analysis provides some evidence to suggest a beneficial effect for EPA treatment, although this was modest and not sustained. These findings therefore differ from those of our previous study that was conducted in a smaller sample of chronic schizophrenic patients, not specifically selected for the presence of TD (Emsley et al., 2002).

There are several possible explanations for the failure of this study to demonstrate a clear-cut antidyskinetic effect. First, it is possible that the dose of 2g/day was too low - in our previous study (Emsley et al., 2002) a dose of 3g/day was used. Second, the study may not have been sufficiently powered to detect a small treatment effect. The trend difference in TD response rates in favour of the EPA group suggest that this may be the case. Third, most of our subjects had TD for a number of years - it is possible that ethyl-EPA may only be effective in cases of shorter duration. This is supported by the significant effect of duration of TD in the linear mixed-model analysis. In this regard it is of interest that, in a double-blind, controlled trial of ethyl-EPA in Huntington disease, it was reported that, although EPA had no overall effect, some benefit was recorded in patients with later onset of disease (Puri et al., 2005). Fourth, it is possible that dietary differences in fatty acid intake could account for the different findings between the studies. Fatty acids compete with one another for uptake, so

that the therapeutic effect of EPA may be most substantial in patients with low dietary intake of fatty acids (Emsley et al., 2003). We consider this unlikely to explain the different outcomes of the two trials however, as the subjects for both studies were from the same catchment area, and from similar ethnic and socio-economic backgrounds. Although blood samples for erythrocyte EPA levels were obtained from subjects at baseline and during the trial, these have not yet been analysed. Finally, it may be that EPA is devoid of an anti-dyskinetic effect, and the previous positive result was spurious, possibly as a consequence of the small sample.

The study also failed to demonstrate an antipsychotic effect for EPA. The lack of an effect on psychotic symptoms was not unanticipated, as our sample comprised largely symptom-free, stable patients. However, even the subset of more symptomatic patients showed no indication of improvement in PANSS scores with EPA treatment. Again, this could be due to the dose being too low, the study being underpowered, the chronicity of the sample, dietary differences in fatty acid intake, or a lack of antipsychotic activity for EPA. The absence of any clear-cut therapeutic effect for EPA in this study precluded us from investigating a relationship between antidyskinetic and antipsychotic effects.

In conclusion, the results of this study do not support the efficacy of ethyl-EPA 2 g/d in the treatment of TD in patients with schizophrenia, although some effect on patients with a more recent onset of TD cannot be ruled out. Further randomized, controlled trials with higher doses of EPA, and in subjects with recent onset of TD are warranted. Based on currently available evidence, patients with established TD should be treated with a new generation antipsychotic where possible. Although no differences in dyskinesia rates were observed between the new generation antipsychotics in a recently published comparative trial of these agents (Lieberman et al., 2005), the best evidence in terms of randomized, controlled trials for an antidyskinetic effect amongst these agents exists for clozapine (Lieberman et al., 1991; Tamminga et al., 1994; Spivak et al., 1997) and quetiapine (Emsley et al., 2004).

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Table 1. Baseline characteristics of the 77 participants with tardive dyskinesia.

Characteristic	Ethyl-EPA	Placebo	P-values
Age	42.4±10.3 yrs	43.4±10.9 yrs	0.7
Gender (M:F)	27:12	24:14	0.6
Duration of schizophrenia	16.0±10.5 yrs	16.8±10.4 yrs	0.7
Duration of TD	5.6±4.4 yrs	6.7±7.4 yrs	0.4
PANSS total score	59.2±13.0	57.5±11.8	0.6
ESRS parkinsonism subscale	8.8±6.6	9.1±6.1	0.9
ESRS dystonia subscale	0.1±0.4	0.7±1.7	<0.0001
ESRS dyskinesia subscale	12.0±4.9	12.5±5.7	0.4
ESRS total score	32.7±12.9	35.3±15.4	0.3
CGI TD	3.5±1.0	4.1±1.1	0.01

Table 2. Details of the fitting of a linear mixed model allowing for random between-subject effects

Coefficient	Value	Std Error	Degrees of Freedom	t-value	P-value
(intercept)	-3.903	1.467	173	-2.660	0.0085
Age	0.045	0.026	62	1.700	0.0942
Duration of TD	0.407	0.148	62	2.742	0.008
Treatment group	5.006	1/245	62	4.020	0.0002
Time point	0.026	0.332	173	0.078	0.9376
Duration of TD: Treatment group	-0.557	0.169	62	-3.299	0.0016
Duration of TD: Time point	-0.114	0.054	173	-2.117	0.0357
Treatment group: Time point	-1.221	0.421	173	-2.897	0.0043
Duration of TD: Treatment group: Time point	0.160	0.060	173	2.672	0.0083

Figure 1a. Change in mean ESRS dyskinesia subscale scores for the EPA treatment group at each timepoint

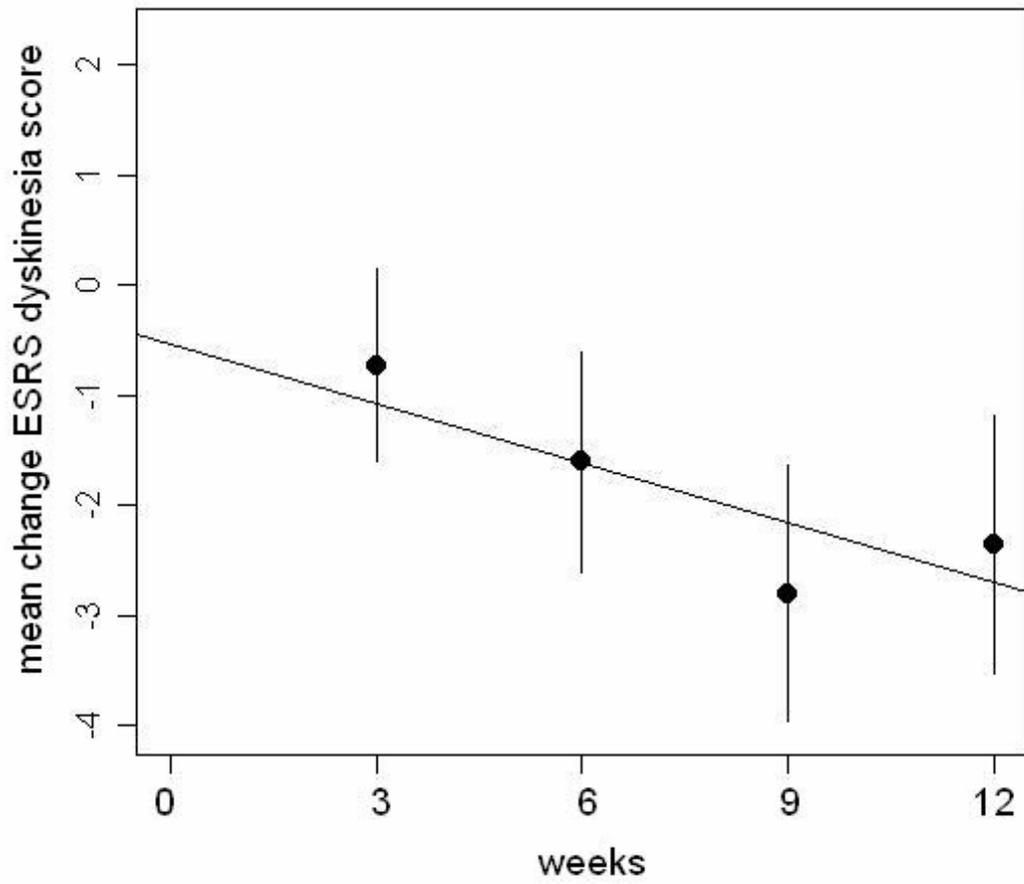


Figure 1b. Change in mean ESRS dyskinesia subscale scores for the placebo-treated group at each timepoint.

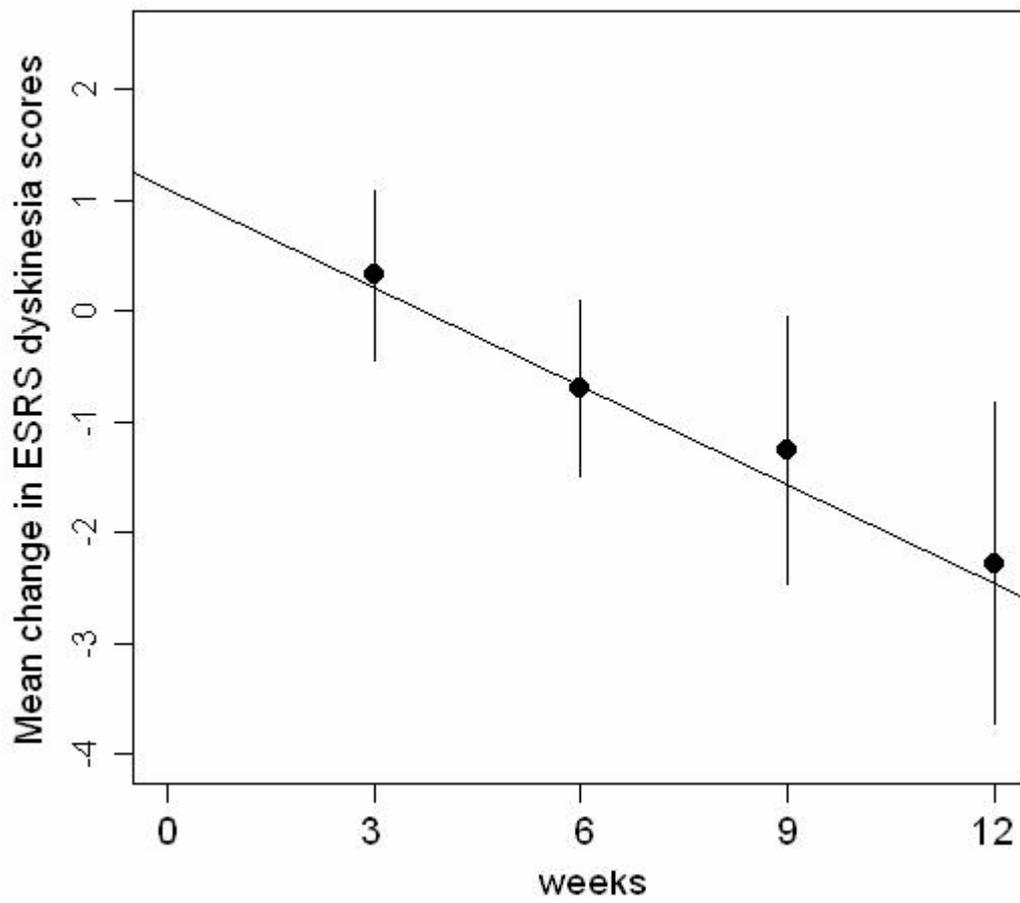
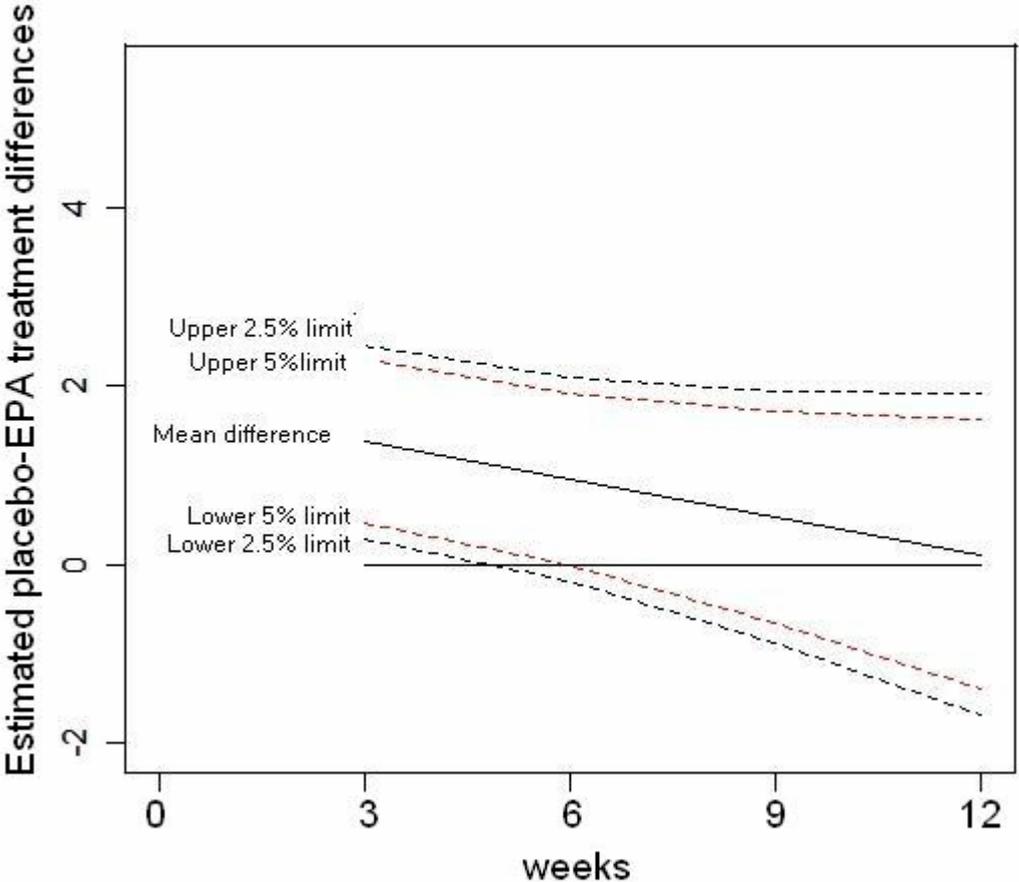


Figure 2. Estimated mean differences between EPA and placebo treatment groups, controlling for duration of TD.



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3.c.i Outcome of first-episode schizophrenia and the new antipsychotics

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This article reviews the English literature over the past 10 years with regard to treatment outcome in first-episode schizophrenia. Particular attention is paid to factors associated with poor outcome and predictors of relapse, and the use of the new antipsychotic agents.

Since the mid-1950s, conventional antipsychotic agents have consistently proved to be the most effective compounds in the treatment of schizophrenia.¹ Considerable variation in individual patient outcome is observed, with approximately 70% of patients showing substantial reduction of symptoms in the short term. Although a multitude of clinical trials has been conducted, no convincing data indicate that any one of these drugs, or a particular class of drugs, is more effective than any other.¹ While the short-term efficacy of antipsychotics is well established, earlier trials generally failed to appreciate that measurement of symptom reduction alone – often after only 6 or 8 weeks of treatment – did not provide an accurate indication of actual treatment outcome. A more comprehensive assessment of outcome is necessary, incorporating multiple outcome criteria such as level of occupational and social functioning, cognitive function, feeling of well-being, severity of side-effects, compliance, frequency of relapses and duration of hospitalisation.^{2,3}

When outcome is considered in these terms, an entirely different picture emerges. In fact, the overall outcome for schizophrenia is anything but satisfactory.^{4,5} Most patients require numerous hospitalisations for recurrence of psychotic symptoms, have impairment of functioning due to persistent negative symptoms and side-effects, are alienated from society, have impairment of cognitive functions (particularly attention, memory and executive functions),^{6,7} and display frequent and protracted periods of depression.⁸ About 10% of patients with schizophrenia eventually commit suicide.⁹

Major limitations of the conventional antipsychotic agents include the following:

1. Negative symptoms respond poorly.¹⁰ Persistence of negative features such as akinesia and poverty of speech results in impairment of social and occupational functioning. The degree of impairment is often severe, so that the majority of patients with schizophrenia are unemployed and socially isolated.
2. Lack of responsiveness to treatment, even with high dosages.¹¹ Treatment refractoriness, if severe, usually results in chronic institutionalisation and severe impairment of function.
3. High incidences of extrapyramidal symptoms (EPS). These side-effects are seen in approximately 75% of patients treated with conventional antipsychotic agents. EPS, particularly akathisia, cause great distress and discomfort, and are the single most important factor contributing to poor compliance.¹² Poor compliance in turn leads to recurrence of psychotic episodes, readmissions to hospital, and increased morbidity.¹³

A new and important development in schizophrenia research has been to focus studies on first-episode schizophrenia (FES).¹⁴ In this way, possible confounding variables such as the effects of medication and the development of chronic or secondary symptoms are eliminated. New information regarding the pathophysiology, psychopathology, course of illness and

response to treatment has emerged. Several methodologically sound longitudinal studies have been conducted, and important findings reported.

With regard to treatment, it has been shown that the clinical response is better in FES than in patients with recurrent episodes, and fewer FES patients are refractory to treatment.^{4,5,15,16} Also, medication is effective at a lower dosage, and FES patients appear more sensitive to EPS.^{5,17} Very importantly, it has been found that the time between the first appearance of psychotic symptoms and initiation of treatment is the best predictor of long-term outcome. Patients with a recent onset of psychotic symptoms fare better in follow-up studies than do those with symptoms of longer duration. Crow et al.¹⁸ reported that among 120 FES patients followed up for 2 years, relapse subsequent to initial hospital discharge was substantially more frequent in those whose pretreatment illness lasted more than 12 months. Loebel et al.¹⁹ followed up 70 FES patients for 3 years. Patients received standardised treatment and uniform assessments. Outcome was measured in terms of time to remission as well as degree of symptom remission. Duration of illness before treatment was found to be associated to a significant extent with time to remission as well as level of remission.

Earlier studies also provide evidence for a relationship between early treatment and favourable outcome. Angrist and Schulz²⁰ reported poorer response to antipsychotics in chronic patients, Lo and Lo²¹ found that a shorter duration of psychosis before treatment was significantly associated with a favourable outcome, and Rabiner et al.²² found in a group of 64 FES patients that the longer the duration of illness, the poorer the outcome. Also, after each subsequent relapse there is a drop-off in response to treatment.²³ It has been suggested that the acute psychotic symptoms could reflect an active morbid process which, if not ameliorated by antipsychotic drug treatment, may result in lasting morbidity.²⁴ Otherwise put, it is possible that an extended period of dopaminergic neural dysfunction may result in a more severe, or less readily reversible, pathophysiological condition. Whatever the mechanism, it is apparent that there is an evolution of resistance to treatment in the progression of the illness.

For this reason, prompt and effective intervention in the early stage of schizophrenia is critical to the outcome. Particular attention should be given to the initial diagnosis and treatment plan. Care needs to be taken in choosing a drug at a dosage that is going to be effective and at the same time well tolerated. According to Lieberman,²⁵ if we can reduce the duration of the acute psychotic phase of the illness, we can reduce the lasting impairment that schizophrenic individuals may sustain.

Another strategy to limit the accrued morbidity in schizophrenia concerns early identification of that important subgroup (10 - 20%) of FES patients who are refractory to treatment. If these patients could be detected as close to the onset of their illness as possible, alternative treatments could be initiated before further deterioration occurs. While factors such as male gender, early onset of illness, low educational level, affective blunting, premorbid personality disorder and high levels of expressed emotions in family members have been associated with poor outcome,²⁵ these findings have not been replicated consistently. The FES studies mentioned earlier in this article provide strong evidence that a longer duration of illness before treatment and frequent previous admissions significantly predict poor outcome. There are a number of biological indicators that may predict which patients are at risk for relapse with reduction or discontinuation of maintenance medication.²⁴ The most promising appears to be dopamine psychostimulant provocative tests – patients displaying transient activation of their symptoms after receiving methylphenidate are likely to relapse.²⁶ Another risk factor identified by the same investigators is the presence of tardive dyskinesia.

A further matter requiring careful attention in FES is the prevention of side-effects, particularly EPS. Very often, with the initiation of treatment, the development of EPS such as severe dystonia or akathisia can have a profound negative impact on the patient's compliance for years to come.¹² It is important to initiate treatment in FES with low-dosage medication, and carefully titrate up until a clinical improvement is observed, or until side-effects emerge. Because FES patients are particularly likely to develop EPS, a strong case can be made out for the prophylactic use of antiparkinsonian medication in an FES. An alternative would be to consider using a new antipsychotic, with a lower risk of inducing EPS.

The new antipsychotics

Several new antipsychotics such as olanzapine, seroquel, ziprasidone and sertindole are at various stages of development, and should be available for clinical use within the next few years. Only two are currently available, namely clozapine and risperidone. Clozapine, of course, is not new, but its re-introduction to clinical practice after being severely restricted when found in rare cases to cause fatal agranulocytosis has been supported by an enormous amount of new safety and efficacy data. The new antipsychotics can be classified according to their receptor-binding profiles – clozapine, olanzapine and seroquel being multireceptor antagonists and risperidone, ziprasidone and sertindole being dopamine (D₂) – serotonin (5HT₂) – norepinephrine (α₁) antagonists.²⁷

There is compelling evidence to suggest that the new antipsychotics have distinct advantages over conventional agents. Clozapine is associated with significantly fewer EPS, has a favourable effect across a broad spectrum of symptoms, and is effective in treatment-resistant schizophrenia.²⁸ Clozapine is also reported to improve cognitive impairment in schizophrenia²⁹ and to reduce suicidality.³⁰ Risperidone, in recommended doses, is reported to be more effective than haloperidol in reducing both positive and negative symptoms of schizophrenia and causes fewer EPS than conventional antipsychotics.³¹⁻³³ There are also indications that risperidone may be superior to the conventional antipsychotics in refractory schizophrenia.³⁴

Experience with these drugs in FES is limited. Szymanski et al.³⁵ have reported a modest outcome in a small cohort of FES patients treated with clozapine relatively early in the course of the illness. Subjects were refractory to conventional antipsychotics in multiple clinical trials. Although none of the patients attained a complete remission, 2 of 10 patients showed a favourable response at 6 weeks and 1 other after 12 weeks. In a large multicentre study,¹⁵ 183 subjects with first-episode schizophreniform disorder were treated with flexible doses of either risperidone or haloperidol for 6 weeks. Efficacy was assessed at weeks 1, 2, 4 and 6 by means of the positive and negative symptoms scale (PANSS), clinical global impressions and brief psychiatric rating scale (BPRS). Clinical improvement was defined as a 50% or more reduction in total PANSS scores at endpoint. EPS were rated according to the EPS rating scale. At endpoint both treatment groups showed significant improvement on the PANSS and BPRS. Sixty-three per cent of the patients on risperidone and 56% of those on haloperidol experienced clinical improvement. Risperidone caused significantly fewer and less severe EPS, and significantly fewer patients on risperidone discontinued treatment.

Cost is often given as the major reason for relegating the new antipsychotics to the second, third, or even last line of treatment for schizophrenia. However, the cost of medication is only a very small part of the total costs involved in treating patients with schizophrenia, so the cheapest drug may not provide the most cost-effective treatment. A re-thinking of this approach is likely. Considering that most schizophrenics do poorly with traditional antipsychotics in the long term, and particularly because recent evidence indicates that early and effective treatment and prevention of relapses has enduring favourable effects on outcome, the use of the new antipsychotics at an earlier stage of the illness needs to be considered seriously. Risperidone has proved to be a safe and effective antipsychotic that can be used as first-line treatment. Whether its reported efficacy for negative symptoms is due to a reduced incidence of EPS or whether it actually has a direct effect on primary negative symptoms, is not clear. Further experience will show whether it is also associated with a reduced rate of tardive dyskinesia and neuroleptic malignant syndrome, and whether it shares some of the other reported benefits of clozapine. Although there is abundant evidence that clozapine has a number of advantages over the conventional antipsychotics, the risk of agranulocytosis will probably prevent it from being used as a first-line drug. However, because its efficacy in refractory schizophrenia is well established, and because favourable long-term outcome depends on early response to treatment, it would be unwise to delay unnecessarily before switching non-responsive patients to clozapine. It has been suggested that if there has been no significant response after 3 months of treatment it would be an appropriate time to consider using clozapine.²

The antipsychotics currently available will soon be augmented by the introduction of other new compounds. Undoubtedly major revisions in our approach to the treatment of schizophrenia are under way, much the same as was the case with the treatment of depression after the introduction of the selective serotonin re-uptake inhibitors.

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3.c.ii Treatment of Schizophrenia in Low-Income Countries.

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Abstract

The introduction of the novel antipsychotics has had a major impact upon the treatment of schizophrenia. However, the greater acquisition costs of these drugs puts them beyond the reach of large sectors of the world's population. Consequently, the gap between the levels of care in high-income and low-income countries is likely to widen even further. Co-ordinated global action is necessary to ensure greater accessibility of these drugs. Cost-effectiveness studies in low-income countries need to be undertaken. The considerable evidence for improved safety and efficacy of low-dose compared to high dose classical antipsychotics offers an alternative that could be implemented immediately in low-income countries.

Introduction

The development of the novel antipsychotic drugs has had a major impact upon our approach to the treatment of patients with schizophrenia. Evidence is accumulating that these drugs hold significant advantages over their predecessors in terms of both efficacy and tolerability. In particular, it has been shown that the newer drugs are less likely to induce acute extrapyramidal symptoms (Thomas and Lewis, 1998), previously a major obstacle to the effective treatment of schizophrenia. Other reported advantages of these drugs include improved efficacy in treatment-refractory patients (Marder, 1996) and patients with negative symptoms (Carman et al, 1995) and depressive symptoms (Tollefson et al, 1998), reduced levels of suicidality (Meltzer and Okayli, 1995), less neurocognitive impairment (Rossi et al, 1997), better subjective quality of life (Franz et al., 1997), reduced incidence of tardive dyskinesia (Beasley et al, 1999) and improved overall outcome (Weiden et al, 1996). While some of these advantages may be modest, they are likely to make a substantial difference to patients in terms of improved social and vocational functioning and general quality of life. The clinical advantages of these drugs appear to be greatest close to the onset of the illness, and they are increasingly being advocated as first-line agents (Lieberman, 1996). The acquisition costs of the novel antipsychotics are, however, much greater than those of the older drugs, and their availability in lower-income countries, particularly in Africa, Latin America, Asia and the Pacific, is extremely limited. In contrast, the generic classical psychotropic drugs used extensively in state health services in developing countries are very cheap. These countries tend to rely on a handful of psychotropic drugs. For example, the South African Essential Drugs List for primary health care has 8 psychotropic drugs, of which 4 are classical antipsychotics (chlorpromazine tablets, fluphenazine decanoate injection, haloperidol injection, and zuclopenthixol acetate injection). There are no novel antipsychotics on the list (Gous et al, 1996). While some low-income countries are apparently making use of generic novel antipsychotics such as clozapine the efficacy and safety of these compounds is undocumented in the literature, and availability limited.

Until recently, psychiatry operated relatively cheaply, with most of its budget being allocated to salaries of mental health workers and a few inexpensive psychotropic drugs. As awareness of newer methods of treatment permeates both the medical profession and the public, we are facing the challenge of having to compete with other specialities for a larger portion of the health budget. In low-income countries, the situation is made more difficult by the limited resources for which disciplines must compete and a lag in official attitudes. Policy makers usually regard mental illness as low priority, with other health issues being perceived as more important (Desjarlais et al, 1995). Thus, while there have often been dramatic improvements in general health care and living standards in developing countries, the same cannot be said

for mental health care. The socio-economic impact of psychiatric disorders has been grossly underrepresented by conventional public health statistics, where the focus has tended to be on mortality rather than morbidity (Desjarlais et al, 1995). Mental health problems are an increasing part of the global health burden, and now rate as one of the largest causes of lost years of quality of life (Sadik, 1992).

Costs of schizophrenia

Schizophrenia obviously forms a significant part of this burden, being the most costly illness that psychiatrists treat (Andreasen, 1991). It imposes a disproportionately large economic burden on patients and their families, health care systems and society, because of its early onset, devastating effects, and usually lifelong course (Glazer and Johnstone, 1997). Cost estimates vary from country to country, but invariably confirm that schizophrenia is an exceptionally expensive illness. In 1993 the disease consumed an estimated \$30 billion in the United States of America, \$18 billion of which were direct costs and \$15 billion indirect costs. This constitutes 2.5% of the annual total health care allocations (National Advisory Mental Health Council, 1993). In England, the identifiable direct and indirect costs of schizophrenia suggest an annual total cost of £2.6 billion, and some indirect costs are omitted from this estimate (Knapp, 1997). In Belgium the mean direct treatment cost was \$12,050 per patient per year, or \$304 million for all schizophrenia patients per year. This constitutes 1.9 percent of the Belgian Government's total health expenditure (De Hert et al, 1998). In the Netherlands about 2% of the total health care budget is spent on the treatment of schizophrenia patients (Evers & Ament, 1995) and in Spain the direct cost per patient per year was \$2,243 (Haro et al, 1998). Direct costs include hospitalisation, day care, residential accommodation, medication, special investigations and disability grant payments. High among the indirect costs are those associated with lost employment or reduced productivity and family costs (e.g. household expenditure, travel costs, lost earnings) (Knapp, 1997). Medications comprise a very small portion of the costs of schizophrenia, estimated at 4% of the direct costs in the United Kingdom (National Health Service Executive, 1996), 5.6% in France (Rouillon et al, 1994) and 1.1% in the Netherlands (Evers & Ament, 1995).

The previous under-recognition of the importance of psychiatric disorders such as schizophrenia was due in part to a lack of available information, resulting in policy makers having to make ill-informed decisions. In the past these policy makers frequently refused to look beyond the acquisition costs of the drugs. However, recent research findings focussing on pharmaco-economics and quality of life issues indicate that, in fact, psychiatric disorders are amongst the most important causes of disability in both developing and developed nations (Murray and Lopez, 1997). These and other similar findings are likely to alter perceptions of the relative importance of mental health. As governments begin to insist on the submission of high-quality economic evaluations before deciding on how to allocate their limited resources, cost-effectiveness analyses will increasingly be introduced into clinical trial protocols (Maynard and Bloor, 1998). A crucial issue in many health-care systems is that the high acquisition costs of the new drugs fall into one part of the system, whereas the cost savings are enjoyed elsewhere in the system. This means that budget allocations need to be adjusted accordingly. While cost-effectiveness studies report advantages for novel antipsychotics over their predecessors in terms of overall cost of treating schizophrenia, these studies have been based in developed countries. Some multinational studies have included developing countries, but there is no specific indication that the overall findings apply in these countries. The findings may not, in fact, be applicable to low-income countries, as schizophrenia has been reported to run a different course in the latter (Sartorius et al, 1986), and the relative contribution of factors to direct and indirect costs probably differs substantially from that in developed countries. Indeed, a cost-effectiveness study carried out in Nigeria indicated that the cost of the antipsychotic drugs accounted for 52.8% of the cost of treating schizophrenia. Factors such as currency devaluation and the lack of both disability benefits and residential facilities were identified as altering the proportional costs of treating the illness (Suleiman et al, 1997). Most patients in such countries are cared for by families at no direct cost to the state, other than outpatient medication. Residential care, when available, tends to be custodial, with relatively low staff and infrastructure expenditure. It would be important to undertake cost-effectiveness studies with the novel antipsychotic agents in developing

countries before it could be effectively argued that these drugs should be made more widely available.

The inaccessibility of new drugs because of economic considerations raises important human rights issues. With the advent of these apparently more expensive new treatment options, there is a very real danger that the gap between levels of psychiatric care in developed and developing countries will widen further. The international psychiatric community needs to take cognizance of the deteriorating situation and the further marginalisation of much of the world's population. Co-ordinated global action is necessary to ensure that effective psychiatric care also reaches people in low-income societies. Concern has been voiced that the increasing globalisation of the pharmaceutical industry may result in the setting of uniform world-wide prices rather than allowing for lower prices to less developed countries (Pécoul et al, 1999). In some parts of the world, pharmaceutical and other private companies have recently involved themselves in psycho-educational programmes, patient support programmes, and other community responsibilities. This seldom results in direct profit, but appears to be motivated by goodwill. It would be encouraging to see them extend this social conscience to poorer countries, possibly in closer collaboration with organisations like the World Health Organisation, UNICEF and the World Bank (Pécoul et al, 1999). Access to an acceptable standard of psychiatric care should be a fundamental right of all people.

It may be argued that in developing countries, access to drugs for treating diseases such as malaria, tuberculosis and bacterial meningitis will always be more important than having a wider range of psychotropic drugs available. However, this "either/or" approach would preclude psychiatrists from campaigning for the global availability of effective mental health-care when in fact the opposite should hold – if psychiatry is to regard itself as a champion of humane medical practice, it should be playing a leading role in this respect.

Another initiative that could fruitfully be pursued is the establishment of consumer advocacy groups in developing countries. Such groups have been very successful in lobbying policy makers and private companies in North America and Europe, and may also prove effective in low-income countries.

Low-dose classical antipsychotics

An interim option for improved treatment of schizophrenia in low-income countries is perhaps more easily attainable – that of low-dose classical antipsychotic medication. There is now substantial evidence that low-dose antipsychotic treatment holds definite advantages over high-dose treatment. Indeed, in a comprehensive survey of dose-effect relationships, no support was found for the use of antipsychotics in daily doses above 500 – 600 mg chlorpromazine equivalents (Baldassarini et al, 1988). In fact, patients receiving 20mg haloperidol per day did significantly worse than those receiving 10mg per day (Van Putten et al, 1990). Other studies have borne out this finding, indicating that doses of haloperidol above 10mg per day, in addition to causing increased side-effects, have no additional benefits, and may in fact be less effective than lower doses (Zimbroff et al, 1997; Donlon et al, 1980; Rifkin et al, 1991). McEvoy et al (1991), by determining the neuroleptic threshold in individual patients, found that 72% recovered clinically within 5 weeks on an average dose of 3.7mg haloperidol per day. Higher dosages given to non-responders did not lead to greater improvement. Further support for low-dose efficacy is forthcoming from positron emission tomographic studies of striatal D₂ receptor occupancy. With conventional antipsychotics clinical efficacy has been reported even with relatively low occupancy. For example, doses of 2 mg haloperidol per day recorded occupancies between 53% and 74% and were associated with clinical efficacy (Kapur et al., 1996). Finally, patients with plasma haloperidol levels above 25ng/ml did significantly worse than those with levels less than 18ng/ml. The high-dose patients who failed to respond showed significant improvement once the dose was reduced. Interestingly, in this study, patients with lower plasma levels of haloperidol also had greater improvement in negative symptom ratings than those with higher plasma levels (Coryell et al, 1998). In spite of the evidence supporting low-dose haloperidol usage, many patients continue to receive dosages far in excess of what they require. This may be particularly the case in low-income countries, where mental health resources are stretched and reliance is placed on sedative side effects for behavioural control of the mentally ill.

Clearly, considerable evidence exists for the advantages of low-dose *versus* high-dose classical antipsychotic treatment in terms of tolerability and probably efficacy. Whether these advantages are comparable to the advantages offered by the novel antipsychotics is not clear, as studies comparing low-dose traditional antipsychotics to the novel antipsychotics are very scarce. Most of the clinical trials comparing the novel antipsychotics to haloperidol have used haloperidol in dosages of 10mg or greater and this may represent a biased comparison in terms of optimal dosage. However, one study suggests that there are advantages for the novel antipsychotics over low-dose haloperidol. Sertindole was compared to haloperidol 4, 8 or 16 mg daily and placebo, and found to have advantages in ameliorating negative symptoms and in avoiding extrapyramidal effects (Zimbroff et al, 1997). This study, representing the first multicentre, placebo-controlled assessment of the dose-response effects of haloperidol, unexpectedly found relatively high rates of EPS, and significant symptom reduction in only some measures of efficacy at the 4mg haloperidol dose level. It would be interesting to see the results of further studies in this vein, to establish whether any of the other advantages of the novel antipsychotics – such as efficacy in refractory schizophrenia, negative symptoms, reduced induction of tardive dyskinesia and increased productivity – can be demonstrated against low-dose classical antipsychotic therapy.

As an interim measure, low-income countries would do well to implement low-dose classical antipsychotic treatment strategies for patients with schizophrenia, while efforts are made to extend the availability of the novel antipsychotics globally.

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3.c.iii Beyond Clozapine: The Role of Atypical Antipsychotics in the Management of Treatment-Resistant Schizophrenia

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Summary

This article reviews the evidence for the atypical antipsychotics other than clozapine in patients with schizophrenia who are resistant to treatment with conventional agents. Clozapine remains the one drug with proven efficacy in severely refractory patients. However, while modestly effective in 30 to 70% of these patients, there are many who are either intolerant of, or non-responsive to clozapine. The initial hope that the new atypical antipsychotics would play a major role here has not really materialised. Nevertheless, it is increasingly recognised that perhaps the majority of patients with schizophrenia have milder degrees of refractoriness – so-called partial responders – and considerable evidence is emerging for an important role for risperidone, olanzapine and quetiapine in these patients. These drugs appear to have advantages over the conventional antipsychotics in terms of both efficacy and tolerability in these patients. More studies are required to establish optimal dosages of the atypical antipsychotics in refractory patients, as well as whether some individuals respond differentially to a particular drug.

1. Introduction

The advent of the atypical antipsychotics has had a major impact upon the way we treat patients with schizophrenia. Evidence is accumulating that these drugs hold significant advantages over their predecessors in terms of both efficacy and tolerability. In particular, it has been shown that the newer drugs are less likely to induce acute extrapyramidal symptoms (EPS),^[1] previously a major obstacle to the effective treatment of schizophrenia. Other reported advantages of these drugs include improved efficacy in treating negative symptoms^[2] and depressive symptoms,^[3] reduced levels of suicidality,^[4] less neurocognitive impairment,^[5] better subjective quality of life,^[6] reduced incidence of tardive dyskinesia^[7] and improved overall outcome.^[8] These advantages are not necessarily shared to the same extent by the currently available atypical antipsychotics, clozapine, risperidone, olanzapine and quetiapine.

Another area where the atypical antipsychotics have raised expectations is in the treatment of patients who are refractory to conventional agents. For years conventional antipsychotics were the only effective drugs in treating schizophrenia and other psychotic disorders, with approximately 70% of patients showing clear-cut symptom reduction in short-term clinical trials.^[9] However, in the longer term, and in real-world clinical practice, a different picture emerges. It has been estimated that two thirds of first-episode schizophrenia patients continue to experience positive symptoms after one year, and about one-third will continue to have them after six years.^[8] The persistence of positive symptoms may have important clinical ramifications, for a number of reasons. First, ongoing positive symptoms, particularly if accompanied by bizarre behaviour, are likely to further stigmatise and marginalise these patients. Further, the risk of relapse is likely to be greater due to reduced insight and compliance. Finally, a longer duration of positive symptoms before effective treatment is associated with a poorer outcome.^[10,11] Indeed, it has been suggested that positive symptoms are clinical manifestations of a progressive encephalopathy, which, if not arrested may result in lasting morbidity.^[12]

Treatment options for refractory schizophrenia were previously extremely limited - a patient who is unresponsive to one conventional antipsychotic, is unlikely to respond to another. Also, increasing the dose of a conventional agent above the usually prescribed range, or adding supplementary drugs, is unlikely to be helpful.^[13]

2. Defining resistant schizophrenia

Schizophrenia by definition requires an extended period of illness with significant social and occupational dysfunction.^[14] Long-term outcome studies indicate that 80 – 90% of patients develop varying degrees of social and occupational impairment.^[15] Historically, treatment resistance has been defined in terms of a lack of response among positive symptoms. However, this is an inadequate definition that needs to be expanded to include other domains such as negative, cognitive and mood symptoms. Marder^[16] proposes that patients should be regarded as refractory to a particular treatment after they have failed an adequate trial with that agent. Most patients should have at least a 6 week trial, and if they demonstrate even a mild degree of improvement it may be reasonable to continue, as further improvement may occur for 3 to 6 months. In most studies, patients are defined as treatment-resistant according to their response to conventional antipsychotics. Perhaps the best definition and the one most frequently referred to in the literature is that of Kane et al.^[17] A failure to respond to at least three periods of treatment in the preceding 5 years with antipsychotic agents from at least two different chemical classes at dosages equivalent to at least 1000 mg of chlorpromazine per day for a period of at least 6 weeks each, and had no period of good functioning within the previous 5 years. In addition, patients in that particular study failed to respond to an open prospective 6-week trial of haloperidol (up to 60mg/day or higher).

3. Clozapine

Clozapine was the first agent to show superior efficacy over conventional antipsychotic drugs in treatment-refractory patients with schizophrenia. The first controlled trial was published in 1988.^[17] The methodology of this study set the standard for future studies, and the so-called Kane criteria described above were subsequently widely adopted to identify a subset of severely refractory patients.

A comprehensive meta-analysis of all available clinical trials published in all languages investigating the efficacy of clozapine versus conventional antipsychotics in schizophrenia was recently published.^[18] This review included 2530 randomly assigned subjects in 30 clinical trials. Clozapine-treated patients showed more clinical improvement and experienced fewer relapses. The evidence for clozapine superiority was clear-cut. However, the effect size, at best, was modest. The improvement corresponded to approximately a 6-point difference in Brief Psychiatric Rating Scale (BPRS) total score after up to 3 months of treatment compared to conventional antipsychotics. Fewer than one third of adult treatment-resistant patients showed clinical improvement, defined as at least a 20% decrease in BPRS or Positive and Negative Syndrome Scale (PANSS) score from baseline. Treatment-resistant children and adolescents seemed to respond more favourably. The evidence for superior efficacy was accompanied by fewer EPS. Clinical improvement was most pronounced in patients with treatment-resistant schizophrenia, but was also significant in non-resistant schizophrenia.

This review does not attempt to cover the considerable literature on clozapine in resistant schizophrenia, but rather aims to focus on the role of the newer atypical antipsychotics. The reader is referred to the various studies published on clozapine in resistant schizophrenia,^[17,20-22] in which the response to clozapine is reported as being between 30% and 70%. There remain however a substantial number of patients with schizophrenia who either do not improve substantially on clozapine treatment, or who are unable to take the drug because of the risk of side-effects or unwillingness to undergo regular hematological monitoring.

4. Risperidone

A recent meta-analysis of risperidone in the treatment of schizophrenia^[23] concluded that, compared with conventional antipsychotics, slightly more patients showed clinical improvement (57% vs 52%), the dropout rate was lower (29.1% vs 33.9%) and the use of

concomitant medications for extrapyramidal symptoms was lower (22.8% vs 38.4%). On the other hand, weight gain and tachycardia were significantly more common in the risperidone patients. Indirect evidence points towards efficacy for risperidone in refractory schizophrenia - in a large multicentre study conducted over 8 weeks,^[24] risperidone 6mg/day had its greatest advantage over haloperidol for patients who had been hospitalised for more than 6 months. These patients were likely to have been treatment resistant.

A number of studies have directly investigated the efficacy and safety of risperidone in treatment-resistant schizophrenia. A randomised, double blind, multicentre study conducted over 8-weeks comparing risperidone to clozapine^[25] The sample comprised 86 inpatients with chronic schizophrenia who were either resistant to, or intolerant of, conventional treatment. Patients had previously failed to respond to or were intolerant of at least two different classes of conventional antipsychotic drugs given in appropriate doses for at least 4 weeks each. This was determined retrospectively from the patients' files. No subject had previously received clozapine. After a one-week titration phase, doses were fixed at 6mg/day of risperidone and 300mg/day of clozapine for one week, and then adjusted according to individual responses. The mean doses prescribed were 6.4mg/day of risperidone and 291.2mg/day of clozapine. At endpoint 67% of the risperidone group and 65% of the clozapine group were clinically improved by 20% or more on the PANSS. Clinical Global Improvement (CGI) change scores were also similar for the two drugs at endpoint. Risperidone appeared to have a faster onset of action (median time to response 14 days for risperidone vs. 21 days for clozapine). Dropout rates were similar in both groups (9 subjects each). Extrapyramidal symptoms and other adverse events were scarce and mild in both groups. This trial provides good evidence for the efficacy of risperidone in refractory patients. Certain concerns have been raised regarding this study.^[26-28] First, the study population was not well defined, and included both neuroleptic intolerant and neuroleptic resistant patients. Also, the sample size was relatively small, so that actual differences between the treatment groups may have been concealed. Further, clozapine dosing was relatively low, and the titration period fairly rapid. Finally, the treatment period was possibly too short, as clozapine has been shown to require up to 6 months to achieve its full benefits.^[20,29] In response, the authors^[25] point out that their sample corresponds with the criteria normally applied when considering patients for clozapine treatment, and suggest that a less restrictive definition of treatment resistance may be more helpful in clinical settings. A further important point to emerge from this study is that relatively low doses of risperidone were found to be effective in this partially refractory sample. This is important in terms of fewer side-effects as well as reduced acquisition costs.

In an open comparison of clozapine and risperidone in severely treatment-resistant schizophrenia^[30] clozapine showed superior efficacy although risperidone appeared to yield better response rates than those reported with classical antipsychotics. The sample comprised 57 subjects treated with clozapine and 29 with risperidone. Patients met DSM IV criteria^[14] for schizophrenia and had a Global Assessment of Function scale (GAF) score of less than 41 in the preceding year, a score on the Degree of Resistance to Treatment scale^[31] of four or five, a total PANSS score of at least 60, and previous adequate trials of at least three different antipsychotic medications from at least two different classes. The mean treatment duration of the trial was 12.1 weeks. The mean dose of clozapine was 420mg, and risperidone 7.75mg. The clozapine group showed greater improvement in PANSS total scores and positive subscale scores. The PANSS-derived factors of excitement, psychosocial withdrawal and psychomotor retardation showed greater improvement in the clozapine group, as did the GAF scores. The CGI scores indicated that 33% of the clozapine group and 14% of the risperidone group were "much improved" or "very much improved". Forty-four percent of the clozapine group and 28% of the risperidone group achieved a 20% reduction in total PANSS scores. Within the obvious limitations of an open trial and the relatively small sample size, this study suggests superiority for clozapine over risperidone in severely refractory patients. However, it also suggests that some severely resistant patients may obtain benefit from risperidone. On the other hand, six patients in the risperidone group were "minimally worse" and three "much worse", compared to only one subject in the clozapine group being regarded as "minimally worse" and none as "much worse".

Four studies undertaken by a research group investigated the effects of risperidone versus haloperidol on certain cognitive functions, as well as on the perception of emotion in treatment resistant patients with schizophrenia. All four of the studies employed a similar design (and possibly included overlapping subjects). Treatment-resistance was defined according to the criteria of Kane et al.^[17] In addition, patients met symptom severity criteria comprising a score of at least 45 on the BPRS, a minimum score of 4 on two of the BPRS psychosis items and a CGI score of at least 4. Patients were randomly assigned to an initial 4 week fixed dose phase of either risperidone 6mg/day or haloperidol 15 mg/day followed by a further 4 week flexible dose phase. In the first study^[32] the effects of risperidone vs. haloperidol on verbal working memory were compared in 59 subjects. Risperidone treatment had a greater beneficial effect on verbal working memory than haloperidol in both the fixed and flexible dose phases. The treatment effect remained significant after controlling for the effects of benzotropine co-treatment, change in psychotic symptoms and change in negative symptoms. In the second study investigating a sample of 56 patients^[33] the effects of risperidone and haloperidol on reaction time, manual dexterity and motor learning were compared. The patients receiving risperidone showed greater improvement in reaction time and manual dexterity than those receiving haloperidol. Again, differences were not related to extrapyramidal symptoms or changes in symptoms. In the third study^[34] the effects of risperidone and haloperidol on secondary memory were compared in 64 subjects. It was found that risperidone-treated patients showed greater improvement than haloperidol-treated patients in general verbal learning ability, suggesting that risperidone may exert a facilitating effect on the acquisition of new verbal information. No significant treatment effects were noted on retention or learning strategy. These three studies provide evidence for superior efficacy of risperidone over haloperidol in treatment resistant patients in terms of specific cognitive functions. The fourth study^[35] compared 20 patients on their ability to perceive emotion. The risperidone patients were better able to identify emotion than the haloperidol patients. These improvements are important in terms of the current broader concept of treatment outcome. The overall outcome in the four above studies has yet to be reported. A possible criticism of these three trials is that the haloperidol dose was too high and may have biased the results in favour of risperidone.

A prospective, open-label study investigated the effects of switching patients with treatment-resistant schizophrenia from clozapine to risperidone in a small sample of 10 patients.^[36] Subjects were inpatients who had been continuously treated with clozapine for at least 13 months. Criteria for treatment resistance were similar to those of Kane et al.^[17] Patients were included if it was felt that a switch was indicated, either due to sub-optimal clozapine response or intolerance to clozapine-induced adverse events. Clozapine was tapered and discontinued over 10 days, and risperidone was then titrated up to 6mg/day over nine days and then continued for 12 weeks. The mean clozapine dose at baseline was 565mg/day. Five subjects failed to complete the 12 weeks of risperidone treatment due to exacerbation of psychotic symptoms or intolerable side-effects. No subjects improved on risperidone. These findings need to be interpreted with caution for a number of reasons. The sample was very small; the study was unblinded; the patients were highly refractory (being poor responders to clozapine); and clozapine withdrawal phenomena^[37] could have accounted for the exacerbation of psychotic symptoms in at least some of these patients. On the other hand, these findings do highlight the fact that great caution is required when switching patients from clozapine to risperidone (and possibly to other antipsychotics as well).

In another study comparing risperidone to clozapine, risperidone was found to be at least as effective as clozapine and significantly better tolerated.^[38] This was a randomised, double-blind study of 4 weeks duration comparing risperidone 4mg (20 patients) and 8mg (19 patients) and clozapine 400mg (20 patients). However, this was a non-treatment refractory sample, and a number of patients were in fact drug-naive. Two studies comparing risperidone and clozapine in treatment-resistant schizophrenia that have been presented as posters have reported equal efficacy for the two drugs.^[39,40] Details of these studies have yet to be published.

Taken together, there is considerable evidence for efficacy of risperidone in treatment-resistant schizophrenia. Less severely refractory patients are more likely to benefit from risperidone. Non-responders to clozapine may do less well, and particular care needs to be taken when switching patients from clozapine to risperidone.

5. Olanzapine

Because of its pharmacological similarities to clozapine, the efficacy of olanzapine in treatment resistant schizophrenia is of great interest. An open-label study in a small sample (N=25) of patients with treatment-refractory schizophrenia reported significant improvement at 6 weeks^[41] In this study refractoriness was defined as an absence of significant improvement with at least two antipsychotics for at least 4 weeks at doses equivalent to at least 750mg/day chlorpromazine. Nine subjects (36%) obtained a 35% or greater reduction in BPRS total score and only one patient discontinued treatment because of an adverse event. Olanzapine doses ranged between 15 and 25mg/day. The drug was well tolerated - no patients reported extrapyramidal symptoms, and none required anticholinergic medication.

In a retrospective analysis of a sub-population of treatment-resistant patients selected from a large, multicentre, double-blind, 6-week study,^[42] the efficacy of olanzapine and haloperidol were compared.^[43] Subjects who met the following criteria were included: 1) failure to respond to at least one antipsychotic over a period of at least 8 weeks during the previous 2 years; 2) BPRS total score of at least 24; and 3) BPRS positive score of at least 8, or scores of at least 4 on any of the BPRS psychosis items. Patients were randomised (2:1) to olanzapine or haloperidol, with starting doses at 5mg/day and increased if necessary to a maximum dose of 20mg. Both last observation carried forward (LOCF) and completers analyses were conducted. Olanzapine was superior to haloperidol for key symptom domains and side-effects. Olanzapine demonstrated significantly greater improvement in PANSS negative symptoms, depressive symptoms, akathisia and EPS with both LOCF and completers analyses. Also, in the completers, olanzapine was significantly superior for BPRS total and PANSS positive symptoms. The olanzapine-treated patients showed significantly greater response rates (47%) than the haloperidol treated patients (35%) in the LOCF analysis.

A prospective randomised double-blind study compared the efficacy of olanzapine versus chlorpromazine in treatment-resistant schizophrenia.^[44] Criteria for resistance were similar to those of Kane et al,^[17] except that only two periods of failed antipsychotic treatment were required. However, the patients were then subjected to a prospective trial of haloperidol 10-40mg/day, and benztropine 4mg/day, for 6 weeks. Previous resistance to clozapine was an exclusion criterion. Of 103 initial subjects, 84 failed to respond to haloperidol (defined as 20% or less decrease in total BPRS score; endpoint BPRS score of 35 or more; and a CGI severity score of greater than 4) and were entered into the double-blind trial. This was an 8-week fixed-dose trial of either olanzapine 25mg/day or chlorpromazine 1200mg/day plus benztropine 4mg/day (both drugs were given at half-dose for the first week). Response was defined as at least a 20% reduction in total BPRS score and a post-treatment CGI score of 3 or less or BPRS score of 35 or less. No differences in efficacy were demonstrated between the two drugs. Seven percent of the olanzapine-treated patients and none of the chlorpromazine patients responded. There were also no differences in dropout rates. Olanzapine was significantly better tolerated than chlorpromazine. The olanzapine-treated patients had fewer motor and cardiovascular side-effects. No antiparkinsonian drugs were necessary in the olanzapine group. This study had essentially the same criteria as other studies assessing clozapine efficacy^[17,19-22] in which clozapine response was reported as between 30% and 70%. Although it is possible that higher doses of olanzapine may be effective, this study indicates that the drug is not as effective as clozapine in severely refractory patients.

In another study the same group of investigators report on switching treatment-resistant patients from olanzapine to clozapine.^[45] The subjects who received clozapine (N=27) were treatment-resistant according to the Kane criteria.^[17] They had failed to experience a greater

than 20% total BPRS score improvement after a prospective 2 to 6 week trial of haloperidol at 10 to 40mg/day, and had failed to respond to olanzapine either in the previously mentioned trial or in open therapy at doses between 12.5 to 25 mg/day. This was an 8-week open label trial. Forty-one percent of the patients responded to clozapine treatment (greater than 20% total BPRS score improvement) at a mean dose of 693mg/day. The authors conclude that, despite extensive pharmacologic similarities, olanzapine and clozapine do not have the same clinical actions in treatment-resistant patients.

In an open-label extension to the trial of Conley et al,^[44] the response to olanzapine in treatment-refractory patients with and without a history of substance abuse was compared.^[46] Subjects received up to 25mg olanzapine per day for 7 weeks. Of the entire group, 63% responded according to a priori criteria (a 20% BPRS fall plus a one-point fall in CGI). Treatment outcomes were comparable in both the substance abusing and non-substance abusing group, and the authors concluded that a history of substance should be considered as a possible indication for olanzapine therapy. The high response rate in this study is very surprising considering that these patients had not responded in the initial double blind study to olanzapine. Possible explanations here include the unblinded nature of the study, slightly less stringent response criteria that were applied and the longer duration of treatment.

In a prospective, 12 -week, open label trial in sixteen hospitalised patients with severely refractory schizophrenia or schizoaffective psychosis, fairly low-dose olanzapine was found not to be effective.^[47] The patients had not responded to at least two antipsychotic drugs for at least 6 weeks each within the past 5 years. Three patients had previously received clozapine, and 10 had received risperidone – none had responded to either atypical agent. The olanzapine dose was 10mg/day for at least the first 6 weeks and never exceeded 20mg/day. Only three patients received more than 10mg/day olanzapine at week eight. Overall, significant clinical improvement was noted only for motor side-effects. Patients frequently became more agitated within the first several weeks of the study, requiring increased use of benzodiazepines and often leading to the discontinuation of olanzapine.

Higher doses of olanzapine in treatment-resistant patients have not yet been properly evaluated. Given the drug's favourable side-effect profile in this and other studies, it would be important to evaluate the effects of higher doses in refractory patients. In a naturalistic case series outcome study, 16 treatment-resistant patients were treated with olanzapine up to 40mg/day for 16 weeks.^[48] Treatment-resistance was defined according to the criteria of Kane et al.^[17] Significant improvement from baseline in BPRS total scores and GAS scores was observed at weeks 4, 8, 12 and 16, and 50% patients responded to olanzapine, as defined by a 20% decrease in BPRS score by week 16. The results of this study are encouraging, and suggest that higher dose olanzapine may be effective in severely refractory patients. However, these findings need to be validated in randomised controlled trials.

The efficacy of olanzapine for treatment-refractory childhood-onset schizophrenia was examined in eight subjects who underwent an 8-week open-label trial.^[49] At least two different conventional antipsychotics had been ineffective. Most patients had undergone trials of high doses of these drugs, as well as risperidone. Some of the patients were intolerant of clozapine, although the drug had been effective. Dosages were titrated to a maximum of 20mg/day. At week 8 there was a mean BPRS improvement of 17%. The mean improvements for the SANS and SAPS scores were, respectively, 27% and 1%. These effect sizes were smaller than that observed in a similarly designed study with clozapine conducted by the same investigators.^[50]

The results of these studies together suggest that olanzapine is an effective and safe drug in refractory patients defined according to less stringent criteria. However, olanzapine appears not to share the efficacy of clozapine in severely refractory patients in doses up to 25mg. It is possible that higher doses given over a longer period may prove beneficial. Switching of refractory patients to olanzapine may sometimes be associated with increased agitation and worsening of psychotic symptoms.

6. Quetiapine

Some anecdotal evidence suggests that quetiapine, the most recently introduced atypical antipsychotic, may be effective in refractory schizophrenia. A case was recently reported of a 14 year old male with childhood onset schizophrenia who failed therapeutic trials with both risperidone and olanzapine, who had a marked remission with quetiapine monotherapy.^[51] Another case was reported where quetiapine 400 mg/day was effective in a patient with schizophrenia who was partially resistant to treatment with conventional antipsychotic agents.^[52]

A recently completed international, multicentre, double-blind, randomised trial^[53] provides evidence that quetiapine has advantages over haloperidol in terms of both efficacy and tolerability in patients with schizophrenia showing partial resistance to conventional antipsychotics. Inclusion criteria were persistent positive symptoms while previously taking therapeutic doses of antipsychotic treatment; a PANSS positive scale score of 15 or more; a score of at least 4 for one or more of the positive scale items; and a CGI score of 3 or more. Eligible patients then entered a 4-week active run-in phase of open treatment with fluphenazine, titrated to 20mg/day. At the end of the 4 weeks, those patients not responding or only partially responding (PANSS score reduction of less than 30% and PANSS positive score of 15 or more) entered the randomisation phase of the trial. This phase compared quetiapine 600mg/day to haloperidol 20mg/day (both agents were titrated over a 7 day period). Of 365 patients initially recruited, 288 continued to meet criteria for partial response and were entered into the randomised phase of the trial. Significantly more patients receiving quetiapine (52%) than haloperidol (38%) showed a clinical response (defined as > 20% reduction in PANSS total scores) at endpoint. There was a non-significant trend towards superiority for quetiapine in the primary efficacy measure of PANSS total score reduction from baseline (LOCF on intention to treat population). Quetiapine patients had a reduced risk of developing EPS ($p < 0.001$ at 12 weeks) and fewer required anticholinergic medication (5% vs. 20% after week 4). This is the largest prospective study to date of an atypical antipsychotic other than clozapine in treatment resistant schizophrenia. The trial was specifically designed to study “partial responders”, who may represent the majority of patients seen in “real-world” clinical practice. While the efficacy of quetiapine in severely refractory patients is not yet known, this study indicates superiority over conventional antipsychotics in this particular group of patients.

7. Other atypical antipsychotics in resistant schizophrenia

Other antipsychotics sometimes regarded as atypical - zotepine, loxapine, amisulpiride and sulpiride – together with atypical drugs that are not currently available in clinical practice such as sertindole and ziprasadone, have proven efficacy in schizophrenia. However, they are not included in this review as no controlled studies in treatment resistant subjects were found in the literature.

8. Conclusions

Within the large group of patients with schizophrenia displaying varying degrees of treatment resistance a strategy for their management is emerging. Clozapine is the most effective treatment in patients with severe refractoriness and remains the treatment of choice for patients meeting the Kane criteria^[17] for treatment resistance. Clozapine is also effective in patients with lesser degrees of refractoriness. However, because of difficulties associated with the administration of this drug, other options should first be considered. Risperidone, olanzapine and quetiapine have been shown to be more effective than conventional antipsychotics. This, together with their generally favourable side-effect profile, make them good options for refractory patients. Unfortunately, it is not possible to make comparisons between the new agents. There are only three double blinded studies measuring general outcome with these new agents,^[25,44,53] all with different comparators and in differently defined refractory schizophrenia populations. Much remains to be established regarding the use of these agents in refractory schizophrenia. For example, the optimal dose for resistant patients is not known. Also, studies need to be conducted to investigate the role of augmentatory agents such as valproate and electroconvulsive therapy together with the atypical

antipsychotics. Hopefully, more and more patients will benefit from an improved knowledge and optimal application of these new agents.

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3.c.iv The new and evolving pharmacotherapy of schizophrenia.

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INTRODUCTION

Following the introduction of the first antipsychotic agents more than 40 years ago, the pharmacotherapy of schizophrenia essentially stagnated for a long time. However, a number of new compounds have been introduced over the past few years, that have considerably changed the way we treat our patients. These additional therapeutic options have provided grounds for heightened optimism for improved clinical outcomes among persons suffering from schizophrenia. Important differences between these compounds are emerging, so that drug choice needs to be tailored for individual patients.

Much literature has already appeared on these new, atypical antipsychotics, and additional findings are being reported at a rapid pace. However, in spite of the burgeoning literature, much remains to be learnt in order to utilise them optimally.

A good deal of this literature needs to be interpreted with caution, owing to a plethora of methodological shortcomings in many of the published studies. This chapter attempts to critically evaluate the evidence for efficacy of the new atypical antipsychotics by selecting only published randomised clinical trials (RCTs) and meta-analytical reviews. The drugs included are risperidone, olanzapine, quetiapine, ziprasidone, sertindole and amisulpride. The role of each drug during key stages in the course of the illness (acute treatment, maintenance, first-episode and refractory) is assessed, as well as differential effects on specific symptom domains. While this chapter focuses purely on efficacy, the adverse effects of these agents being dealt with in a separate chapter, it is obviously necessary, in selecting a drug, to consider many other aspects.

TREATMENT OF ACUTE SYMPTOMS

Atypical antipsychotics versus placebo

In spite of ethical and scientific concerns associated with these trials, it is still generally accepted that efficacy of a new compound needs to be established against placebo.(1)

Risperidone

Two RCTs compared risperidone 2, 6, 10 or 16 mg /day, haloperidol 20 mg/day, or placebo over 8 weeks in the treatment of schizophrenia. The first investigated 135 inpatients with chronic schizophrenia. Doses of 6 to 16mg/day were superior to placebo in overall and positive symptom improvement, while only risperidone 6mg/day was significantly better than placebo on negative symptom improvement.(2) The second study comprised 388 subjects with schizophrenia. Compared with placebo, significant improvements were found for risperidone 6 and 16 mg/day for overall clinical improvement and negative symptoms, and for risperidone 6, 10 and 16 mg/day for positive symptoms.(3)

Olanzapine

Two studies comparing olanzapine to placebo for 6-weeks in acute schizophrenia reported significant advantages for olanzapine in overall symptom improvement, as well as improvement in positive and negative symptoms.(4;5) The first study involved 152 subjects

who received fixed doses of either olanzapine 1mg/day or 10mg/day, or placebo. The significant differences were all between the olanzapine 10mg/day group versus placebo, with the olanzapine 1mg/day subjects showing no differences from the placebo group.(4) The second study involved 335 subjects who received olanzapine in dose ranges of 5 ± 2.5 mg/day, 10 ± 2.5 mg/day or 15 ± 2.5 mg/day, or placebo. Advantages were for the medium and high dose ranges of olanzapine for overall and positive symptomatology, and for the low and high dose ranges for negative symptomatology.(5)

Quetiapine

In a multicentre RCT 286 hospitalised subjects with chronic or subchronic schizophrenia received 6 weeks of treatment with high-dose quetiapine (750mg/day), low-dose quetiapine (250mg/day) or placebo. High withdrawal rates were recorded in all three treatment groups (42%, 57% and 59%), primarily because of treatment failure. High-dose quetiapine was significantly better than placebo in reducing Brief Psychiatric Rating Scale (BPRS) total, BPRS positive and Clinical Global Impression (CGI) scores. Reduction of negative symptoms was less consistent; quetiapine was significantly better than placebo for Scale for the Assessment of Negative Symptoms (SANS), but not on the PANSS negative subscale.(6) A multiple fixed dose study of quetiapine (75, 150, 300, 600 and 750mg/day), haloperidol (12mg/day) and placebo conducted in 361 subjects over 6 weeks reported significant differences between the four highest doses of quetiapine and placebo for BPRS total, BPRS positive symptoms and CGI Severity of Illness scores and between quetiapine 300mg/day and placebo for SANS summary score.(7)

Ziprasidone

A RCT was conducted in 139 subjects with acute exacerbation of schizophrenia, comparing ziprasidone 40 or 120mg/day and placebo for 28 days. Ziprasidone 120mg/day was significantly more effective than placebo in improving the BPRS total, CGI-S, BPRS depression cluster and BPRS anergia cluster scores, and had significantly more responders (>30% BPRS reduction) than placebo.(8) In another study 302 subjects were randomised to either ziprasidone 80 or 160mg/day or placebo for 6 weeks. Both doses of ziprasidone were significantly more effective than placebo in reducing PANSS total, BPRS total, BPRS core items, CGI-S, and PANSS negative subscale scores. Ziprasidone 160mg/day significantly improved depressive symptoms in subjects with higher baseline depression compared with placebo.(9)

Sertindole

A 40-day RCT in 205 previously treatment responsive, hospitalised patients with schizophrenia compared sertindole 4, 8, 12 and 20mg/day with placebo. A dose-related improvement was observed for PANSS total, BPRS and CGI scores, with significant differences being recorded between sertindole 20mg/day and placebo.(10) A further study compared sertindole 12, 20 and 24mg/day with haloperidol 4, 8 and 16mg/day, and placebo in 497 hospitalised patients with schizophrenia over 8 weeks. All doses were significantly more effective than placebo. For treating negative symptoms, only sertindole 20mg/day was superior to placebo.(11)

Amisulpride

Low-dose:

Three RCTs were conducted to assess efficacy of low-dose amisulpride (50-300mg/day) versus placebo in treating negative symptoms in subjects with predominantly negative symptoms over 6 to 12 weeks.(12-14) Amisulpride was consistently better than placebo in these studies, and the effect on negative symptoms was apparently unrelated to any changes in positive symptoms.(14)

High-dose:

No controlled studies were found comparing high-dose amisulpride with placebo. However, fixed doses of amisulpride (400, 800 and 1200mg/day) and haloperidol 16 mg/day were compared with a sub-therapeutic dose of amisulpride (100mg/day) for 4 weeks in 319 subjects with acute exacerbation of schizophrenia. The greatest improvement, in terms of BPRS total reductions, occurred in the two groups taking 400mg or 800mg amisulpride/day.(15)

Atypical antipsychotics versus haloperidol

Risperidone

A dose-finding study comparing risperidone 2, 6, 10 or 16 mg /day, haloperidol 20 mg/day, or placebo over 8 weeks in 135 inpatients with chronic schizophrenia found that risperidone 6mg/day was significantly superior to haloperidol on the total PANSS, General Psychopathology, and BPRS scales.(2) A similar study in 388 subjects found risperidone 6mg/day and 16mg/day groups to have significantly more responders (defined as > 20% reduction in total PANSS scores), although no other efficacy differences were found between risperidone and haloperidol.(3) A small (n=35) RCT compared risperidone to haloperidol over 8 weeks and reported no differences in outcome.(16) A large multinational study compared risperidone 1, 4, 8, 12 and 16 mg/day with haloperidol 10mg/day over 8 weeks in 1362 patients. The optimum risperidone doses were 4mg and 8mg/day, but no significant efficacy advantages over haloperidol were reported.(17) However, a later sub-analysis of patients from Germany, Austria and Switzerland reported significant advantages for risperidone over haloperidol according to PANSS total and subscale scores.(18) Further post-hoc sub-analyses reported that patients receiving risperidone 4mg/day improved more rapidly than those receiving haloperidol,(19) and those hospitalised for >60 days (median 351 days) who received risperidone 4mg/day improved significantly more than those treated with haloperidol.(20)

Olanzapine

Three large RCTs have compared olanzapine with haloperidol.(5;21;22). In these studies olanzapine demonstrated several efficacy advantages over haloperidol. In the first study (n=335) olanzapine 15 ± 2.5mg/day was significantly better than haloperidol 15 ± 5mg/day in reducing negative symptoms after 6 weeks, (5) while in the second study (n=431) olanzapine 15 ± 2.5mg/day over 6 weeks was equal to haloperidol 15 ± 5mg/day on all efficacy measures.(21) In a study with a very large sample (n=1,996) olanzapine 5-20mg/day (mean 13.2mg/day) was significantly better than haloperidol 5-20mg/day (mean 11.8mg/day) over 6 weeks in reducing overall psychopathology,(21) positive symptoms, (21) negative symptoms(5;22) and depressive symptoms.(22) A recent RCT compared olanzapine with haloperidol over a period of 8 weeks in a sample of 182 Asian patients with chronic schizophrenia. Olanzapine was found to be as effective as haloperidol in treating overall symptomatology, and significantly superior in treating negative symptoms.(23)

Quetiapine

In the multiple fixed dose study of quetiapine (75, 150, 300, 600 and 750mg/day) versus haloperidol (12mg/day) and placebo conducted in 361 subjects over 6 weeks,(7) differences between quetiapine and haloperidol were not significant for any of the efficacy measures. Another RCT compared flexible doses of quetiapine (mean 455mg/day) and haloperidol (mean 8mg/day) over 6 weeks in 448 hospitalised patients with acute exacerbation of schizophrenia. Both quetiapine and haloperidol produced clear reduction in symptoms, with equal efficacy.(24)

Ziprasidone

Ninety patients with schizophrenia or schizo-affective disorder participated in this dose-finding study comparing ziprasidone 4, 10, 40 and 160 mg/day and haloperidol 15mg/day for 4 weeks. Ziprasidone 160mg/day was found to be comparable with haloperidol in reducing overall psychopathology and positive symptoms, as well as overall response rate.(25)

Sertindole

In the study comparing sertindole 12, 20 and 24mg/day with haloperidol 4, 8 and 16mg/day, and placebo in 497 hospitalised patients with schizophrenia over 8 weeks, sertindole and haloperidol were comparably effective.(11)

Amisulpride

In a RCT of 41 subjects with schizophrenia, flexible doses of amisulpride or haloperidol were given over 42 days. Both groups showed similar overall improvement, with amisulpride patients doing significantly better regarding depressive symptoms.(26) in a further study, fixed doses of amisulpride (100, 400, 800 and 1200mg/day) and haloperidol 16 mg/day were compared for 4 weeks in 319 subjects with acute exacerbations of schizophrenia. The greatest improvement, in terms of BPRS total reductions, occurred in the two groups taking 400mg or 800mg amisulpride/day.(15) Amisulpride 800mg/day was also compared to haloperidol 20mg/day over 6 weeks in 191 patients with acute exacerbations of schizophrenia. Amisulpride was as effective as haloperidol for positive symptoms, and significantly more effective against negative symptoms (PANSS negative subscale).(27) In a

flexible dose study, 199 subjects with schizophrenia or schizophreniform disorder received amisulpride 400-1200mg/day or haloperidol 10-30mg/day for 4 months. The drugs were equally effective in reducing BPRS total scores and PANSS positive scores, while PANSS negative score reduction was significantly greater with amisulpride, as was the percentage of CGI responders.(28)

Atypical antipsychotics versus other conventional antipsychotics

Risperidone

Flexible doses of risperidone (mean dose 8mg/day) and flupenthixol (mean dose 38mg/day) were compared over 6 weeks in 98 subjects with acute exacerbation of schizophrenia or schizophreniform disorder. Both groups displayed comparable efficacy, with the onset of action being significantly faster in the risperidone group.(29)

Quetiapine

A 6-week RCT compared flexible doses of quetiapine (mean endpoint dose 407mg/day) and chlorpromazine (mean endpoint dose 384mg/day) in 201 hospitalised patients with acute exacerbation of schizophrenia. Both treatments were equally effective in treatment of positive and negative symptoms.(30)

Amisulpride

Amisulpride 1000mg/day was compared with flupenthixol 25mg/day in 132 patients with acute exacerbation of schizophrenia over 6 weeks. Results were similar for both drugs, except that amisulpride was significantly better in reducing positive symptoms.(31)

Head-to-head comparisons of atypical antipsychotics

Risperidone versus olanzapine

Two multi-site RCTs have compared olanzapine with risperidone. The first, sponsored by Eli-Lilly, evaluated 339 subjects over a 28-week period. Both olanzapine (10-20mg/day) and risperidone (4-12mg/day) were found to be effective, with olanzapine demonstrating superiority over risperidone in reducing negative symptoms, overall response rate and maintenance of response at 28 weeks.(32) The second study, sponsored by Janssen-Cilag, investigated a sample of 377 subjects over 8 weeks. Once again, both olanzapine (5-20mg/day, mean 12.4 mg/day) and risperidone (2-6mg/day, mean 4.8mg/day) were found to be effective. There were no differences in efficacy between the groups according to the last-observation carried forward analysis, although the completers analysis reported significant advantages for risperidone in treating both positive and anxiety/depression symptoms.(33)

Risperidone versus clozapine (non-refractory sample)

Risperidone 4mg/day (n=20), 8mg/day(n=19) and clozapine 400mg/day (n=20) were compared over 28 days in a non-refractory sample. No differences in efficacy were reported.(34) Other studies comparing risperidone and clozapine were in samples with various degrees of refractoriness, and are dealt with below.

Risperidone versus amisulpride

Amisulpride (800mg/day) was compared with risperidone (8mg/day) over 8 weeks in a RCT of 228 patients with acute exacerbation of schizophrenia. The drugs showed equal efficacy.(35)

In a meta-analysis 9 RCTs (5 with clozapine; three with olanzapine and one with amisulpride), olanzapine and risperidone appeared to be broadly similar in terms of response rates, while olanzapine caused fewer people to leave the study early. Amisulpride seemed broadly similar to risperidone. High attrition rates, short-term follow-up and doses of risperidone higher than those recommended in practice were some of the limitations highlighted by the authors.(36)

Acute intramuscular administration

Olanzapine

The efficacy of intramuscular olanzapine has been compared to intramuscular haloperidol and intramuscular placebo in treating acute agitation in hospitalised patients with

schizophrenia. Subjects received one to three injections of olanzapine 10mg, haloperidol 7.5mg or placebo over a 24-hour period. Intramuscular olanzapine provided rapid, effective and safe treatment for acute agitation, showing superiority over haloperidol at 15, 30 and 45 minutes following the first injection. Both olanzapine and haloperidol reduced agitation significantly more than placebo at 2 and 24 hours following the first injection.(37)

Ziprasidone

A RCT conducted in acutely agitated psychotic patients compared 2mg with 10mg intramuscular ziprasidone injections (up to 4 injections in 24 hrs) in 119 subjects. The 10mg dose was significantly more effective up to 4 hrs after the first injection.(38) In an identical trial design, ziprasidone 2mg and 20mg injections were compared in a sample of 79. The 20mg dose substantially and significantly reduced symptoms of acute agitation.(39)

MAINTENANCE TREATMENT

Some empirical evidence is emerging to suggest that atypical antipsychotics may differ from conventional agents in altering the long-term course of schizophrenia.

Risperidone

A RCT compared relapse rates in 397 clinically stable adult outpatients with schizophrenia or schizoaffective disorder receiving flexible doses of risperidone or haloperidol for a minimum of one year. Risk of relapse at the end of the study was significantly lower for the risperidone group (34%) than for the haloperidol group (60%).(40) By using the National Psychiatric Hospital Case Registry of Israel, rehospitalisation status over two years was monitored for subjects discharged while taking risperidone (n=268) and olanzapine (n=313). Rehospitalisation rates of risperidone and olanzapine subjects were similar, both being more effective than conventional antipsychotics.(41)

Olanzapine

The efficacy of standard-dose oral olanzapine (5-15mg/day) was compared with placebo and with ineffective-dose olanzapine (1mg/day) in maintenance therapy of 120 subjects with schizophrenia. The standard-dose olanzapine treated patients experienced significantly lower relapse risk over one year compared to patients treated with placebo or ineffective-dose olanzapine.(42) Three RCTs compared olanzapine and haloperidol in maintenance treatment for schizophrenia and related psychoses.(5;21;22) All were double-blind extensions of acute studies. Data from these three studies were pooled and results reported separately.(43) Fewer subjects experienced relapse at one year with olanzapine(19.7%) than with haloperidol (28%). Olanzapine has also been compared with risperidone for prevention of relapse in a RCT conducted over 28 weeks. Survival analysis revealed that significantly more olanzapine patients maintained their response at endpoint.(44)

Sertindole

Long-term efficacy was assessed in 282 clinically stable treatment-responsive outpatients with schizophrenia treated up to one year with sertindole or haloperidol. Time to treatment failure was not significantly different between the groups, but sertindole patients remained free of hospitalisation for exacerbation of schizophrenia and remained compliant significantly longer than did the haloperidol treated patients.(45)

Amisulpride

A study again involving schizophrenics with predominantly negative symptoms compared low-dose amisulpride (100mg/day) and placebo over 6 months in 141 subjects. Significantly more amisulpride patients completed the study - dropout rates were 27% with amisulpride and 47% with placebo.(46)

No blinded maintenance studies were found for quetiapine and ziprasadone.

META-ANALYTICAL REVIEWS

Risperidone

A meta-analysis of 11 RCTs comparing risperidone to conventional antipsychotics concluded that short-term efficacy of risperidone is comparable to that of other antipsychotics. The risperidone patients showed slightly greater clinical improvement and lower overall dropout rate.(47) Another meta-analysis of 6 trials comparing risperidone with haloperidol in subjects with chronic schizophrenia treated for at least 4 weeks in RCTs

reported significantly higher response rates with risperidone and lower dropout rates.(48) A Cochrane review reported on 12 short-term studies and 2 long-term studies comparing risperidone with conventional antipsychotics, providing data on 3401 subjects. Risperidone increased the odds of moderate clinical improvement, but appeared to have little or no additional effect on the positive and negative symptoms of schizophrenia. When data from subjects on higher doses of haloperidol (>10mg/day) was excluded the advantage for risperidone was lost. (49)

Olanzapine

In a Cochrane review of 20 RCTs comparing olanzapine to placebo or any antipsychotic treatment in subjects with schizophrenia or schizophreniform psychosis, olanzapine appeared superior to placebo (but results were equivocal regarding negative symptoms), and equally as effective as typical antipsychotics. These authors point out that high attrition rates in both the olanzapine and typical antipsychotic groups make it difficult to draw firm conclusions from these studies.(50)

Quetiapine

A Cochrane review including 11 RCTs comparing quetiapine to placebo and other antipsychotic agents reported as follows: In comparison to placebo, data suggest that people allocated to quetiapine were less likely to leave the study early, particularly for treatment failure. Psychotic symptoms showed significant improvement in the quetiapine group. Compared to conventional antipsychotics, the proportion of people leaving the studies early was marginally, but significantly, less for the quetiapine group. Symptom reduction was significantly greater in the high dose range of quetiapine. High dropout rates and short duration of studies were cited as factors limiting interpretation of these studies.(51)

Ziprasidone

A Cochrane review of available RCT's reported that in studies ranging from one week (intramuscular preparation) to over 6 months, ziprasidone seemed more effective than placebo and as effective as haloperidol. The authors noted that data are currently limited, and that well-planned, conducted and reported long-term RCT's are needed.(52)

Sertindole

A Cochrane review included only two RCT's, as data on two others were incomplete. The evidence suggested that sertindole was more effective than placebo. The authors expressed reservations about its use in clinical practice because of cardiac problems that were evident in the trials.(53)

TREATMENT OF SPECIFIC SYMPTOM DOMAINS

It has been suggested that the atypical antipsychotics may have a broader spectrum of efficacy than conventional agents. In addition to positive symptoms, their effects on negative, cognitive, depressive and excited symptoms have been investigated. It has been suggested that they may differ from one another in their effects on these domains, as well as aspects such as overall quality of life, and hospitalisation status.(54)

Negative symptoms

Contrary to popular belief, conventional antipsychotics are effective in treating negative symptoms,(55) although the effect is modest at best. Atypical antipsychotics have been reported to ameliorate negative symptoms to various degrees when compared to high doses of conventional antipsychotics. However, few trials have specifically examined primary negative symptomatology and it has been suggested that improvements may be related to decreases in positive symptoms, reduced sedation or fewer extrapyramidal side-effects.(56)

Risperidone

A meta-analysis of the pooled results from 6 RCTs comparing risperidone to conventional antipsychotics (haloperidol, perphenazine and zuclopenthixol) reported that risperidone at doses between 4 and 8mg/day had a significantly higher negative symptom response rate (>20% reduction in PANSS negative subscale).(57)

Olanzapine

Three of four RCTs comparing olanzapine with conventional antipsychotics reported superior efficacy for olanzapine (see Table 2). A post-hoc analysis of a RCT comparing low, medium and high dose ranges of olanzapine with 10-20mg of haloperidol and placebo for up to 52 weeks focussed on negative symptom outcome. Significantly greater improvement was

observed in negative symptoms for the high dose olanzapine group compared to both placebo and haloperidol. Path analysis suggested that this was a direct medication effect.(58)

Amisulpride

Low-dose amisulpride improved negative symptoms compared to placebo in subjects with predominantly deficit symptomatology (Table 1). Also, two of 4 RCTs comparing higher dosage of amisulpride with conventional antipsychotics reported superiority for amisulpride in improving negative symptoms (Table 2).

Cognitive symptoms

Risperidone

Three studies, employing a similar design, investigated the effects of risperidone versus haloperidol on cognitive functions in treatment resistant schizophrenia. Risperidone treatment had a greater beneficial effect on verbal working memory,(59) reaction time and manual dexterity(60) and greater improvement in general verbal learning ability.(61)

Olanzapine

In a neuropsychological study 65 patients were randomly assigned in a double-blind design to olanzapine (5-20mg/day), risperidone (4-10mg/day) or haloperidol (5-20mg/day) over 6, 30 and 54 weeks. Olanzapine patients showed significantly greater improvement in general cognitive function at 6, 30 and 54 weeks, compared to both haloperidol and risperidone.(62)

Quetiapine

A RCT compared neuropsychological changes in 25 patients treated with either quetiapine or haloperidol. Quetiapine subjects showed improvement on cognitive skills, particularly verbal reasoning and fluency skills and immediate recall, with additional improvements on executive skills and visuomotor tracking.(63)

Depressive symptoms

Risperidone

In a retrospective analysis of pooled data from 6 RCTs, change scores on the PANSS anxious/depressive cluster were significantly greater for risperidone than for haloperidol or placebo.(64)

Olanzapine

In a separate analysis of a previously discussed RCT(5) in which 335 subjects were treated for 6 weeks with 3 fixed dose ranges of olanzapine, haloperidol 10-20mg or placebo, BPRS depression/anxiety depression cluster was significantly improved for two dose ranges of olanzapine (10 ± 2.5 mg/day and 15 ± 2.5 mg/day), whereas haloperidol was not.(65) Another post-hoc analysis of the largest olanzapine pivotal study (22) reported that olanzapine therapy was associated with greater baseline to endpoint improvement in BPRS anxiety/depression symptom cluster compared to haloperidol.(65) A post-hoc evaluation of the respective effects of olanzapine and risperidone on the PANSS depression cluster in a 28-week prospective, double-blind, randomised study reported that olanzapine was associated with a significantly greater improvement in depressive symptoms. In the risperidone group the patients with a greater degree of improvement in depressive symptoms had a significantly greater chance of psychotic relapse.(66) In the other head-to-head study comparing olanzapine and risperidone no significant differences were found with a last-observation carried forward analysis, although a completers analysis revealed an advantage for risperidone in reducing depressive/anxiety symptoms.(33)

Quetiapine

A post-hoc analysis of quetiapine versus haloperidol subjects with schizophrenia who displayed a partial response to treatment(67) found that quetiapine produced a greater reduction in depressive scores than haloperidol. Path analyses indicated that this was a direct effect on depressive symptoms (manuscript submitted).

Excitement/hostility

Risperidone

The effect on PANSS hostility item scores was compared in 139 subjects who participated in a multicentre study comparing risperidone, haloperidol and placebo. Risperidone had a greater selective effect on hostility than did haloperidol or placebo.(68)

PANSS five factor domains

In a post-hoc analysis combining two RCTs, 513 patients with chronic schizophrenia who received either risperidone (2, 6, 10 and 16mg/day), haloperidol (20mg/day) or placebo over 8 weeks were compared in terms of the 5 symptom domains identified by a factor analysis of the PANSS items (positive, negative, cognitive, excited and depression/anxiety). Factor score reduction was significantly greater for patients receiving risperidone 6-16mg/day than in patients receiving haloperidol or placebo. Differences were greatest for negative symptoms, uncontrolled hostility/excitement, and anxiety/depression, but were also significant for positive symptoms and disorganised thought.(69)

OTHER MEASURES OF OUTCOME

Pharmacoeconomic studies

Olanzapine

Clinical, quality-of-life and resource utilization data were prospectively collected from patients with schizophrenia who were participating in a multicentre, randomised, double-blind clinical trial comparing olanzapine 5-20mg/day (n=551) with haloperidol 5-20mg/day (n=266) for 6-weeks. Responders entered a 46-week maintenance phase. Olanzapine was more effective than haloperidol in producing a clinical response in the acute phase, but no significant differences in clinical improvement were observed in the maintenance phase. However, olanzapine led to reductions in inpatient and outpatient costs that more than offset olanzapine's higher acquisition costs.(70)

Olanzapine versus risperidone

A RCT compared clinical and economic outcomes in 150 subjects receiving either olanzapine (10-20mg/day) or risperidone (4-12mg/day) for up to 28 weeks. Olanzapine patients were reported to be more likely to maintain response, translating into savings in costs of care for both inpatient and outpatient services.(71)

A review of the evidence from pharmacoeconomic studies reported that clozapine is a cost-effective treatment for refractory schizophrenia. Compared to conventional antipsychotics, risperidone and olanzapine appear to be cost-neutral to slightly cost-saving while there is too little available data for quetiapine, ziprasidone and sertindole.(72)

Quality of life

In a separate analysis of the study reported above,(70) quality of life (QOL) was assessed as an outcome measure by means of the Quality of Life Scale (QLS) and SF-36 Health Survey. Compared to haloperidol, olanzapine treatment resulted in modestly better improvement in overall QOL, as well as on various subscale scores, both during the 6-week acute phase and during the extension phase.(73)

Another separate analysis of a previously reported RCT comparing 3 dose-ranges of olanzapine with haloperidol 10-20mg/day and placebo examined quality of life outcome in responders who were entered into a 46-week extension. Advantages were reported for olanzapine-treated subjects.(74)

FIRST-EPISODE SCHIZOPHRENIA

Risperidone

An international RCT was conducted in 183 patients with a first episode of schizophrenia or schizophreniform disorder. Flexible doses of risperidone (mean endpoint dose 6.1mg/day) and haloperidol (mean endpoint dose 5.6mg/day) were given over 8 weeks. The two compounds showed similar efficacy, with response rates for risperidone and haloperidol being 63% and 56% respectively.(75)

Olanzapine

A post-hoc analysis of a subpopulation of first-episode patients from a larger RCT(22) reported a significantly greater reduction in the BPRS total and negative scores and the PANSS total and positive scores, as well as a significantly higher response rate for the olanzapine subjects compared to the haloperidol subjects.(76)

REFRACTORY SCHIZOPHRENIA

Risperidone

Risperidone (mean dose 6.4 mg/day) was compared to clozapine (mean dose 291.2mg/day) over 8 weeks in 86 patients with chronic schizophrenia who were either resistant or intolerant to conventional antipsychotics. Treatments were found to be essentially similar, with a more rapid onset of action reported for risperidone.(77) While this trial provides good evidence for the efficacy of risperidone in moderately refractory patients, certain concerns have been voiced: The study population was not well defined, the sample size was relatively small, clozapine dosing was relatively low, and the treatment period was possibly too brief.(78) (79) (80) The authors responded by pointing out that their sample corresponds with the criteria normally applied when considering patients for clozapine treatment, and suggested that a less restrictive definition of treatment resistance may be more appropriate in clinical settings. In a RCT of 29 patients with partial response to conventional antipsychotics, risperidone was compared to clozapine over 6 weeks. Endpoint dose was 5.9mg/day for risperidone and 403.6mg/day for clozapine. Clozapine was superior to risperidone for positive symptoms, while total symptoms, negative symptoms and depression did not differ between groups.(81) A recent RCT compared increasing increments of risperidone and clozapine over 8 weeks in 273 subjects with severe chronic schizophrenia. The magnitude of improvement in mean BPRS and CGI scores was significantly greater in the clozapine group, as were most of the secondary efficacy measures.(82)

A RCT investigated the effects of risperidone versus haloperidol in a severely refractory sample of subjects with schizophrenia. Patients were randomly assigned to an initial 4 week fixed dose phase of either risperidone 6mg/day or haloperidol 15 mg/day followed by a further 4 week flexible dose phase. Risperidone was significantly better than haloperidol in reducing overall symptomatology at 4 weeks, but not at endpoint.(83)

Olanzapine

A prospective randomised double-blind study compared the efficacy of olanzapine versus chlorpromazine in treatment-resistant schizophrenia.(84) Criteria for resistance were similar to those of Kane et al,(85). This was an 8-week fixed-dose trial of either olanzapine 25mg/day or chlorpromazine 1200mg/day plus benztropine 4mg/day (both drugs were given at half-dose for the first week). No differences in efficacy were demonstrated between the two drugs. Seven percent of the olanzapine-treated patients and none of the chlorpromazine patients met a priori criteria for clinical response. There were also no differences in dropout rates.

Quetiapine

A RCT was conducted to assess the efficacy of quetiapine in 288 patients with schizophrenia who had been partially responsive to treatment. Subjects who experienced persistent symptoms on conventional antipsychotics were subjected to 4 weeks open treatment with fluphenazine, and those showing partial or no response were randomised to quetiapine 600mg/day and haloperidol 20mg/day for 8 weeks. Treatments were equally effective in total PANSS symptom reduction, while quetiapine patients had a significantly greater response rate(67) and significantly greater reduction of depressive symptoms (submitted).

In a recently reported RCT, clozapine, olanzapine, risperidone and haloperidol were compared in a sample of 157 inpatients with chronic schizophrenia who had not responded adequately to other antipsychotic medications. Trial duration was 14 weeks (8 weeks fixed-dose, followed by 6-week flexible dose). Respective mean endpoint doses for clozapine, olanzapine, risperidone and haloperidol were 526.6, 30.4, 11.6 and 25.7 mg/day. Compared to haloperidol, there were significant advantages for clozapine and olanzapine regarding

overall improvement (PANSS total), and general psychopathology, and for clozapine, risperidone and olanzapine regarding negative symptoms.(86)

A review and meta-analysis of 12 studies comparing typical and atypical antipsychotics in subjects with refractory schizophrenia reported that clozapine exhibits superiority over typical antipsychotics in terms of both efficacy and safety. However, the magnitude of the advantage for clozapine was not consistently robust. Efficacy data for other atypical antipsychotics in the treatment of refractory schizophrenia were inconclusive.(87)

CONCLUSIONS

Based on the evidence presented here, the following tentative conclusions can be drawn. Atypical antipsychotics (except amisulpride) have demonstrated superiority over placebo in acute schizophrenia. Compared to conventional antipsychotics, they are at least as effective. Generally, analyses employing conservative criteria (eg Cochrane reviews) report few efficacy differences between atypical and conventional agents. However, there are now a considerable number of well-controlled studies indicating modest advantages for the atypical antipsychotics, particularly in specific symptom domains. For the treatment of negative symptoms, olanzapine and to a lesser extent amisulpride appear most promising. Risperidone, olanzapine and quetiapine display advantages in improving cognitive and depressive symptoms. There are indications that the atypical antipsychotics are associated with decreased likelihood of re-hospitalisation and improved quality of life. In head-to-head comparisons of atypical antipsychotics, none have shown consistent efficacy advantages. In severely refractory samples, no atypical antipsychotics have consistently been shown to be as effective as clozapine, or superior to conventional agents. However, there are indications that risperidone, olanzapine and quetiapine have advantages over conventional agents in less severely refractory patients. Surprisingly few maintenance RCTs have been published, and efficacy advantages for atypical antipsychotics in prospective RCTs in first-episode schizophrenia have yet to be reported.

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Table 1. Acute randomised controlled trials of atypical antipsychotics versus placebo

Ref.no	N	Duration	Dose (mg/day)	Outcome vs.placebo		
				Overall	Positive symptoms	Negative symptoms
Risperidone						
2	135	8 weeks	2, 6, 10, 16	6-16mg superior	6-16mg superior	6mg superior
3	388	8 weeks	2, 6, 10, 16	6-16mg superior	6-16mg superior	6 & 16mg superior
Olanzapine						
4	152	6 weeks	1 and 10	10mg superior	10mg superior	10mg superior
5	335	6 weeks	5±2.5; 10±2.5 and 15±2.5	Medium & high dose superior	Medium & high dose superior	Low & high dose superior
Quetiapine						
6	286	6 weeks	250 and 750	750mg superior	750mg superior	750mg superior on SANS, not PANSS neg.
7	361	6 weeks	75, 150, 300, 600 and 750	150-750mg superior	150-750mg superior	300mg superior
Ziprasidone						
8	139	4 weeks	40 and 120	120mg superior	No differences	No differences
9	302	6 weeks	80 and 120	Both doses superior	Both doses superior	Both doses superior
Sertindole						
10	205	40 days	4, 8, 12, 20	20mg superior	No differences	No differences
11	497	8 weeks	12, 20, 24	All doses superior	20 and 24mg superior	20mg superior
Amisulpride						
12	27	6 weeks	50 to 100	No differences	No differences	Superior
13	104	6 weeks	100 and 300	Not assessed	Not assessed	Both doses superior
14	243	12 weeks	50 and 100	Not assessed	Not assessed	Both doses superior

Table 2. Acute randomised controlled trials of atypical antipsychotics versus conventional antipsychotics

Ref.no	N	Duration	Dose (mg/day)	Outcome vs. conventional agent		
				Overall	Positive symptoms	Negative symptoms
Risperidone						
2	135	8 weeks	2, 6, 10, 16	6mg superior	Equal	Equal
3	388	8 weeks	2, 6, 10, 16	Equal	Equal	Equal
17	1362	8 weeks	1, 4, 8, 12, 16	Equal	Equal	Equal
29	98	6 weeks	Mean 8	Equal	Equal	Equal
Olanzapine						
5	335	6 weeks	5±2.5; 10±2.5 and 15±2.5	Equal	Equal	15±2.5mg superior
21	431	6 weeks	5±2.5; 10±2.5 and 15±2.5	Equal	Equal	Equal
22	1996	6 weeks	5-20	Superior	Superior	Superior
23	182	8 weeks	5-15	Equal	Equal	Superior
Quetiapine						
7	361	6 weeks	75, 150, 300, 600 and 750	Equal	Equal	Equal
24	448	6 weeks	Mean 455	Equal	Equal	Equal
30	201	6 weeks	Mean 407	Equal	Equal	Equal
Ziprasidone						
25	90	4 weeks	4, 10, 40 and 160	160mg equal	160mg equal	160mg equal
Sertindole						
11	497	8 weeks	12, 20, 24	Equal	Equal	Equal
Amisulpride						
26	41	6 weeks		Equal	Equal	Equal
15	319	4 weeks	100, 400, 800, 1200	400 & 800mg equal	400 & 800mg equal	400 & 800mg equal
27	191	6 weeks	800	Equal	Equal	Superior
28	199	4 months	400-1200	Equal	Equal	Superior
31	132	6 weeks	1000	Equal	Superior	Equal

Table 3. Head-to-head randomised controlled trials of atypical antipsychotics in non-refractory samples

Ref.no	N	Duration	Dose (mg/day)	Outcome vs. conventional agent		
				Overall	Positive symptoms	Negative symptoms
Risperidone vs olanzapine						
32	339	28 weeks	OI 10-20 Ris 4-12	Equal	Equal	Olanzapine superior
33	377	8 weeks	OI 5-20 Ris 2-6	Equal	Equal	Equal
Risperidone vs clozapine						
34	59	4 weeks	Ris 4 and 8 Clo 400	Equal	Equal	Equal
Risperidone vs amisulpride						
35	228	8 weeks	Ris 8 Ami 800	Equal	Equal	Equal

Table 4. Randomised controlled trials of atypical antipsychotics in refractory schizophrenia.

Ref.no	N	Sample description	Duration	Dose (mg/day)	Outcome vs. conventional agent		
					Overall	Positive symptoms	Negative symptoms
Risperidone vs clozapine							
72	86	Resistant or intolerant	8 weeks	Ri mean 6.4 CI mean 291	Equal	Equal	Equal
76	29	Partial response	6 weeks	Ri mean 5.9 CI mean 403.6	Equal	Clozapine superior	Equal
77	273	Severe chronic schizophrenia	8 weeks	Ri 9 CI 642	Clozapine superior	Clozapine superior	Clozapine superior
Risperidone vs haloperidol							
82	67	Severe resistance	8 weeks	Ri mean 7.5	Equal	Equal	Equal
Olanzapine vs chlorpromazine							
83	84	Severe resistance	8 weeks	OI 25	Equal	Equal	Equal
Clozapine, olanzapine and risperidone vs haloperidol							
Ref	157	Chronic schizophrenia with inadequate response	14 weeks	Mean doses: CI 526.6 OI 30.4 Ri 11.6	Clozapine and olanzapine superior	Equal	Clozapine, olanzapine and risperidone superior
Quetiapine vs haloperidol							
64	288	Partial responders	8 weeks	Qu 600	Equal	Equal	Equal

BRIEF SYNOPSIS

This chapter reviews the published randomised controlled trials and meta-analyses in which the new atypical antipsychotics are compared with placebo, conventional antipsychotics or head-to-head comparisons. Agents included are risperidone, olanzapine, quetiapine, ziprasidone, sertindole and amisulpride. Efficacy has been demonstrated against placebo, and studies show at least equal efficacy compared with conventional antipsychotics. Although not always consistent, there are indications of superior efficacy for the domains of negative, depressive and cognitive symptoms, as well as reduced re-hospitalisation rates and improved quality of life.

3.c.v Evidence based antipsychotic treatment of schizophrenia

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Abstract

The introduction of the new generation antipsychotics has changed the way we treat patients with schizophrenia. This article reviews these agents, focussing mainly on the published randomised controlled trials and meta-analyses in which the new generation antipsychotics are compared with placebo, conventional antipsychotics or with one another. Agents included are risperidone, olanzapine, quetiapine, ziprasidone, sertindole, amisulpride and aripiprazole. Acute-phase and maintenance studies are reviewed, as well as randomised trials for pre-psychotic, first-episode schizophrenia and refractory schizophrenia. Finally, specific areas of current clinical interest are dealt with. These are: conventional versus new generation antipsychotics, head-to-head comparisons of new generation antipsychotics, and side-effect profiles.

Introduction

The introduction of the new generation antipsychotics has changed the way we treat patients with schizophrenia. A number of agents are now available, providing new treatment options and producing heightened optimism for improved clinical outcomes. While commonly lumped together as a class, important differences are emerging among these compounds, particularly regarding their side-effect profiles. A great deal has been published on these agents and new important studies regularly appear in the literature. However, unanswered questions remain regarding their safety and efficacy, and a much remains to be learnt in order to place them in their correct perspective.

For antipsychotic trials, demonstration of superiority over placebo is still a requirement of most regulatory authorities (Laughren 2001). Most of the earlier randomised controlled trials (RCTs) for the new generation antipsychotics used haloperidol as a comparator. However, a recent Cochrane meta-analysis of haloperidol versus placebo in clinical trials highlighted the neurotoxicity of the compound. The authors recommend that, for countries where haloperidol is not widely used, it should not be a control drug of choice for randomised trials of new antipsychotics (Joy et al. 2001). Most studies undertaken these days compare one new generation antipsychotic with another.

This paper evaluates the evidence for efficacy, tolerability and safety of the new generation antipsychotics risperidone, olanzapine, quetiapine, ziprasidone, sertindole, amisulpride and aripiprazole. It attempts to address the following: 1) the best first-line treatment of schizophrenia, 2) the best approach to treatment-resistant patients, and 3) recommendations for maintenance treatment. In order to avoid the potential pitfalls of uncontrolled studies, we have focused mainly on published RCTs and meta analytical reviews. A PubMed (National Library of Medicine) search of the English language literature was undertaken, using each of the individual compounds names as a search term. The drugs are discussed separately, under the following headings: acute treatment; maintenance treatment; side-effect profiles; prodromal; first-episode; and refractory schizophrenia. Finally the following focuses of current clinical interest are addressed: conventional versus new generation antipsychotics, head-to-head comparisons of new generation antipsychotics, and side-effect profiles.

RISPERIDONE

Acute phase trials

Versus placebo

The efficacy of oral risperidone has been demonstrated in two placebo-controlled trials. A dose-ranging study found risperidone 6 to 16mg/day to be superior to placebo in overall and positive symptom improvement, while only 6mg/day was better than placebo on negative symptom improvement (Chouinard et al. 1993b). A similar study reported significant improvements for 6 and 16 mg/day for overall clinical improvement, positive and negative symptoms, and 10 mg/day for positive symptoms only. The incidence of extrapyramidal symptoms (EPS) was significantly higher in patients treated with 16mg of risperidone and 20mg of haloperidol (Marder and Meibach 1994).

Versus conventional antipsychotics

In one dose-ranging study, risperidone 6mg/day was significantly better than haloperidol in reducing the Positive and Negative Symptom Scale (PANSS) total and General Psychopathology scores. Haloperidol produced significantly more EPS than risperidone or placebo (Chouinard et al. 1993a). In another dose-ranging study, risperidone 6 and 16 mg/day were significantly better than haloperidol 20mg/day in reducing overall symptoms. Significantly more subjects responded to risperidone 6 mg/day. The incidence of EPS was significantly higher in patients treated with 16mg of risperidone and 20mg of haloperidol (Marder and Meibach 1994). A large multinational study compared risperidone 1, 4, 8, 12 and 16 mg/day with haloperidol 10mg/day. The optimum risperidone doses were 4mg and 8mg/day, but no significant efficacy advantages over haloperidol were reported. Total EPS were greater in the haloperidol-treated patients than in the risperidone 1, 4, 8 and 12mg groups (Peuskens 1995). However, a later sub-analysis of patients from Germany, Austria and Switzerland reported significant advantages for risperidone over haloperidol according to PANSS total and subscale scores (Moller et al. 1997a). Further post-hoc sub-analyses reported that patients receiving risperidone 4mg/day improved more rapidly than those receiving haloperidol (Rabinowitz et al. 2001), and those hospitalised for >60 days (i.e. probably the more refractory patients) who received risperidone 4mg/day improved significantly more than those treated with haloperidol (Rabinowitz and Davidson 2001).

Flexible doses of risperidone (mean dose 8mg/day) and flupenthixol (mean dose 38mg/day) displayed comparable efficacy, and fewer patients experienced EPS with risperidone (Huttunen et al. 1995). A small RCT (n=35) compared risperidone to haloperidol and reported no differences in outcome, with risperidone causing fewer side-effects (Min et al. 1993).

Long acting risperidone injection

The first long-acting new generation antipsychotic has recently been introduced. A RCT comparing long-acting injectable risperidone (25mg, 50mg, or 75mg 2-weekly) to placebo in 400 patients over 12 weeks reported it to be effective and well tolerated. No efficacy advantages were reported for 75mg compared to 25 or 50mg 2-weekly (Kane et al. 2003).

Versus other new generation antipsychotics

Risperidone has been compared to other new generation antipsychotics in several studies. Two RCTs have been reported comparing risperidone with olanzapine. In the first, 339 subjects were evaluated over 28-weeks. Both olanzapine (10-20mg/day) and risperidone (4-12mg/day) were found to be effective, with olanzapine demonstrating superiority over risperidone in reducing negative symptoms, overall response rate and maintenance of response at 28 weeks. A greater proportion of olanzapine subjects maintained their response at 28 weeks. The incidence of EPS, hyperprolactinaemia and sexual dysfunction was greater in the risperidone treated patients (Tran et al. 1997b). The second study, this time with a lower dose of risperidone, investigated 377 subjects with schizophrenia over 8 weeks. Once again, both olanzapine (5-20mg/day, mean 12.4 mg/day) and risperidone (2-6mg/day, mean 4.8mg/day) were found to be effective. There were no differences in efficacy between the groups according to the last-observation carried forward analysis, although the completers analysis reported significant advantages for risperidone in treating both positive and

anxiety/depression symptoms. EPS were similar in the two groups. Greater weight gain was associated with olanzapine treatment (Conley and Mahmoud 2001).

In a small RCT, risperidone 4mg/day (n=20), 8mg/day (n=19) and clozapine 400mg/day (n=20) were compared over 28 days in a non-refractory sample of patients with schizophrenia. No differences in efficacy were reported and risperidone appeared to be better tolerated (Klieser et al. 1995). Three studies have compared risperidone and amisulpride. Risperidone (8mg/day) was compared with amisulpride (800mg/day) over 8 weeks in a 228 patients with acute exacerbation of schizophrenia. The drugs showed equal efficacy, with both demonstrating good safety profiles. EPS did not differ between the two groups (Peuskens et al. 1999). A 6-month trial in 309 subjects comparing amisulpride (400-1000mg/day) and risperidone (4-10mg/day) reported a superior response rate for amisulpride, similar incidence of EPS and less weight-gain and endocrine/sexual symptoms with amisulpride (Sechter et al. 2002). A small (n=48) trial reported similar efficacy and EPS for amisulpride (400-800mg/day) and risperidone (4-8mg/day), with greater weight gain for risperidone (Hwang et al. 2003).

The efficacy and safety of clozapine, olanzapine, risperidone and haloperidol were compared over 14 weeks in 150 patients with a suboptimal treatment response. Clozapine, risperidone and olanzapine (but not haloperidol) treatment resulted in significant PANSS total score improvements. Negative symptoms improved significantly more for clozapine and olanzapine than haloperidol treated patients. Olanzapine and clozapine were associated with weight gain (Volavka et al. 2002). In a separate report of the neurocognitive effects of treatment in the same sample, global cognitive function improved significantly more with olanzapine and risperidone than with haloperidol (Bilder et al. 2002).

Maintenance treatment

Until recently, very few RCTs had evaluated the efficacy and safety of the new generation antipsychotics in the maintenance treatment of schizophrenia. However, there are now a few studies suggesting advantages for new generation antipsychotics over their predecessors.

A RCT compared relapse rates in 365 clinically stable adult outpatients with schizophrenia or schizoaffective disorder receiving flexible doses of risperidone or haloperidol for a minimum of one year. Risk of relapse at the end of the study was significantly lower for the risperidone group (34%) than for the haloperidol group (60%). Early discontinuation of treatment was more frequent among the haloperidol patients. Risperidone patients had greater reductions in EPS scores (Csernansky et al. 2002). In a 2-year maintenance trial comparing risperidone 6mg/day with haloperidol 6mg/day in 63 stable patients, both groups experienced similar improvements in symptoms and similar risks of psychotic exacerbations. However, risperidone-treated patients appeared to feel subjectively better, as indicated by less anxiety and depression and fewer extrapyramidal side effects (Marder et al. 2003a)

Meta-analyses

A meta-analysis of 11 RCTs comparing risperidone to conventional antipsychotics concluded that short-term efficacy of risperidone is comparable to that of other antipsychotics. Risperidone patients showed slightly greater clinical improvement and lower overall dropout rate. Weight gain and tachycardia were more common in risperidone. There were significantly fewer EPS with risperidone (Song 1997). Another meta-analysis of 6 trials comparing risperidone with haloperidol in subjects with chronic schizophrenia treated for at least 4 weeks in RCTs reported significantly higher response rates with risperidone and lower dropout rates. There was also significantly less prescribing of anticholinergic medication with risperidone patients (Davies et al. 1998). A Cochrane review reported that in both the short and long term risperidone was more likely to produce improvement in symptoms, and to reduce the relapse rate at 12 months. Risperidone was less likely to cause motor disorders, but more likely to cause weight gain (Hunter et al. 2003).

OLANZAPINE

Acute phase trials

Versus placebo

Two pivotal dose-ranging studies found olanzapine to be significantly better than placebo in overall symptom improvement, as well as improvement in positive and negative symptoms

(Beasley et al. 1996a; Beasley et al. 1997). The most common treatment-emergent adverse events were somnolence, agitation, asthenia and nervousness (Beasley et al. 1996a). Plasma prolactin elevation did not differ from placebo (Beasley et al. 1996a).

Versus conventional antipsychotics

Three RCTs have compared olanzapine with haloperidol (Beasley et al. 1996b; Danion et al. 1999; Tollefson et al. 1997). Olanzapine demonstrated some efficacy advantages over haloperidol in these studies. In the first, (n=335) olanzapine 15 ± 2.5 mg/day was significantly better than haloperidol 15 ± 5 mg/day in reducing negative symptoms after 6 weeks, (Beasley et al. 1996b) while in the second study (n=431) olanzapine 15 ± 2.5 mg/day over 6 weeks was equal to haloperidol 15 ± 5 mg/day on all efficacy measures (Beasley et al. 1997). In a very large study (n=1,996) olanzapine 5-20mg/day (mean 13.2mg/day) was significantly better than haloperidol 5-20mg/day (mean 11.8mg/day) over 6 weeks in reducing overall psychopathology (Beasley, Jr. et al. 1997), positive symptoms (Beasley et al. 1997), negative symptoms (Beasley et al. 1996b; Wyatt et al. 1998) and depressive symptoms (Tollefson et al. 1997). Significant advantages for olanzapine over haloperidol treatment were found for EPS (Beasley et al. 1996b; Beasley et al. 1997; Tollefson et al. 1997). A RCT compared olanzapine with haloperidol in a sample of 182 Asian patients with schizophrenia. Olanzapine was as effective as haloperidol in treating overall symptomatology, and significantly superior in treating negative symptoms and EPS (Ishigooka et al. 2001). In a recently reported non-industry sponsored multi-site RCT the long-term (12 month) effectiveness of olanzapine 5-20mg/day versus haloperidol 5-20mg/day (with prophylactic benztropine) was evaluated in 309 subjects with serious symptoms, and serious dysfunction for the previous 2 years. There were no significant differences between groups in study retention; positive, negative, or total symptoms; quality of life; or overall EPS. Olanzapine was associated with reduced akathisia, possibly less TD and slight cognitive advantages, but more frequent reports of weight gain (Rosenheck et al. 2003).

Intramuscular (IM) olanzapine

IM olanzapine was compared to IM haloperidol and IM placebo in treating acute agitation over a 24-hour period in hospitalised patients with schizophrenia. Olanzapine showed superiority over haloperidol at 15, 30 and 45 minutes following the first injection. Both olanzapine and haloperidol reduced agitation significantly more than placebo at 2 and 24 hours following the first injection. No patients treated with olanzapine experienced acute dystonia, compared with 7% of those treated with haloperidol (Wright et al. 2001). In a similar study in 270 acutely agitated patients with schizophrenia olanzapine (2.5mg; 5mg; 7.5mg or 10mg) showed a dose-response relationship in reduction of agitation. All doses of olanzapine, except 2.5mg, were more effective than placebo at 30 minutes after injection, although not more effective than haloperidol. The lower doses of olanzapine (2.5mg; 5mg and 7.5mg), produced less treatment-emergent parkinsonism than haloperidol (Breier et al. 2002).

Versus other new generation antipsychotics

Two studies comparing olanzapine and risperidone are reported above. A RCT comparing amisulpride (200-800mg/day) and olanzapine (5-20mg/day) in 377 subjects reported similar efficacy and low EPS in both groups. Weight gain was significantly greater in the olanzapine treated patients (Martin et al. 2002).

Maintenance treatment

The efficacy of a standard-dose of oral olanzapine (5-15mg/day) was compared with placebo and with an ineffective-dose olanzapine (1mg/day) in maintenance therapy of 120 subjects with schizophrenia. The standard-dose olanzapine treated patients experienced significantly lower relapse risk over one year compared to patients treated with placebo or ineffective-dose olanzapine (Dellva et al. 1997). Data from three double-blind extensions of acute studies (Beasley et al. 1996b; Beasley et al. 1997; Meltzer 1999) comparing olanzapine and haloperidol in maintenance treatment were pooled and reported together. Fewer subjects experienced relapse at one year with olanzapine (19.7%) than with haloperidol (28%) (Tran et al. 1998). Olanzapine has also been compared with risperidone for prevention of relapse in a RCT conducted over 28 weeks. Survival analysis revealed that significantly more olanzapine patients maintained their response at endpoint. The incidence of EPS, hyperprolactinaemia

and sexual dysfunction was significantly lower in the olanzapine treated patients (Tran et al. 1997a).

Meta-analyses

A Cochrane review included 21 RCTs comparing olanzapine to placebo or any antipsychotic treatment in subjects with schizophrenia or schizophreniform psychosis. Olanzapine was found to be superior to placebo (although results were equivocal for negative symptoms), and equally as effective as conventional antipsychotics. There were fewer EPS with olanzapine than with haloperidol. Weight change data were not conclusive. (Duggan et al. 2003).

QUETIAPINE

Acute phase trials

Versus placebo

High-dose (750mg/day) and low-dose (250mg/day) quetiapine were compared to placebo over 6 weeks in 286 hospitalised subjects. High withdrawal rates were recorded in all three treatment groups (42%, 57% and 59%), primarily because of treatment failure. High-dose quetiapine was significantly better than placebo in reducing overall and positive scores. Reduction of negative symptoms was less consistent. Quetiapine was well tolerated, and did not induce EPS, sustained elevations of prolactin, or clinically significant haematological changes (Small et al. 1997). A multiple fixed dose study of quetiapine (75, 150, 300, 600 and 750mg/day), haloperidol (12mg/day) and placebo reported significant differences between the four highest doses of quetiapine and placebo for overall and positive symptoms, and between quetiapine 300mg/day and placebo for negative scores. Across the dose range, quetiapine was no different from placebo regarding the incidence of EPS or change in prolactin concentrations (Arvanitis and Miller 1997).

Versus conventional antipsychotics

In the above dose-ranging study, there were no differences between quetiapine and haloperidol regarding the efficacy measures (Arvanitis and Miller 1997). In a study comparing flexible doses of quetiapine (mean 455 mg/day) and haloperidol (mean 8 mg/day) both compounds produced clear reductions in symptoms. At endpoint, the mean PANSS total score was reduced by -18.7 in the quetiapine group, and -22.1 in the haloperidol group ($P = 0.13$, between-treatment). Significantly fewer EPS and reduced prolactin levels were reported at endpoint for the quetiapine treated patients (Copolov et al. 2000). Flexible doses of quetiapine (mean endpoint dose 407 mg/day) and chlorpromazine (mean dose 384 mg/day) were equally effective in the treatment of positive and negative symptoms. The quetiapine group had a lower incidence of adverse events and EPS than the chlorpromazine group (Peuskens and Link 1997).

Versus other new generation antipsychotics

No RCTs were found comparing quetiapine to other new generation antipsychotics.

Maintenance studies

No blinded maintenance studies were found for quetiapine.

Meta-analyses

A Cochrane systems review included 11 RCTs comparing quetiapine to placebo and other antipsychotic agents, and found that, compared to placebo, people treated with quetiapine showed greater symptom reduction and were less likely to leave the study early, particularly for treatment failure. Compared to conventional antipsychotics, the proportion of people leaving the studies early was marginally, but significantly, less for the quetiapine group. Symptom reduction was significantly greater in the high dose range of quetiapine. Less anticholinergic medication was required in the quetiapine-treated patients. It was noted that most data are very short term (Srisurapanont et al. 2000).

ZIPRASIDONE

Acute phase trials

Versus placebo

A study comparing ziprasidone 40 or 120mg/day and placebo found 120mg/day to be significantly more effective than placebo in improving the overall, depressive and anergia

scores, and had significantly more responders than placebo. The most frequently reported adverse events were dyspepsia, constipation, nausea and abdominal pain. There were no differences between ziprasidone and placebo regarding EPS (Keck, Jr. et al. 1998). In another placebo-controlled trial comparing ziprasidone 80 or 160mg/day, both doses of ziprasidone were significantly more effective than placebo in reducing overall, core-item and negative symptom scores. Ziprasidone had a very low liability for inducing movement disorders and weight-gain (Daniel et al. 1999).

Versus conventional antipsychotics

A dose-finding RCT comparing ziprasidone 4, 10, 40 and 160 mg/day and haloperidol 15mg/day found ziprasidone 160mg/day to be comparable with haloperidol in reducing overall psychopathology and positive symptoms, as well as overall response rate. In ziprasidone patients, only transient elevations in prolactin were recorded, and fewer required benztropine to treat EPS (Goff et al. 1998).

IM ziprasidone

A RCT evaluated IM ziprasidone (2mg and 10mg) injections in acutely agitated psychotic patients. The 10mg dose was significantly more effective in reducing agitation up to 4 hrs after the first injection. No acute dystonia was reported (Lesem et al. 2001). In another similar study, ziprasidone 2mg and 20mg injections were compared. The 20mg dose substantially and significantly reduced symptoms of acute agitation. Both doses were well tolerated, and were not associated with EPS (Daniel et al. 2001).

Maintenance studies

Patients with stable, chronic schizophrenia were treated with ziprasidone 40mg/day; 80mg/day or 160mg/day or placebo for one year. All the ziprasidone groups showed a lower probability of relapse than placebo. Discontinuation due to adverse events was similar for ziprasidone and placebo. Ziprasidone treatment was not associated with increased risk of movement disorders, weight gain or cardiovascular abnormalities (Arato et al. 2002). Another study compared ziprasidone (modal dose 80 mg/day) with haloperidol (modal dose 5 mg/day) in stable patients over 28 weeks. Similar reductions in all mean efficacy variables were observed. More ziprasidone treated patients were negative symptom responders. Despite the low dose of haloperidol, ziprasidone had clear advantages in all evaluations of movement disorders. Changes in body weight were negligible with both treatments. No significant laboratory or cardiovascular changes were observed (Hirsch et al. 2002).

Meta-analyses

A Cochrane review of available RCT's reported that in studies ranging from one week (IM preparation) to over 6 months, ziprasidone seemed more effective than placebo and as effective as haloperidol. There were fewer EPS in the ziprasidone-treated patients. The authors noted that data for ziprasidone were limited at that stage (Bagnall et al. 2000).

SERTINDOLE

Acute phase trials

Versus placebo

A RCT compared sertindole 4, 8, 12 and 20mg/day and placebo. A dose-related improvement was observed for total scores, with significant differences being recorded between sertindole 20mg/day and placebo. EPS-related events were comparable in the placebo and sertindole groups (van Kammen et al. 1996). Another RCT compared sertindole 12, 20 and 24mg/day with haloperidol 4, 8 and 16mg/day, and placebo. All doses were more effective than placebo. For treating negative symptoms, only sertindole 20mg/day was superior to placebo (Zimbroff et al. 1997).

Versus conventional antipsychotics

In two dose-ranging studies, sertindole and haloperidol were comparably effective. For EPS measures, sertindole was indistinguishable from placebo, and rates of EPS were not dose related. All dose levels of haloperidol produced significantly more EPS than placebo or sertindole. Adverse events associated with sertindole treatment were mild in severity (van Kammen et al. 1996; Zimbroff et al. 1997).

Maintenance studies

Long-term efficacy and time to treatment failure was assessed in 282 clinically stable treatment-responsive outpatients with schizophrenia treated up to one year with sertindole or haloperidol. Time to treatment failure was not significantly different between the groups, but sertindole patients remained free of hospitalisation for exacerbation of schizophrenia and remained compliant significantly longer than did the haloperidol treated patients. There were also significantly fewer reports of EPS in the sertindole patients (Daniel et al. 1998).

Meta-analyses

A Cochrane review of sertindole versus placebo and other antipsychotics in schizophrenia included only two RCT's, as data on two others were incomplete. The evidence suggested that sertindole was more effective than placebo. Sertindole was associated with fewer EPS than haloperidol, but caused more weight gain. The authors expressed reservations about its use in clinical practice because of cardiac problems that arose in the trials (Lewis et al. 2000).

AMISULPRIDE

Acute phase trials

Versus placebo

The efficacy of low-doses (50-300mg/day) of amisulpride versus placebo for negative symptoms has been assessed in three RCTs (Boyer et al. 1995; Danion et al. 1999; Paillere-Martinot et al. 1995). (Boyer et al. 1995; Danion et al. 1999) Amisulpride was consistently better than placebo in these studies, and the effect on negative symptoms was apparently unrelated to any changes in positive symptoms (Danion et al. 1999). No controlled studies were found comparing high-dose amisulpride with placebo.

Versus conventional antipsychotics

Fixed doses of amisulpride (400, 800 and 1200mg/day) and haloperidol 16 mg/day were compared with a sub-therapeutic dose of amisulpride (100mg/day). Total score reductions were greatest in the groups taking 400mg or 800mg amisulpride/day. Symptoms of parkinsonism did not increase for the amisulpride groups, whereas with haloperidol they did (Puech et al. 1998). In a small flexible-dose study (n=41) both amisulpride or haloperidol groups showed similar symptom reduction, with amisulpride doing significantly better regarding reduction of depressive symptoms. Significantly fewer EPS were recorded in the amisulpride group (Delcker et al. 1990). In another study, amisulpride 800mg/day was as effective as haloperidol 20mg/day for positive symptoms, and significantly more effective for negative symptoms. The amisulpride patients exhibited significantly fewer EPS (Moller et al. 1997b). In a flexible dose study comparing amisulpride 400-1200mg/day to haloperidol 10-30mg/day, overall and positive scores were equally reduced, while negative score reduction and percentage of responders was significantly greater with amisulpride. Haloperidol was associated with a greater incidence of EPS (Carriere et al. 2000). Amisulpride (1000mg/day) was compared with flupenthixol (25mg/day) in a fixed-dose RCT. Efficacy results were similar for both drugs, except that amisulpride was significantly better in reducing positive symptoms. There were fewer EPS in the amisulpride group (Wetzel et al. 1998).

Versus other new generation antipsychotics

Three studies comparing amisulpride with risperidone, and one with olanzapine, are reported above.

Maintenance studies

Low-dose amisulpride (100mg/day) and placebo were compared in patients with predominantly negative symptoms over 6 months. Significantly more amisulpride patients completed the study. Dropout rates were 27% with amisulpride and 47% with placebo. The incidence of EPS was similar in both groups (Loo et al. 1997).

Meta-analyses

A meta-analysis of 11 RCTs, comparing amisulpride to conventional antipsychotics, concluded that amisulpride was more effective than conventional antipsychotics for both global schizophrenic symptoms and negative symptoms. Amisulpride was associated with significantly lower use of antiparkinsonian medication and fewer dropouts due to adverse

events (Leucht et al. 2002). Another meta-analysis specifically assessed the evidence for negative symptom efficacy. The overall analysis reported improvement of negative symptoms that could probably not be accounted for by improvement of positive symptoms, depressive symptoms or EPS (Storosum et al. 2002). A Cochrane review of 19 randomised studies with a total of 2443 participants found that, compared to typical antipsychotics, amisulpride was more effective in improving global state, and the negative symptoms of schizophrenia. Regarding positive symptoms, amisulpride was as effective as typical antipsychotics. Amisulpride was less prone to cause EPS or to require the use of antiparkinson medication, and also seemed to be more acceptable to patients than conventional drugs (Mota et al. 2002).

ARIPIPRAZOLE

Acute phase trials

Versus placebo and conventional agents

A RCT comparing aripiprazole 15 and 30 mg/day to placebo and haloperidol 10 mg/day found both doses of aripiprazole and haloperidol produced significant improvements in total and positive scores. Aripiprazole 15 mg, and haloperidol 10 mg significantly improved negative scores. Unlike haloperidol, aripiprazole was not associated with significant EPS or prolactin elevation. There were no significant changes in body weight, and no clinically significant increases in QTc interval (Kane et al. 2002). In another study, aripiprazole 20 or 30 mg/day and risperidone 6 mg/day were significantly better than placebo on all efficacy measures. There were no significant differences between aripiprazole and placebo in EPS. Mean prolactin levels decreased with aripiprazole but significantly increased 5-fold with risperidone. Mean change in QTc interval did not differ significantly from placebo with any active treatment group. Both aripiprazole and risperidone groups showed similar low incidence of weight gain (Potkin et al. 2003). A pooled analysis reported data from five acute-phase RCTs involving patients treated with aripiprazole (n=932), placebo (n=416), or haloperidol (n=201). Aripiprazole was well tolerated, with similar adverse event incidence rates to placebo, and lower rates than haloperidol for EPS and somnolence. There was minimal mean weight change with aripiprazole and haloperidol, and no QTc prolongation. Serum prolactin increased with haloperidol, but not with aripiprazole (Marder et al. 2003b).

Maintenance treatment

In a 26-week RCT stable patients received fixed doses of aripiprazole 15 mg, or placebo. Time to relapse was significantly longer for aripiprazole compared with placebo. More patients relapsed with placebo (57%) than aripiprazole (34%). Aripiprazole was significantly superior to placebo from baseline to endpoint in PANSS total and positive scores. Aripiprazole was well tolerated, with no evidence of marked sedation and no evidence of hyperprolactinemia or prolonged QTc. EPS were comparable with placebo. There was a slight mean weight loss at endpoint in both groups (Pigott et al. 2003). The prospectively pooled results of two 52-week RCTs evaluating aripiprazole 30 mg/day versus haloperidol 10 mg/day in 1294 patients were recently reported. Aripiprazole demonstrated efficacy comparable to haloperidol across most symptom measures, and greater improvements for negative and depressive scores. The time to discontinuation was significantly greater with aripiprazole than with haloperidol. Aripiprazole was associated with significantly lower scores than haloperidol on all EPS assessments (Kasper et al. 2003).

SPECIAL POPULATIONS OF SCHIZOPHRENIA

Prepsychotic period

A RCT compared low-dose risperidone (mean dose 1.3mg/day) and cognitive behavioural therapy (CBT) with need-based intervention in 59 subjects at incipient risk of progression to first-episode psychosis. Both risperidone and CBT reduced the risk of early transition to psychosis (McGorry et al. 2002). Another RCT evaluated the short-term efficacy (8 weeks) of olanzapine 5-15 mg/day versus placebo in 60 patients with prodromal schizophrenia. Results suggest that olanzapine is associated with significantly greater symptom improvement, but also significantly greater weight gain than placebo (Woods et al. 2003).

First-episode schizophrenia

In spite of increasing attention focussing on early intervention, few RCTs have evaluated the efficacy and safety of new generation antipsychotic medications directly in patients with a first episode of psychosis. An international RCT compared flexible doses of risperidone (mean 6.1mg/day) and haloperidol (mean 5.6mg/day) over 8 weeks. The two compounds showed similar efficacy, with response rates for risperidone and haloperidol being 63% and 56% respectively. Both groups experienced considerable EPS, although this was significantly lower in the risperidone group. A post-hoc analysis showed that lower doses (<6mg/day) were efficacious, and associated with far fewer EPS (Emsley 1999).

A post-hoc analysis was conducted in a subpopulation of patients experiencing their first-episode of psychosis from a larger RCT (Tollefson et al. 1997). A greater reduction in total, positive and negative scores, as well as a significantly higher response rate was found for the olanzapine subjects compared to the haloperidol subjects. Olanzapine treated patients showed a significant reduction in EPS, while haloperidol treated patients showed an increase in EPS (Sanger et al. 1999). A large (n=263) prospective RCT compared olanzapine with haloperidol in first-episode psychosis. Twelve-week results reported similar symptom reduction for the two treatments with last-observation-carried-forward analyses, but greater decreases in PANSS total, negative and general psychopathology scales for olanzapine with a mixed-model analysis. Significantly more olanzapine-treated subjects than haloperidol-treated subjects completed the acute phase of the study. Olanzapine-treated patients experienced a lower rate of treatment-emergent parkinsonism and akathisia but had significantly more weight gain. (Lieberman et al. 2003).

Refractory schizophrenia

Clozapine is the most effective treatment in patients with severe, refractory schizophrenia and remains the treatment of choice (Kane et al. 1988). However, the benefits of clozapine are limited, and many patients tolerate the drug poorly (Kane et al. 1988). The new generation antipsychotics have raised expectations in the treatment of patients who are refractory to conventional agents, although studies to date have not been entirely convincing.

Risperidone

A RCT compared risperidone (mean dose 6.4 mg/day) to clozapine (mean dose 291.2mg/day) over 8 weeks in 86 subjects with chronic schizophrenia who were either resistant or intolerant to conventional antipsychotics. Both drugs were found to be essentially similar, with a more rapid onset of action reported for risperidone. EPS and other adverse events were scarce and mild in both groups (Bondolfi et al. 1998). This study does not represent a purely refractory sample, and has been criticised because the sample was not well defined, the sample size was relatively small, clozapine dosing was relatively low, and the treatment period was possibly too brief (Dunayevich and Chatterjee 1999;Meltzer 1999;Rubin 1999). In a small RCT (n=29) of subjects showing only a partial response to conventional antipsychotics, risperidone (mean 5.9mg/day) was compared to clozapine (mean 403.6mg/day) over 6 weeks. Clozapine was superior to risperidone for positive symptoms, while total symptoms, negative symptoms and depression did not differ between the groups (Breier et al. 1999). Another RCT compared flexible doses of risperidone and clozapine over 8 weeks in 273 subjects with severe chronic schizophrenia. Improvement in mean BPRS, CGI scores and most of the secondary efficacy measures was significantly greater in the clozapine group (Azorin et al. 2001). A RCT investigated the effects of risperidone versus haloperidol in a severely refractory sample of subjects with schizophrenia. Risperidone was significantly better than haloperidol in reducing overall symptomatology at 4 weeks, but not at endpoint (Wirshing et al. 1999).

Olanzapine

A RCT compared the efficacy of olanzapine (25mg/day) versus chlorpromazine (1200mg/day) in treatment-resistant schizophrenia (Conley et al. 1998). No differences in efficacy were demonstrated between the two drugs. Seven percent of the olanzapine-treated patients and none of the chlorpromazine patients met *a priori* criteria for clinical response. There were also no differences in dropout rates. Olanzapine was significantly better tolerated than chlorpromazine. The olanzapine-treated patients had fewer motor and cardiovascular side-effects. No antiparkinsonian drugs were necessary in the olanzapine group.

Quetiapine

A RCT was conducted to assess the efficacy of quetiapine in patients who were partially responsive to conventional antipsychotic treatment. Subjects were randomised to quetiapine 600mg/day and haloperidol 20mg/day for 8 weeks. Treatments were equally effective in symptom reduction, while quetiapine patients had a significantly greater response rate (Emsley et al. 2000) and significantly greater reduction of depressive symptoms (Emsley et al. 2003b). The quetiapine treated patients experienced fewer EPS and had lower serum prolactin levels.

In a recently reported RCT, clozapine, olanzapine, risperidone and haloperidol were compared in inpatients with chronic schizophrenia who had not responded adequately to other antipsychotic medications. Respective mean endpoint doses for clozapine, olanzapine, risperidone and haloperidol were 526.6, 30.4, 11.6 and 25.7 mg/day. Compared to haloperidol, there were significant advantages for clozapine and olanzapine regarding overall improvement, and general psychopathology, and for clozapine, risperidone and olanzapine regarding negative symptoms (Volavka et al. 2002). A review and meta-analysis of 12 studies comparing typical and new generation antipsychotics in subjects with refractory schizophrenia reported that clozapine exhibits superiority over conventional antipsychotics in terms of both efficacy and tolerability. However, the magnitude of the advantage for clozapine was not consistently robust. Efficacy data for other new generation antipsychotics in the treatment of refractory schizophrenia were inconclusive (Chakos et al. 2001).

CONVENTIONAL VERSUS NEW GENERATION ANTIPSYCHOTICS: THE ONGOING DEBATE

The most robust difference between the conventional and new generation antipsychotics has been the reduced propensity of the latter to produce EPS. However, it could be argued that this difference is spurious, and may be explained on the basis that the dose of the conventional comparators (usually haloperidol) was too high. In fact, by employing strategies to reduce the EPS risk with conventional antipsychotics, differences between the conventional and new generation agents are less obvious. Three strategies have been adopted to reduce EPS with conventional antipsychotics, namely the use of low doses, the addition of prophylactic anticholinergic agents and the use of low-potency conventional antipsychotics. First, the use of low-doses of haloperidol has been shown to be effective and well tolerated (Oosthuizen et al. 2001), and haloperidol 2mg/day was at least as effective, with significantly fewer EPS than 8mg/day in the acute treatment of first-episode schizophrenia (Oosthuizen et al. 2003b). Second, the addition of prophylactic benztropine to reduce the risk of EPS with haloperidol in a RCT comparing it with olanzapine reported no significant differences between groups in study retention; positive, negative, or total symptoms of schizophrenia; quality of life; or EPS. While olanzapine showed benefits in reducing akathisia and improving cognition, the authors pointed out that this has to be balanced with the problems of weight gain and higher cost (Rosenheck et al. 2003). Third, a recent meta-analysis of studies comparing new generation antipsychotics to low-potency conventional agents reported that mean doses less than 600 mg/day of chlorpromazine or its equivalent had no higher risk of EPS than new generation antipsychotics (Leucht et al. 2003). However, even when utilizing these strategies, important differences exist between conventional and new generation agents. Thus, even at very low-doses conventional agents are associated with some acute EPS (Oosthuizen et al. 2003b), and importantly, no reduction in the incidence of TD (Oosthuizen et al. 2003a). Also, studies of conventional versus new generation agents in which more appropriately low doses of haloperidol were used showed significant differences in EPS in favour of the new generation antipsychotics (Emsley 1999;Hirsch et al. 2002;Lieberman et al. 2003;Marder et al. 2003a;Zimbroff et al. 1997). Finally, although low-potency antipsychotics did not cause more EPS, they were found to be moderately less effective than new generation antipsychotics (Leucht et al. 2003).

A meta-regression analysis of 52 RCTs comparing new generation antipsychotics (clozapine, risperidone, olanzapine, quetiapine, amisulpride, and sertindole) with conventional antipsychotics or alternative new generation antipsychotics found that the dose of conventional antipsychotics was a confounding factor. When compared to ≤ 6 mg/day haloperidol, new generation antipsychotics had no benefits in terms of efficacy or overall tolerability, although they still caused fewer EPS (Geddes et al. 2000). A recent meta-analysis

of RCTs comparing new generation antipsychotics with conventional agents or other new generations reported that, compared to conventional agents clozapine, amisulpride, risperidone and olanzapine had significantly greater effect sizes (0.49, 0.29, 0.25 and 0.21, respectively). Unlike Geddes et al (Geddes et al. 2000), these authors found no evidence that haloperidol dose affected the results (Davis et al. 2003).

HEAD-TO-HEAD COMPARISONS OF NEW GENERATION ANTIPSYCHOTICS

A number of direct comparisons of new generation antipsychotics have now been published, allowing some comparison between these agents. It can be seen that few, if any efficacy differences have been demonstrated between these agents. However, side-effect profiles differ considerably.

FOCUSSING ON SIDE-EFFECT PROFILES

As can be seen from the above, to date no conclusive evidence exists for efficacy superiority of any of the new generation antipsychotics other than clozapine. However, the clear-cut differences in side-effect profiles have become a critical focus area for clinicians when choosing an antipsychotic. The most important side-effects to consider are EPS, weight-gain, cardiotoxicity, and hyperprolactinaemia.

Extrapyramidal symptoms

By definition, new generation antipsychotics are effective at doses below those that would normally cause EPS. However, there are significant intra-class differences in the EPS risk between the new generation antipsychotics. Risperidone and amisulpride, while not differing from placebo at the lower end of their therapeutic range, cause EPS in a dose-dependent manner. On the other hand, clozapine and quetiapine have a very low risk of inducing EPS (Seeman 2002).

Weight gain

Whereas the treatment of schizophrenia previously focussed mainly on the control of acute psychotic symptoms and strategies to minimise EPS, the substantially increased risk of medical morbidity and mortality in these patients has more recently become an area of attention. It has become apparent that new generation antipsychotics may contribute to this risk. Weight gain has been consistently associated with some of these agents, particularly clozapine and olanzapine. Risperidone appears to be associated with a modest risk, with ziprasidone, amisulpride and aripiprazole having a low risk of weight gain (Bobes et al. 2003; Nasrallah 2003). A meta-analysis and random effects meta-regression that estimated the weight change after 10 weeks of treatment with a standard dose of each of the new generation antipsychotics showed the following mean increases in weight: clozapine, 4.45kg; olanzapine, 4.15kg; sertindole, 2.19kg; risperidone, 2.10kg and ziprasidone, 0.04kg (Allison et al. 1999).

The possible metabolic concomitants of obesity, namely diabetes and hypertriglyceridemia have raised concern, and psychiatrists are now having to develop a better understanding of these conditions. Clozapine, olanzapine and possibly risperidone have been significantly associated with glucose intolerance (Hedenmalm et al. 2002; Wirshing et al. 2002) and there appears to be an increased risk of diabetes mellitus in patients receiving new generation antipsychotics (Citrome and Jaffe 2003). In a RCT conducted over 14 weeks, the effects of clozapine, olanzapine, risperidone and haloperidol on glucose and cholesterol levels were assessed. Clozapine, olanzapine and haloperidol were associated with an increase of plasma glucose, and clozapine and olanzapine were associated with an increase in cholesterol levels (Lindenmayer et al. 2003). The combined risk factors of weight gain and elevated blood glucose and triglyceride levels increases the risk for coronary artery disease. For this reason, it has been recommended that routine monitoring of glucose and lipid levels should be undertaken during treatment with new generation antipsychotics (Wirshing et al. 2002).

Hyperprolactinaemia

Prolactin secretion is controlled by complex mechanisms, of which dopamine is the principal inhibitory component (Petty 1999). Hyperprolactinemia may be a concern in the treatment of patients with schizophrenia, although correlations between prolactin elevations and clinical

symptoms have not been well-established. Elevated levels of prolactin in females cause menstrual disturbances and galactorrhoea, are associated with reduced bone density (Sauer and Howard 2002), have been linked with disturbed sexual function in terms of desire, erection and orgasm in the male and may even cause hypogonadism (Wilson 1993).

Treatment with conventional antipsychotics has a profound effect on prolactin levels, producing increases of around two to three times above normal in most patients (Green and Brown 1988). The majority of the new generation antipsychotics have much less of an effect on prolactin, although there are considerable differences between compounds. At the one end of the spectrum, clozapine and quetiapine produce minimal sustained increases in prolactin levels that are no different from placebo, while olanzapine produces a transient increase in prolactin levels (Hamner 2002). With risperidone and amisulpiride, the effect is largely dose-dependent, with higher doses causing a marked increase in prolactin levels (Peuskens 1995; Peuskens et al. 1999). (Peuskens et al. 1999) There is evidence that with risperidone, the risk of hyperprolactinaemia is even greater than that with conventional antipsychotics (Kinon et al. 2003; Yasui-Furukori et al. 2002). Risperidone has been associated with decreases in bone mineral density in premenopausal females (Becker et al. 2003), as well as high levels of sexual dysfunction (Knegtering et al. 2003).

QT interval prolongation

QTc prolongation by antipsychotic drugs has become a major concern, as it appears to be linked to an increased risk of sudden death (Zareba and Lin 2003). Among antipsychotics available in the UK, droperidol was withdrawn, sertindole was voluntarily suspended, and restricted labelling was introduced for thioridazine and pimozide. The degree of QTc prolongation is dose-dependent, and varies amongst agents (Haddad and Anderson 2002). Ziprasidone prolongs QTc to a moderate degree, though to a greater extent than quetiapine, risperidone, olanzapine and haloperidol (Taylor 2003).

Arrhythmias are more likely to occur if associated with other risk-factors, such as another drug prolonging the QTc interval, electrolyte imbalance, congenital long QT syndromes, heart failure, bradycardia, female sex, restraint, old-age, hepatic or renal impairment, and slow metaboliser status (Haddad and Anderson 2002).

CONCLUSIONS

The new generation antipsychotics discussed here are at least as effective as the conventional antipsychotics in the treatment of positive symptoms. Furthermore, there is some evidence of superiority in treatment of specific symptom domains, particularly negative symptoms (Carman et al. 1995; Moller et al. 1997b), mood symptoms (Emsley et al. 2003a; Peuskens et al. 2000; Tollefson et al. 1998; Tollefson et al. 1999) and cognitive symptoms (Green et al. 1997; Kern et al. 1998; Kern et al. 1999; Purdon et al. 2000; Purdon et al. 2001) as well as advantages in maintaining/enhancing quality of life (Hamilton et al. 1998; Revicki et al. 1999; Hamilton et al. 1998). There is also a small, but growing literature on the pharmaco-economic advantages of the new generation antipsychotics (Edgell et al. 2000; Revicki 2000). But the most marked advantage of the new generation antipsychotics is their superiority over traditional antipsychotics in terms of EPS. This is of great importance, since EPS have been shown to be the principal cause of non-adherence to medication (Hoge et al. 1990; Van Putten 1974).

Taken together, there is extensive evidence to support the use of the new generation antipsychotics (excluding clozapine) as first-line treatment agents for schizophrenia. However, it needs to be borne in mind that these agents are not free of side-effects and appropriate caution should be exercised when prescribing them. In an acute setting, IM olanzapine or ziprasidone offer ensured drug delivery. In patients with partial refractoriness, quetiapine, risperidone and olanzapine may have some efficacy advantages over conventional antipsychotics. For subjects with persistent negative symptoms, addition of low-doses of amisulpiride might be of benefit. In patients who do not respond adequately to the new generation antipsychotics, as well as severely refractory subjects, clozapine is the treatment of choice. For maintenance treatment, risperidone and olanzapine have demonstrated reduced relapse rates compared to haloperidol. Conventional depot antipsychotics were extensively used in the past. They simplified administration and improved patient compliance

considerably, and were better than their oral counterparts in reducing relapse rates in schizophrenia. They fell out of favour when the better tolerated new generation antipsychotics were introduced. The introduction of long-acting risperidone injection is likely to herald a return to the large scale use of this method of administration of antipsychotics.

Statement of Interest

Robin Emsley has participated in speakers/advisory boards and received honoraria from AstraZeneca, Bristol-Myers Squibb, Janssen, Lundbeck, Organon and Pfizer. Piet Oosthuizen has participated in speakers/advisory boards and received honoraria from AstraZeneca and Eli-Lilly.

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Table 1. Acute phase randomised controlled trials for risperidone.

Comparator	Authors	N	Duration of trial	Dose of risperidone (mg/day)	Efficacy (overall, positive and negative symptoms)
Placebo	Chouinard et al, 1993	135	8 weeks	2, 6, 10, 16	6-16 mg superior overall and positive, 6mg superior negative symptoms
Placebo	Marder & Meibach, 1994	388	8 weeks	2, 6, 10, 16	6-16 mg superior overall and positive, 6 & 16 mg superior negative symptoms
Placebo	Kane et al, 2003	400	12 weeks	25, 50, 75 mg IM 2 weekly	Superior overall, positive and negative symptoms
Haloperidol	Chouinard et al, 1993	135	8 weeks	2, 6, 10, 16	6 mg superior overall
Haloperidol	Marder & Meibach, 1994	388	8 weeks	2, 6, 10, 16	6 & 16 mg superior overall
Haloperidol	Peuskens et al, 1995	1362	8 weeks	1, 4, 8, 12, 16	Equal
Haloperidol	Huttunen et al, 1995	98	6 weeks	Mean 8	Equal
Haloperidol	Emsley et al, 1999	183	6 weeks	6	Equal
Olanzapine	Tran et al, 1997	339	28 weeks	4-12	Olanzapine superior for negative symptoms
Olanzapine	Conley & Mahmoud, 2001	377	8 weeks	2-6	Equal
Clozapine	Klieser et al, 2002	59	4 weeks	4 and 8	Equal
Amisulpride	Peuskens et al, 1999	228	8 weeks	8	Equal
Amisulpride	Sechter et al, 2002	309	6 months	4-10	Equal
Amisulpride	Hwang et al, 2003	48	6 weeks	4-8	Equal

Table 2. Acute phase randomised controlled trials for olanzapine.

Comparator	Authors	N	Duration of trial	Dose of olanzapine (mg/day)	Efficacy (overall, positive and negative symptoms)
Placebo	Beasley et al, 1996a	152	6 weeks	1 and 10	10mg superior overall, positive and negative
Placebo	Beasley et al, 1996b	335	6 weeks	5±2.5; 10±2.5 and 15±2.5	Medium & high dose superior overall and positive, low & high dose superior negative
Haloperidol	Beasley et al, 1996b	335	6 weeks	5±2.5; 10±2.5 and 15±2.5	All doses equal overall and positive, 15±2.5mg superior for negative
Haloperidol	Beasley et al, 1997	431	6 weeks	5±2.5; 10±2.5 &	Equal

				15±2.5	
Haloperidol	Tollefson et al, 1997	1996	6 weeks	5-20	Superior overall, positive and negative
Haloperidol	Ishigooka et al, 2001	182	8 weeks	5-15	Equal
Haloperidol	Lieberman et al, 2003	263	12 weeks	Mean 9.1	Superior overall and negative, equal positive
Risperidone	Tran et al, 1997	339	28 weeks	10-20	Olanzapine superior negative
Risperidone	Conley & Mahmoud, 2001	377	8 weeks	5-20	Equal
Amisulpride	Martin et al, 2002	377	8 weeks	5-20	Equal

Table 3. Acute phase randomised controlled trials for quetiapine

Comparator	Authors	N	Duration of trial	Dose of quetiapine (mg/day)	Efficacy (overall, positive and negative symptoms)
Placebo	Small et al, 1997	286	6 weeks	250 and 750	750 mg superior overall, positive and negative
Placebo	Arvanitis et al, 1997	361	6 weeks	75, 150, 300, 600 and 750	150-750mg superior overall and positive, 300mg superior negative
Haloperidol	Arvanitis et al, 1997	361	6 weeks	75, 150, 300, 600 and 750	Equal
Haloperidol	Copolov et al, 2000	448	6 weeks	Mean 455	Equal
Chlorpromazine	Peuskens & Link, 1997	201	6 weeks	Mean 407	Equal

Table 4. Acute phase randomised controlled trials for ziprasidone

Comparator	Authors	N	Duration of trial	Dose of ziprasidone (mg/day)	Efficacy (overall, positive and negative symptoms)
Placebo	Keck et al, 1998	139	4 weeks	40 and 120	120mg superior overall
Placebo	Daniel et al, 1999	302	6 weeks	80 and 120	Both doses superior overall, positive and negative
Haloperidol	Goff et al, 1998	90	4 weeks	4, 10, 40 and 160	160mg equal

Table 5. Acute phase randomised controlled trials for sertindole

Comparator	Authors	N	Duration of trial	Dose of sertindole (mg/day)	Efficacy (overall, positive and negative symptoms)
Placebo	Van Kamen et al, 1996	205	40 days	4, 8, 12, 20	20mg superior overall
Placebo	Zimbhoff et al, 1997	497	8 weeks	12, 20, 24	All doses superior overall, 20 and 24 mg superior positive, 20mg superior negative
Haloperidol	Zimbhoff et al, 1997	497	8 weeks	12, 20, 24	Equal

Table 6. Acute phase randomised controlled trials for amisulpride

Comparator	Authors	N	Duration of trial	Dose of amisulpride (mg/day)	Efficacy (overall, positive and negative symptoms)
Placebo	Paillere-Martinot et al, 1995	27	6 weeks	50 to 100	Superior for negative symptoms
Placebo	Boyer et al, 1995	104	6 weeks	100 and 300	Both doses superior for negative symptoms
Placebo	Danion et al, 1999	243	12 weeks	50 and 100	Both doses superior for negative symptoms
Haloperidol	Delcker et al, 1990	41	6 weeks		Equal
Haloperidol	Peuch et al, 1998	319	4 weeks	100, 400, 800, 1200	400 & 800mg equal
Haloperidol	Moller et al, 1997	191	6 weeks	800	Superior for negative symptoms
Haloperidol	Carriere et al, 2000	199	4 months	400-1200	Superior for negative symptoms
Haloperidol	Wetzel et al, 1998	132	6 weeks	1000	Superior for positive symptoms
Risperidone	Peuskens et al, 1999	228	8 weeks	800	Equal
Risperidone	Sechter et al, 2002	309	6 months		Equal
Risperidone	Hwang et al, 2003	48	6 weeks	400-800	Equal
Olanzapine	Martin et al, 2002	377	8 weeks	200-800	Equal

Table 7. Acute phase randomised controlled trials for aripiprazole

Comparator	Authors	N	Duration of trial	Dose of aripiprazole (mg/day)	Efficacy (overall, positive and negative symptoms)
Placebo	Kane et al, 2002	414	4 weeks	15 and 30	Both doses superior overall and positive, 30mg superior negative
Placebo	Potkin et al, 2003	404	4 weeks	20 and 30	Superior
Haloperidol	Kane et al, 2002	414	4 weeks	15 and 30	Equal
Risperidone	Potkin et al, 2003	404	4 weeks	20 and 30	Equal

Table 8. Head-to-head randomised controlled trials of atypical antipsychotics.

	Authors	N	Duration of trial	Efficacy	Tolerability
Risperidone vs. Olanzapine	Tran et al, 1997	339	28 weeks	Olanzapine superior for negative symptoms	Risperidone > EPS, hyperprolactinaemia, sexual dysfunction
Risperidone vs. Olanzapine	Conley & Mahmoud, 2001	377	8 weeks	Similar	Olanzapine > weight gain
Risperidone vs. Clozapine	Klieser et al, 2002	59	4 weeks	Similar	Risperidone better tolerated
Risperidone vs. Amisulpride	Peuskens et al, 1999	228	8 weeks	Similar	Equal EPS
Risperidone vs. Amisulpride	Sechter et al, 2002	309	6 months	Similar	Equal EPS. Risperidone > weight gain, sexual dysfunction
Risperidone vs. Amisulpride	Hwang et al, 2003	48	6 weeks	Similar	Equal EPS. Risperidone > weight gain
Olanzapine vs. Amisulpride	Martin et al, 2002	377	8 weeks	Similar	Equal EPS. Olanzapine > weight gain
Risperidone vs. aripiprazole	Potkin et al, 2003	404	4 weeks	Similar	Equal EPS. Risperidone > prolactin

3.c.vi Risperidone in the Treatment of First-Episode Psychotic Patients: A Double-Blind Multicenter Study

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Abstract

An international, multicenter, double-blind study was conducted in 183 patients with a first psychotic episode (provisional schizophreniform disorder or schizophrenia; *DSM-III-R*) treated with flexible doses of risperidone or haloperidol for 6 weeks. At endpoint, 63 percent of risperidone-treated patients and 56 percent of haloperidol-treated patients were clinically improved ($\geq 50\%$ reduction in Positive and Negative Syndrome Scale total scores). Risperidone was better tolerated than haloperidol: the severity of extrapyramidal symptoms was significantly lower in the risperidone-treated patients; significantly fewer risperidone-treated patients required antiparkinsonian medication; and significantly fewer discontinued treatment because of adverse events. A post hoc analysis revealed that low doses of these antipsychotics were efficacious in some patients. Furthermore, the severity of extrapyramidal symptoms and the use of antiparkinsonian medications were significantly lower in patients receiving low doses (maximum, ≤ 6 mg/day) than high doses (maximum, > 6 mg/day) of risperidone or haloperidol. These findings are consistent with the suggestion that patients with a first psychotic episode may require low doses of antipsychotic medications. Studies designed specifically to compare low and high doses of antipsychotics are warranted to help optimize treatment for these patients.

Risperidone is both effective and well tolerated in patients with chronic schizophrenia (Chouinard et al. 1993; Marder and Meibach 1994; Peuskens 1995). In the present randomized, controlled study we assessed the efficacy and safety of risperidone in first-episode psychotic patients.

Few prospective studies have been conducted on the effects of antipsychotic agents in first-episode patients during the initial weeks after hospital admission (Scottish Schizophrenia Research Group 1987; Lieberman et al. 1989; Chakos et al. 1992; Syzanski et al. 1996). In general, these studies indicate that neuroleptic treatment reduces the severity of positive symptoms of schizophrenia but results in a high incidence of extrapyramidal symptoms (Scottish Schizophrenia Research Group 1987; Lieberman et al. 1989; Chakos et al. 1992). Thus it was postulated that an atypical antipsychotic agent such as risperidone, with its low propensity to induce extrapyramidal symptoms at therapeutically effective doses, would be preferable to conventional neuroleptics in the management of these patients. Clinical experience with risperidone has shown that a regimen consisting of low doses (≤ 6 mg/day) and slow titration is essential to optimize patient outcome. The results of the present study support the use of risperidone in patients with a first psychotic episode and are consistent with the recommendation for low doses to optimize outcome for many patients.

Methods

This double-blind, comparative study of risperidone and haloperidol was conducted at 61 psychiatric centers in 10 countries: Australia, Belgium, Canada, France, Germany, Great Britain, Korea, The Netherlands, South Africa, and Sweden.

Patients. Patients were included in the study if they were ages 15 to 45 years; had a diagnosis of provisional schizophreniform disorder (295.40) or schizophrenia without prior treatment according to *DSM-III-R* (American Psychiatric Association 1987); had psychotic symptoms requiring treatment with an oral antipsychotic agent; had received a maximum of 3 days of emergency treatment for this disorder; had no clinically relevant neurological, electrocardiographic, or laboratory test abnormalities; and had given their informed consent (or that of relatives or guardians) to participate in the study.

Excluded from the study were pregnant or lactating women; women of reproductive age not using adequate contraception; patients with mental illness other than schizophreniform disorder or schizophrenia (according to Axis I of *DSM-III-R*); patients with psychoactive substance abuse (*DSM-III-R* criteria); patients who had received emergency antipsychotic treatment for more than 3 days before study entry or previous depot antipsychotic treatment; patients with clinically significant organic disease; and patients who had participated in clinical trials of investigational drugs within 4 weeks of entry.

Study Procedure. Patients were randomly assigned to receive risperidone or haloperidol for 6 weeks at a starting dose of 2 mg twice daily. The investigator could increase the dose in increments of 2 mg/day according to patients' needs to a maximum of 8 mg twice daily. Initially, patients could receive up to 10 mg twice daily, but this was later reduced to 8 mg twice daily. The dose could be reduced at any time because of clinical response or adverse events; the minimum dose was 2 mg once daily. Whenever possible, patients were kept in the hospital for the first 2 weeks of the study. All antiparkinsonian drugs and psychotropic agents other than the study drugs were discontinued at selection. Antiparkinsonian drugs or benzodiazepines were administered only if essential.

Treatment Efficacy. Treatment efficacy was assessed at weeks 1, 2, 4, and 6 by the Positive and Negative Syndrome Scale (PANSS; Kay et al. 1987) and the Clinical Global Impression scale (CGI; Guy 1976). The PANSS is a validated 30-item scale consisting of three subscales: the positive and negative symptom subscales of 7 items each and the general psychopathology subscale of 16 items. Each item is scored from 1, absent, to 7, extreme. The 18 items that constitute the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962) are included in the PANSS. Clinical improvement, the primary measure of treatment efficacy, was defined a priori as a 50 percent or more reduction in total PANSS scores at endpoint. The percentage of patients who had a 50 percent reduction in total PANSS-derived BPRS scores is also reported. This stringent criterion for clinical improvement was chosen because of the nature of the patient population. Patients with an acute first psychotic episode are likely to have high baseline PANSS scores and to be drug naïve; both factors could increase the likelihood of observing a clinical effect from antipsychotic drug treatment.

The CGI is a global rating of the severity of illness (rated from 1, not ill, to 7, extremely ill) and of the overall change from baseline to endpoint (rated from 1, very much improved, to 7, very much worse).

Treatment Safety. Extrapyramidal symptoms were rated according to the Extrapyramidal Symptom Rating Scale (ESRS; Chouinard et al. 1980). All adverse events that occurred during the trial (including intercurrent disease) and that were mentioned or reported by the patient either spontaneously or in response to questioning were noted and rated by the investigator. At the first and last visit, an electrocardiogram was obtained from each patient and blood samples were drawn for standard laboratory tests. Vital signs were measured weekly.

Statistical Analyses. All enrolled patients were included in the intent-to-treat (endpoint) analysis. A minimum of 77 patients per treatment group as required to detect a 25 percent difference in the primary efficacy endpoint at the 5 percent significance level (two-tailed) with 90 percent power. Analyses were performed to control for country effects. Between-group differences in PANSS total and subscale scores and PANSS-derived BPRS scores were analyzed by the Mann-Whitney *U* test. A two-way analysis of variance (ANOVA) with factors for treatment and country and their interaction was used. If the treatment by country

interaction was nonsignificant, the interaction term was omitted from the ANOVA. Nonparametric tests were applied to data not normally distributed (Mann-Whitney *U* test).

The numbers of patients showing a clinical response at endpoint were analyzed using a Cochran-Mantel-Haenszel test for general association, which controlled for differences between countries. CGI severity scores were analyzed by the Cochran-Mantel-Haenszel mean score test and CGI change scores by the Mann-Whitney *U* test. Between-treatment differences in the changes in ESRS scores from baseline to the highest scores recorded during treatment were compared using the Mann-Whitney *U* test, supplemented by the ANOVA model described above. Numbers of patients using antiparkinsonian medications were analyzed by Fisher's exact test. The frequency of other adverse events in each treatment group was compared using Fisher's exact test. A post hoc analysis was used to determine the effects of risperidone and haloperidol treatment at low (maximum, ≤ 6 mg/day) and high (maximum, > 6 mg/day) doses.

Results

One hundred eighty-three patients were recruited for the study, 1 to 43 per country with an average of 18.3 per country (table 1). Most were young white men, with a median age of 26 years (risperidone group) and 24 years (haloperidol group). Primary diagnoses at study entry were provisional schizophreniform disorder in 93 percent and schizophrenia in 7 percent. The Global Assessment of Functioning indicated severe mental illness in most patients.

The 6-week study was completed by 137 patients (79 in the risperidone group and 58 in the haloperidol group). Six patients (8%) treated with risperidone withdrew because of adverse events (sometimes in combination with other reasons) compared with 15 patients (26%) treated with haloperidol ($p = 0.02$, Fisher's exact test). More patients withdrew from the study because of adverse events or insufficient efficacy, or both, in the haloperidol group (17 patients) than in the risperidone group (9 patients; $p = 0.03$, Fisher's exact test). Other reasons for noncompletion (e.g., ineligibility, intercurrent event, lost to follow-up, good response, and treatment deviation) were reported in 11 percent of patients in each treatment group. Fifty-five patients (55%) in the risperidone group and 43 (51%) in the haloperidol group were receiving medication when they entered the study. Benzodiazepines were most common (42 in the risperidone group and 31 in the haloperidol group). Duration of trial treatment was 1 to 42 days in both groups. The mean daily dose at endpoint was 6.1 mg of risperidone (range, 2 to 16 mg) and 5.6 mg of haloperidol (range, 2 to 16 mg).

Treatment Outcome in Risperidone- and Haloperidol-Treated Patients. Patients in the risperidone and haloperidol groups had comparable PANSS and ESRS baseline scores (tables 2 and 3). At endpoint, 63 percent of the risperidone patients and 56 percent of the haloperidol patients were clinically improved according to total PANSS scores ($p = 0.19$), and 65 percent and 55 percent were improved according to total BPRS scores ($p = 0.08$) (figure 1). PANSS and BPRS total scores and PANSS subscale scores were significantly improved compared with baseline at all time points in both treatment groups ($p < 0.001$); between-treatment differences were not statistically significant (table 2).

At the start of the study most of the patients (69% of each group) had marked to severe illness. At endpoint, most patients (67% of the risperidone group; 63% of the haloperidol group; $p = 0.59$, Cochran-Mantel-Haenszel mean score test, controlling for country) were not ill or had mild symptoms. According to the CGI change scale, at endpoint 71 percent of the risperidone group and 70 percent of the haloperidol group were much or very much improved; 21 percent and 25 percent, respectively, were minimally improved or unchanged; and 8 percent and 5 percent were worse. The between-group differences were not significant ($p = 0.817$, Cochran-Mantel-Haenszel mean score test, controlling for country).

Extrapyramidal symptoms were more severe in the haloperidol group than in the risperidone group on each of the ESRS items (table 3). Significantly greater shifts from baseline to worst score with haloperidol than risperidone were seen on the hyperkinesia factor ($p < 0.01$) and total ESRS (parkinsonism + dystonia + dyskinesia) ($p < 0.05$), as well as on the parkinsonism symptoms of rigidity ($p < 0.05$), gait and posture ($p < 0.05$), tremor ($p < 0.05$), and akathisia (p

< 0.01). In addition, antiparkinsonian medications were required by significantly more haloperidol- than risperidone-treated patients (75% vs. 50%; $p < 0.001$, Cochran-Mantel-Haenszel test, controlling for country).

Other adverse events. Total adverse events were reported by significantly more haloperidol patients than risperidone patients (90% vs. 78%; $p < 0.05$, Fisher's exact test). Nonextrapyramidal side effects were reported by 59 percent of the risperidone-treated patients and 62 percent of the haloperidol-treated patients. Adverse events other than extrapyramidal symptoms included insomnia (10% of the risperidone group and 16% of the haloperidol group), headache (10% of each group), agitation (8% and 11%), and anxiety (8% of each group).

Safety measures. No clinically relevant abnormalities were observed in electrocardiograms, heart rate, blood pressure, or laboratory test results.

	Risperidone (n = 99)	Haloperidol (n = 84)
Men/women	68/31	54/30
Age (yr)		
Median	26	24
Range	15-50	16-45
Age at onset of first symptoms of psychosis (yr)		
Median	24	23
Range	15-44	2-45
Race (%)		
White	62	62
Oriental	16	17
Black	12	18
Other	10	4
Primary diagnosis (%) ¹		
Provisional schizophreniform disorder	93	94
Paranoid schizophrenia	4	5
Undifferentiated schizophrenia	2	1
Disorganized schizophrenia	1	0
Level of functioning (%) ²		
1-20	11	12
21-50	76	73
51-80	13	15

¹DSM-III-R, Axis 1.

²Global Assessment of Functioning (DSM-III-R, Axis V).

Table 2. Mean (\pm SEM) baseline PANSS and BPRS scores and change from baseline to endpoint in patients receiving risperidone (R) or haloperidol (H)

		Baseline		Endpoint	95% CI	p ³
		n ¹	Mean	Change ²		
PANSS						
Total	R	98	89.1 \pm 1.9	-30.9 \pm 2.5	-35.8 - -26.0	
	H	84	89.6 \pm 2.2	-29.3 \pm 2.7	-34.7 - -23.9	
						0.412
						0.683
Positive	R	98	23.7 \pm 0.5	-10.6 \pm 0.7	-12.0 - -9.2	
	H	84	23.8 \pm 0.6	-10.5 \pm 0.8	-12.1 - -8.9	
						0.553
Negative	R	98	21.2 \pm 0.7	-5.8 \pm 0.7	-7.3 - -4.3	
	H	84	21.2 \pm 0.9	-5.3 \pm 0.8	-7.0 - -3.7	
						0.336
GPS	R	98	44.2 \pm 1.1	-14.5 \pm 1.3	-17.2 - -11.9	
	H	84	44.7 \pm 1.3	-13.4 \pm 1.5	-16.4 - -10.5	
						0.410
BPRS						

Total	R	98	51.1 ± 1.1	-17.9 ± 1.4	-20.7 - -15.0
	H	84	51.5 ± 1.2	-16.8 ± 1.6	-20.0 - -13.6

Note. – SEM = standard error of the mean; PANSS = Positive and Negative Syndrome Scale; BPRS = Brief Psychiatric Rating Scale; CI = confidence interval; GPS = General Psychopathology Scale.

¹**Number of patients assessed; excludes patients with missing data.**

²Within-group changes in each variable were significant in both patient groups at all time points ($p < 0.001$, Wilcoxon signed-rank test).

³Analysis of variance, F test for treatment effects.

Table 3. Mean baseline ESRS scores and shifts from baseline to worst score in patients receiving risperidone (R) or haloperidol (H)¹

		Baseline		Shift from Baseline		p^2
		Mean	95% CI	Mean	95% CI	
Questionnaire	R	1.4	0.9-1.9	3.9	3.0-4.9	0.101
	H	1.5	1.0-2.0	5.1	4.0-6.1	
Hypokinesia factor ³ 0.273	R	1.4	0.8-2.1	4.5	3.5-5.6	
	H	1.3	0.8-1.8	5.4	4.2-6.5	
Hyperkinesia factor ⁴ 0.007	R	0.3	0.1-0.4	1.4	1.0-1.8	
	H	0.3	0.2-0.5	2.4	1.8-2.9	
Parkinsonism total 0.060	R	1.8	1.1-2.5	6.1	4.7-7.5	
	H	1.8	1.1-2.4	8.1	6.4-9.8	
Parkinsonism + dystonia 0.060	R	1.8	1.1-2.5	6.3	4.9-7.8	
	H	1.8	1.2-2.5	8.6	6.8-10.4	
Parkinsonism + dystonia + dyskinesia	R	1.9	1.2-2.6	6.5	5.0-7.9	0.046 H
	H	1.9	1.2-2.5	9.0	7.1-10.9	
CGI Parkinsonism severity	R	0.3	0.1-0.4	1.9	1.5-2.2	0.150
	H	0.4	0.2-0.5	2.2	1.8-2.6	

Note. – ESRS = Extrapyramidal Symptom Rating Scale; CI = confidence interval; CGI = Clinical Global Impression.

¹**ESRS clusters are included if the change from baseline to worst score ≥ 1 . Worst scores available for 94 patients in the risperidone group and 80 in the haloperidol group.**

²Mann-Whitney U test.

³Expressive autonomic movements, bradykinesia, rigidity, gait and posture, and sialorrhea.

⁴Tremor and akathisia.

Figure 1. Percentages of patients receiving risperidone or haloperidol who were clinically improved at endpoint according to a $\geq 50\%$ reduction in total Positive and Negative Syndrome Scale (PANSS) or PANSS-derived Brief Psychiatric Rating Scale (BPRS) scores

Post-Hoc Analysis – Low- and High-Dose Treatment

Treatment Outcome in Patients Receiving Low and High Doses of Risperidone.

Maximum dose data were available for 96 risperidone-treated patients ($n = 34, \leq 6$ mg/day; $n = 62, > 6$ mg/day). A post hoc analysis showed that low-dose risperidone (maximum, ≤ 6 mg/day) was efficacious in many patients and better tolerated than treatment with high-dose risperidone (maximum, > 6 mg/day). Patients receiving low and high doses of risperidone had comparable baseline PANSS and ESRS scores. Patients in both the low- and high-dose groups were clinically improved at endpoint according to total PANSS scores (74% and 59%, respectively). PANSS scores were improved in both groups at most postbaseline time points.

Shifts to worst ESRS scores were significantly greater in the high-dose than the low-dose group on the hypokinesia factor, hyperkinesia factor, total parkinsonism, total ESRS (parkinsonism + dystonia + dyskinesia), and CGI severity of parkinsonism scores ($p < 0.05$, Mann-Whitney U test) (table 4). In addition, antiparkinsonian medications were used by more patients in the high-dose risperidone group than in the low-dose group (40% and 25%, respectively; $p = 0.19$, Cochran-Mantel-Haenszel test, controlling for country). The numbers of patients requiring antiparkinsonian medication increased significantly with the dose ($p = 0.03$; Cochran-Armitage trend test).

Treatment Outcome in Patients Receiving Low and High Doses of Haloperidol.

Maximum dose data were available for 81 haloperidol-treated patients ($n = 34, \leq 6$ mg/day; $n = 47, > 6$ mg/day). Again, patients in both the low- and high-dose groups were clinically improved at endpoint according to total PANSS scores (62% and 55%, respectively). Low doses of haloperidol were better tolerated than higher doses: ESRS shifts to worst scores were greater in the high-dose group on several ESRS clusters (table 4); and antiparkinsonian medications were used by more patients in the high-dose group than in the low-dose group (53% and 46%, respectively; $p = 0.66$, Cochran-Mantel-Haenszel test, controlling for country). The numbers of patients requiring antiparkinsonian medication also increased significantly with the dose of haloperidol ($p = 0.004$; Cochran-Armitage trend test).

Table 4. Mean baseline ESRS scores and shifts from baseline to worst score in patients receiving low-dose (≤ 6 mg) or high-dose (> 6 mg) risperidone (R) and haloperidol (H)¹

	Haloperidol			Risperidone							
	Baseline	Baseline Shift from Baseline		Baseline Shift from Baseline			Dose	Mean			
		95% CI	Mean	95% CI	Mean	95% CI		p^2	Dose	Mean	
Questionnaire	≤ 6 mg 1.4-4.5	1.6	0.5-2.6	2.9	1.4-4.4	0.143	≤ 6 mg	2.1	1.1-3.1	3.0	
	6.6	5.2-8.0	> 6 mg	1.2	0.6-1.8	4.5	3.3-5.6	> 6 mg	1.1	0.6-	
Hypokinesia factor ³	≤ 6 mg 2.0	3.1	1.4-4.8	1.8	0.4-3.2	2.8	1.1-4.5	0.009	≤ 6 mg	1.2	0.4-
	1.9	7.0	5.6-8.5	> 6 mg	1.2	0.5-1.8	5.4	4.1-6.7	> 6 mg	1.2	0.5-
Hyperkinesia factor ⁴	≤ 6 mg 0.01-0.7	1.7	0.9-2.5	0.2	-0.1-0.5	0.8	0.4-1.3	0.041	< 6 mg	0.3	-
	0.6	2.9	2.1-3.6	> 6 mg	0.3	0.1-0.4	1.7	1.2-2.2	> 6 mg	0.4	0.1-
Parkinsonism total	≤ 6 mg 2.6	5.0	2.6-7.4	2.1	0.6-3.6	3.8	1.8-5.9	0.004	≤ 6 mg	1.6	0.6-
	2.7	10.4	8.3-12.6	> 6 mg	1.5	0.8-2.3	7.3	5.6-9.1	> 6 mg	1.8	0.8-
Parkinsonism + dystonia	≤ 6 mg 2.8	11.0	8.6-13.3	2.1	0.6-3.6	3.9	1.9-5.9	0.223	≤ 6 mg	1.6	0.6-2.6
				> 6 mg	1.5	0.8-2.3	7.7	5.8-9.5	> 6 mg	1.9	0.9-
Parkinsonism + dystonia+dyskinesia	≤ 6 mg 2.8	11.6	9.0-14.1	2.1	0.6-3.6	3.9	1.9-6.0	0.005	≤ 6 mg	1.7	0.7-2.7
				> 6 mg	1.7	0.9-2.4	7.8	5.9-9.8	> 6 mg	1.9	1.0-
CGI Parkinsonism severity	≤ 6 mg 0.6	1.7	1.1-2.3	0.4	0.01-0.8	1.1	0.6-1.7	0.002	≤ 6 mg	0.3	
	0.6	2.7	2.2-3.2	> 6 mg	0.2	0.03-0.4	2.3	1.8-2.7	> 6 mg	0.4	0.1-

Note. - ESRS = Extrapyrarnidal Symptom Rating Scale; CI = confidence interval; CGI = Clinical Global Impression.

¹ESRS clusters and ESRS parkinsonism items are included if the change from baseline to worst score ≥ 1 . Worst scores available for 33 patients in the low-dose risperidone group; 61 in the high-dose risperidone group; 32 in the low-dose haloperidol group; and 47 in the high-dose haloperidol group.

²Mann-Whitney *U* test.

³Expressive autonomic movements, bradykinesia, rigidity, gait and posture, and sialorrhea.

⁴Tremor and akathisia.

Discussion

It is well established that risperidone is a safe and effective antipsychotic agent in patients with chronic schizophrenia. The results of the present study show that it is also efficacious and well tolerated in patients with a first psychotic episode. The severity of psychotic symptoms (PANSS scores) was significantly reduced with risperidone treatment, and the severity of extrapyramidal symptoms (ESRS scores) was significantly lower in patients receiving risperidone than haloperidol. An important issue in the management of these patients was raised in the post hoc analysis. This analysis of patients receiving low and high doses was carried out because the trial was performed before the need for gradual titration and the optimal risperidone dose (≤ 6 mg/day) were well established. Results showed that low-dose risperidone (maximum, ≤ 6 mg/day) was efficacious in some patients and associated with significantly fewer severe extrapyramidal symptoms than high-dose risperidone (maximum, > 6 mg/day). Similar findings were observed in patients receiving haloperidol, a conventional antipsychotic that differs from risperidone in chemical structure, receptor binding profile, and clinical effects. Although illness heterogeneity likely contributed to the breakdown of patients who received low and high doses, the results show that low doses of these agents are efficacious as well as better tolerated in many patients. These data are consistent with the idea that low doses of risperidone, haloperidol, and possibly other antipsychotic agents, may be best for many first-episode patients; these patients appear to be more sensitive to the therapeutic and extrapyramidal effects of antipsychotic medications. A controlled study showed that neuroleptic threshold doses of haloperidol were as efficacious and more tolerable than higher doses in patients with schizophrenia or schizoaffective disorder (McEvoy et al. 1991). A recent open-label study of 22 patients with first-episode schizophrenia showed that low-dose (2-4 mg/day) compared with high-dose (5-8 mg/day) risperidone was associated with a superior outcome (Kopala et al. 1997). Further studies specifically designed to test this hypothesis are clearly warranted.

This dosing issue is particularly important because several studies have shown that patients experiencing a first psychotic episode are at a greater risk of extrapyramidal symptoms than patients with chronic disease. In the 5-week Scottish trial (Scottish Schizophrenia Research Group 1987) of 46 first-episode schizophrenia patients treated with conventional antipsychotic agents (pimozide or flupenthixol), 38 patients (83%) required antiparkinsonian medications; 78 percent and 85 percent of patients received pimozide and flupenthixol, respectively. In the current study, antiparkinsonian medications were used by 75 percent of haloperidol-treated patients and 50 percent of risperidone-treated patients. Lieberman et al. (1989) reported that 79 percent of 53 patients experiencing a first psychotic episode exhibited acute extrapyramidal symptoms during treatment with fluphenazine (20 mg/day). In a further study (Chakos et al. 1992) of first-episode schizophrenia, 41 (62%) of 66 patients treated with fluphenazine experienced acute extrapyramidal symptoms (parkinsonism, akathisia, and dystonia); 85 percent of these patients experienced the extrapyramidal symptoms before the end of the sixth week of treatment. In a study of 29 first-episode schizophrenia patients treated with conventional neuroleptics, Chakos et al. (1994) found that increases in caudate volume were associated with higher doses of neuroleptic and younger age at onset of illness. Keshavan et al. (1994) reported that the caudate nucleus increased in size bilaterally and substantially in treatment-naïve first-episode patients during treatment with conventional neuroleptics. These findings suggest that patients experiencing a first psychotic episode may be at high risk of extrapyramidal symptoms caused by dopamine D₂ antagonism. The results of these trials indicate that first-episode patients may be particularly sensitive to neuroleptic-induced extrapyramidal disorders.

For risperidone, the manufacturer now recommends that treatment should be initiated at 1 mg twice daily for most patients with schizophrenia (Risperdal 1996). An even lower starting dose (≤ 1 mg/day) combined with slow increases (≤ 1 mg/day at intervals of at least 1 week) may be appropriate in neuroleptic-naïve patients experiencing a first psychotic episode. The current data suggest doses of 3 mg daily or less are appropriate for most of these patients. As always, the target dose should be the lowest efficacious dose.

Nonetheless, even with the dosing regimen used in the present study, the severity of extrapyramidal symptoms was significantly lower with risperidone than with haloperidol.

Moreover, significantly fewer risperidone patients required antiparkinsonian medication, and significantly fewer discontinued treatment because of adverse events. These findings in first-episode patients are consistent with results of studies in patients with chronic schizophrenia (Chouinard et al. 1993; Marder and Meibach 1994; Peuskens 1995).

The severity of psychotic symptoms was reduced in both risperidone- and haloperidol-treated patients, and clinical improvement was observed in 63 percent and 56 percent of patients, respectively; between-group differences were not statistically significant. In the Scottish first-episode schizophrenia study (Scottish Schizophrenia Research Group 1987), the patients' mental state improved significantly (reduction in Krawiecka et al. [1977] total scores from baseline) during each week of the 5 weeks of treatment, with no significant between-group differences (23 patients received pimozide and 23 received flupenthixol). Positive symptoms also improved significantly, but no change was seen in negative symptoms. In the 53 first-episode patients studied by Lieberman et al. (1989), positive symptom ratings (Endicott and Spitzer 1978) were reduced 50 percent within the first 10 weeks of treatment with fluphenazine, but only a 10 percent reduction was seen in negative symptom scores (Andreasen 1983). In contrast, risperidone and haloperidol effectively reduced both positive and negative symptoms in our patients. The absence of between-group differences in changes in negative symptoms in the present study may have resulted from the low baseline negative symptom scores in both patient groups (table 2). Risperidone was shown to be significantly more effective than haloperidol against negative symptoms in patients with chronic schizophrenia in the North American trial (Marder and Meibach 1994) and in the meta-analysis of these data by Carman et al. (1995) and the path analysis of Möller et al. (1995).

The efficacy of risperidone in ameliorating positive and negative symptoms in patients with a first psychotic episode supports the results of Kopala et al. (1996). This study reported significant positive and negative symptom improvement with risperidone in first-episode psychotic patients: Mean changes in PANSS positive and negative subscale scores and in the positive and negative factors of the five-factor analysis were statistically significant.

Prompt and effective amelioration of psychotic symptoms is important because many acutely ill patients are in great distress from frightening and confusing ideas and perceptions. The effective control of symptoms without substantial adverse events, particularly extrapyramidal symptoms, can contribute to long-term compliance and optimal long-term outcome with these patients.

Conclusions

This is the largest study to date of first-episode psychotic patients in whom an atypical antipsychotic was assessed, and it points to some important facts relevant to the treatment of these patients. The study supports the idea that first-episode psychotic patients should receive low doses of risperidone, haloperidol, and possibly other antipsychotic agents. Both risperidone and haloperidol at maximum daily doses of 6 mg or less were efficacious in some patients and better tolerated than maximum daily doses greater than 6 mg. Also, risperidone was at least as effective as haloperidol in ameliorating psychotic symptoms in these acutely ill patients and was better tolerated. Because a patient's first experiences with a drug are crucial in determining compliance, this good tolerance for risperidone may improve the long-term outcome in patients with schizophrenia and other psychoses.

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3.c.vii A comparison of the effects of quetiapine ('Seroquel') and haloperidol in schizophrenic patients with a history of and a demonstrated, partial response to conventional antipsychotic treatment

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Quetiapine ('Seroquel') is a well-tolerated, novel, atypical antipsychotic with consistent efficacy in the treatment of schizophrenia. To date, no clinical studies have evaluated the effect of quetiapine in patients who only partially respond to conventional antipsychotics, yet this type of patient is most frequently seen by psychiatrists. Therefore, this international, multicentre, double-blind study was conducted to compare the efficacy and tolerability of 8 weeks' treatment of quetiapine 600 mg/day with haloperidol 20 mg/day in 288 patients who had a history of partial response to conventional antipsychotics and displayed a partial or no response to 1 month of fluphenazine (20 mg/day) treatment. Patients on quetiapine tended to have greater improvement than those on haloperidol in the primary efficacy measure, mean Positive and Negative Symptom Scale (PANSS) score, after 4 weeks' treatment (-9.05, -5.82, respectively, $P = 0.061$) and at study end (-11.50, -8.87, respectively, $P = 0.234$). Similarly, there was a trend towards patients on quetiapine demonstrating greater improvements in the secondary efficacy measures (Clinical Global Impression, PANSS subscale and Brief Psychiatric Rating Scale scores) [week 4 (baseline) to week 12 (end)], but the difference between treatments did not reach significance. Significantly more patients on quetiapine than on haloperidol showed a clinical response – patient response rates, defined as $\geq 20\%$ reduction in PANSS total score between weeks 4 and 12, were 52.2% for quetiapine and 38.0% for haloperidol ($P = 0.043$). Patients receiving quetiapine required less anticholinergic medication ($P \leq 0.011$), had greater reduction in extrapyramidal symptoms (EPS) ($P = 0.005$) and fewer treatment-emergent EPS-related adverse events compared to those on haloperidol ($P < 0.001$). Serum prolactin concentrations were elevated at the end of fluphenazine treatment in 73% of patients. Between weeks 4 and 12, elevated serum prolactin concentrations significantly decreased in quetiapine-treated patients compared to those receiving haloperidol ($P < 0.001$). At the end of quetiapine treatment, 83% of patients had normal prolactin levels while only 21% of patients receiving haloperidol were within the normal range. These results suggest that quetiapine may make a valuable contribution to the management of patients with a history of partial response to conventional antipsychotics.

INTRODUCTION

The majority of patients with schizophrenia are treated as outpatients. For many, treatment with conventional antipsychotics is not fully effective and they continue to display clinically significant symptoms (Goldman and Manderscheid, 1987; Katz, 1987; Rosenstein *et al.*, 1989). This population may be referred to as partial responders (Breier *et al.*, 1994) and represents the majority of schizophrenic patients that a practising psychiatrist is most likely to treat. Their treatment may be problematic since they may receive many different antipsychotic agents until a suitable therapy is found. Such patients have not been studied extensively in conventional clinical trials and the concept of partial responders is not formally well established. Results from clinical trials that have excluded such patients may not be strictly transferable to the heterogenous population seen in clinical practice.

Quetiapine ('Seroquel') is a novel, atypical antipsychotic with consistent efficacy in treating the positive and negative symptoms of schizophrenia (Borison *et al.*, 1996; Arvanitis *et al.*, 1997;

Small *et al.*, 1997) and is at least as effective as haloperidol (Arvanitis *et al.*, 1997; Copolov *et al.*, 2000) and chlorpromazine (Peuskens and Link, 1997). A recent case report has shown quetiapine (maintenance dose 400 mg/day) to be effective in a male schizophrenic patient aged ≥ 40 years who was diagnosed as being partially responsive to neuroleptic treatment, despite good compliance (Chincilla *et al.*, 1997). The incidence of extrapyramidal symptoms (EPS) observed with quetiapine across the full dosage range is not significantly different from placebo (Arvanitis *et al.*, 1997), and the drug does not cause sustained elevation of plasma prolactin levels (Arvanitis *et al.*, 1997), unlike many conventional antipsychotics and some newer agents.

To date, no clinical trials have evaluated the effects of quetiapine in a specific population of schizophrenic patients who are partial responders to conventional antipsychotics. The aim of this international, multicentre, double-blind study was to compare the efficacy and tolerability of 8 weeks' treatment with quetiapine 600 mg/day or haloperidol 20 mg/day in patients who had a history of partial response to conventional antipsychotics.

METHODS

Patients

Before entry into the randomization phase of the study, all patients received fluphenazine for 4 weeks. Key criteria for inclusion into the fluphenazine run-in phase of the trial were: male or female aged 18 years or over; schizophrenia according to the DSM-IV diagnostic criteria (American Psychiatric Association, 1994) for either catatonic, disorganized, paranoid or undifferentiated type: persistent positive symptoms while previously taking therapeutic doses of antipsychotic treatment; a total score of at least 15 on the positive scale of the Positive and Negative Symptom Scale (PANSS) (Kay *et al.*, 1987), with a score of at least 4 (moderate) for one or more of the following items: delusions, conceptual disorganization, hallucinatory behaviour and suspiciousness / persecution; and a score of at least 3 (mildly ill) on the Clinical Global Impression (CGI) (Guy and Bonato, 1970) Severity of Illness item. All patients gave their written informed consent and were required to withdraw from psychotropic medication before entry to the fluphenazine run-in phase, with the exception of long-term use of benzodiazepine treatment.

Key exclusion criteria were patients known to be resistant to standard antipsychotic medication; those known to be clozapine non-responders; those who had experienced acute exacerbation of schizophrenia within the previous 3 months, and those who had known sensitivity to drugs evaluated in this trial or a history of idiopathic or drug-induced agranulocytosis.

Patients were eligible for randomization to either quetiapine or haloperidol treatment if they had a history of unsuccessful therapy for schizophrenia and had shown either a partial response or no response to 1 month of treatment with the conventional antipsychotic, fluphenazine. Because these patients were considered to be difficult to treat, the quetiapine and haloperidol dosages were towards the upper end of their recommended dosage ranges, namely 600 mg/day and 20 mg/day, respectively.

Study design and treatments

The study was an international, multicentre, double-blind, randomized trial where medications were administered according to a twice-daily regimen (Fig. 1). After undergoing a pre-trial screen, eligible patients entered a 4-week active run-in phase of open treatment with fluphenazine, the dosage of which was escalated from 5-15 mg/day during the first week and maintained at 20 mg/day for the next 3 weeks. At the end of the fluphenazine run-in phase (week 4), patients were evaluated for their response to the drug. Those patients not responding (defined as no change from week 1 to week 4 in PANSS total score or an increase at week 4) or considered to have a partial response to fluphenazine (defined as a reduction

from week 1 to week 4 in PANSS total score of < 30% and a PANSS positive score of ≥ 15) were eligible to enter the randomization phase of the trial. These patients were randomized to receive either quetiapine or haloperidol twice daily, dosages of which were titrated over a 7-day period during week 5 up to 600 mg/day and 20 mg/day, respectively. During the next 7 weeks (weeks 6-12), dosages of quetiapine and haloperidol were fixed at 600 mg/day and 20 mg/day, respectively. Use of benzodiazepines or anticholinergics was permitted to treat any cases of acute agitation, severe insomnia, EPS or akathisia that emerged during the trial, and the continuation of long-term treatment with benzodiazepines was allowed. Other concomitant medication was allowed at the discretion of the investigator.

Evaluation of efficacy

The severity of schizophrenic symptomatology during the trial was measured using the PANSS (1-7 scoring scale) and the CGI Severity of Illness score at weeks 1, 4, 8 and 12. The primary efficacy endpoint was the change in PANSS total score from week 4 (baseline) to week 8 and week 12. Secondary efficacy endpoints were change in score or response to treatment between week 4 (baseline) and week 12 measured by the PANSS subscale (positive, negative and general psychopathology); derived Brief Psychiatric Rating Scale (BPRS; total, positive subscale and mood cluster) (Overall and Gorham, 1962); and CGI Severity of Illness. The CGI Global Improvement score was analysed at week 12. Response to treatment was measured according to three criteria: (A) those patients who had a decrease in PANSS total score of $\geq 20\%$ from week 4 to week 12; (B) those who had CGI Severity of Illness score ≤ 3 at week 12; and (C) those who fulfilled both of these criteria. The criterion for a response to treatment being defined as a decrease in PANSS total score of $\geq 20\%$ was based on current literature of trials involving refractory patients (Bondolfi *et al.*, 1998; Conley *et al.*, 1998., Flynn *et al.*, 1998; Kane *et al.*, 1988; Conley *et al.*, 1999).

Evaluation of safety and tolerability

Drug safety and tolerability were secondary endpoints in this trial. These were evaluated by monitoring: the proportion of patients receiving anticholinergic medication between weeks 4 and 12; the proportion of patients experiencing adverse events related to EPS between weeks 4 and 12; the proportion of patients experiencing worsening EPS between weeks 4 and 12; indicated by an increase in the Simpson Scale score (Simpson and Angus, 1970) which included an item for akathisia; the proportion of patients developing clinically significant EPS between weeks 4 and 12 (defined by an increase in Simpson Scale score, which also included an item for akathisia to ≥ 14 at some point between weeks 4 and 12; and absolute change in serum prolactin from week 4 to week 12. Adverse events were recorded throughout the trial. Adverse events related to EPS were defined as: hypertonia, neck rigidity, cogwheel rigidity, tremor, hypokinesia, akinesia, extrapyramidal syndrome, akathisia, dystonia, oculogyric crisis and torticollis. Haematological tests and clinical chemistry were monitored pre-trial and at weeks 4, 8 and 12. Vital signs were recorded at the pre-trial screen and at weeks 4 and 12.

Statistical analysis

The size of the trial population was calculated based on that required to show a clinically meaningful difference in efficacy between quetiapine and haloperidol at the 5% significance level and with 90% power. All statistical tests were two-sided.

Efficacy

The main analysis was a last-value-carried forward (LVCF) analysis conducted on the intent-to-treat population (ITT), which consisted of all randomized patients who received quetiapine or haloperidol treatment and provided efficacy data for at least one visit after randomization. Two additional analyses were conducted to examine the statistical robustness of the main analysis. These analyses were conducted on the ITT population without LVCF, i.e. observed-cases analysis, and LVCF analysis on a per-protocol (PP) population, where data were excluded from patients who violated / deviated from the protocol in such a way as to affect the analysis. The changes in PANSS total score (primary endpoint) from week 4 (baseline) to weeks 8 and 12 were analysed using analysis of covariance; this model included baseline score, treatment, centre and centre-by-treatment interaction as factors. Differences between treatments were measured and presented with associated *P*-values and confidence intervals. Statistical analysis of the changes in secondary endpoint measures (PANSS subscale scores, derived BPRS scores and CGI scores) from week 4 to week 12 was performed as for the primary endpoint. The response to treatment at week 12 was analysed using logistic regression; this model included treatment, centre and centre-by-treatment interaction as factors.

Safety and tolerability

Assessment of the secondary safety and tolerability endpoints was conducted on the ITT population using logistic regression analysis; this model included treatment, centre and centre-by-treatment as factors. As for the efficacy endpoints, LVCF analysis was conducted on the endpoints which measured the proportion of patients receiving anticholinergic medication during weeks 4–12; the proportion of patients experiencing adverse events related to EPS during weeks 4–12; the proportion of patients experiencing a worsening of EPS during weeks 4–12; the proportion of patients developing clinically significant EPS during weeks 4–12; and change in serum prolactin levels. The model included treatment, centre and centre-by-treatment interaction as factors. Estimates of time to taking anticholinergic medication were evaluated using Kaplan-Meier survival curves. No formal statistical analyses were performed on non-EPS adverse events, haematology, clinical chemistry or vital signs test results.

Table 1. Patient demographics

characteristic	Demographic	
	Quetiapine	Haloperidol
Number of patients exposed	143	145
Age (years)		
Mean (SD)		37.7 (10.8)
Range		18-75
Sex: number (%) of patients		
Male		102 (71.3)
Female	41 (28.7)	44 (30.3)
Race: number (%) of patients		
Caucasian		113 (79.0)
Afro-Caribbean	10 (7.0)	4 (2.6)
Hispanic		9 (6.3)
Asian		3 (2.1)
Oriental	2 (1.4)	2 (1.4)
Mixed		2 (1.4)
Other		4 (2.8)

RESULTS

Patient population

A total of 365 patients with a history of partial response to conventional antipsychotic treatment were recruited into the fluphenazine run-in phase of the trial. The mean (\pm SD) rating scale scores at trial entry for those subsequently randomized to quetiapine and haloperidol were PANSS total 91.1 (\pm 7.9), 93.2 (\pm 21.4); PANSS Positive Subscale 23.0 (\pm 4.5), 24.1 (\pm 5.7); and CGI Severity of Illness 3.7 (\pm 1.3), 3.9 (\pm 1.2), respectively. Two hundred and eighty-eight patients were randomized to treatment with either quetiapine (n = 143) or haloperidol (n = 145). Seventy-seven patients were not randomized due to: condition deterioration (n = 9); lost to follow-up (n = 4); adverse events (n = 14); protocol non-compliance (n = 10); informed consent withdrawn (n = 16); other reasons (n = 24). Ninety-five (quetiapine n = 54; haloperidol n = 41) of the 288 patients randomized did not respond to fluphenazine. Of these 288 patients, seven were excluded from the randomized population as they did not have post-baseline efficacy assessments and hence the ITT population (n = 281) comprised 140 patients on quetiapine and 141 patients on haloperidol. A per protocol population (n = 262) defined as those patients who had not violated / deviated from the protocol in such a way as to affect the analysis comprised 127 patients on quetiapine and 135 patients on haloperidol. All randomized patients were included in the safety population.

The quetiapine and haloperidol groups were well-matched demographically (Table 1). The majority of patients in the quetiapine and haloperidol groups had paranoid schizophrenia (73% versus 76%, respectively) and were moderately to markedly ill (mean baseline CGI Severity of Illness score of 4.4 and 4.5, respectively; Table 2).

Table 2. Baseline scores (week 4) and changes in rating scale scores from baseline to week 12 in patients receiving either quetiapine 600 mg/day or haloperidol 20 mg/day for 8 weeks who were partially responsive to conventional antipsychotic treatment

	baseline ^b	Quetiapine			Haloperidol	
		Baseline Difference (SE)	Difference between treatments		Baseline	Change from
			Change 95% CI	P-value		
			from baseline ^a			
PANSS total score	88.2	-11.50			88.1	-
8.87	-2.64 (2.21)	-6.99, 1.72	0.234			(n =
141)						
PANSS subscale score						
Positive Scale	21.7	-3.43			22.1	-2.85
	-0.58 (0.74)	-2.05, 0.88	0.433			(n =
140)						
Negative Scale	24.0	-3.00			23.3	-2.39
	-0.61 (0.60)	-1.80, 0.57	0.309			(n =
140)						
GP Scale	42.5	-4.93			42.8	-
3.72	-1.21 (1.09)	-3.36, 0.94	0.267			(n =
141)						
Derived BPRS scores						
Total	49.4	-6.95			49.2	-
4.78	-2.16 (1.33)	-4.79, 0.46	0.105			(n =
141)						
Positive Subscale	12.0	-2.19			12.2	-
1.61	-0.58 (0.38)	-1.33, 0.18	0.136			(n =
141)						
Mood cluster	9.9	-1.21			10.0	-
0.68	-0.53 (0.39)	-1.29, 0.23	0.173			(n =
141)						
CGI item scores						
Severity of illness	4.4	-0.53			4.5	-
0.38	-0.15 (0.12)	-0.39, 0.09	0.221			(n =
141)						
Global Improvement ^b	-	2.86			-	2.97
	-0.11 (0.16)	-0.42, 0.20	0.471			(n =
121)						

^aLeast squares mean, a negative mean change indicates an improvement from baseline

^bThe values at week 12 are presented: a low Clinical Global Improvement value indicates a greater improvement.

Efficacy

Primary endpoint

The results of the main analysis (LVCF on ITT population) showed that quetiapine and haloperidol were associated with marked mean reductions in PANSS total scores over time (Fig. 2). The difference in the reduction in PANSS total score after 4 weeks' treatment was greater with quetiapine (week 8) compared to haloperidol and approached statistical significance ($P = 0.061$). Similarly, the magnitude of reduction in PANSS total score at week 12 was greater for quetiapine than haloperidol but the difference between the two treatments was not statistically significant ($P = 0.234$). The results of the additional analyses (observed cases on ITT and LVCF on PP populations) were consistent with the results of the main analysis.

Secondary endpoints

In the main analysis (LVCF on ITT population), response rates to treatment, defined as the proportion of patients experiencing a decrease in PANSS total score of $\geq 20\%$ from weeks 4-12 (A), were higher in the quetiapine group than in the haloperidol group and reached statistical significance in favour of quetiapine at endpoint ($P = 0.043$) (Fig. 3). The two other definitions of response to treatment were the proportion of patients demonstrating a CGI Severity of Illness score ≤ 3 at week 12 (B) and the proportion of patients who fulfilled both these definitions (i.e. A and B) of treatment response (C). A higher proportion of patients on quetiapine demonstrated a CGI Severity of Illness score ≤ 3 at week 12 (B) compared to those on haloperidol (46% and 35%, respectively), but this difference was not significant ($P = 0.09$). The proportion of patients who fulfilled both these definitions of treatment response (C) was greater in the quetiapine group than the haloperidol group (36% and 24%, respectively), but the difference between treatments only approached significance ($P = 0.08$). The results of the additional analysis (LVCF on PP population) were significant, in favour of quetiapine for all three definitions of response to treatment (A, $P = 0.02$; B, $P = 0.03$; C, $P = 0.02$).

The results of the main analysis (LVCF on ITT population) showed that both treatments were associated with improvements in score from week 4 to week 12 for the PANSS subscale scores, derived BPRS scores and CGI item scores (Table 2). Quetiapine was associated with a greater improvement than haloperidol for the majority of these rating scale scores, but none of the differences reached statistical significance (Table 2). The results of the additional analyses (observed cases on ITT and LVCF on PP populations) were consistent with the results of the main analysis of these endpoints.

Safety and tolerability

The mean (range) durations of exposure to quetiapine and haloperidol were 49 (2-97) days and 50 (4-68) days, respectively. The result of the main analysis (ITT) showed that, despite no washout period being allowed between the fluphenazine run-in and randomization, the proportion of patients who received anticholinergic medication between weeks 4 and 12 was significantly lower in the quetiapine group than the haloperidol group (44% and 60%, respectively; $P = 0.011$). Of the 62 patients receiving quetiapine who required anticholinergic medication, only 5% (3 / 62) were given anticholinergics after week 4 (i.e. after the fluphenazine run-in phase), compared to 20% (17 / 84) of the 84 haloperidol patients during the same period of time. The Kaplan-Meier survival estimate (ITT population) for time to treatment with anticholinergic medication was higher for the quetiapine group (0.555) compared to that for the haloperidol group (0.394), showing that patients on quetiapine had less risk of using anticholinergic medication than those patients on haloperidol (Fig. 4). Similarly, the proportion of patients on quetiapine who required the use of anticholinergic medication decreased from week 4 to week 12 (41% versus 32%, respectively) whereas, during the same period, the proportion of patients in the haloperidol group using anticholinergic medication increased (47% versus 53%, respectively).

Evaluation of the ITT population showed that treatment with quetiapine between weeks 4 and 12 was associated with a reduced risk of developing EPS-related adverse events ($P < 0.001$) compared to haloperidol (14% versus 31%, respectively) (Fig. 5). Similarly, the proportion of patients with an increase in the Simpson Scale score from week 4 to any time up to week 12 was significantly greater in the haloperidol-treated group compared to the quetiapine group (39% versus 24%, respectively, $P = 0.005$) (Fig. 5). Furthermore, the proportion of patients whose Simpson Scale score increased to ≥ 14 from week 4 onwards was significantly greater in the haloperidol group than in the quetiapine group (28% versus 14%, $P = 0.002$) (Fig. 5).

Serum prolactin concentrations were elevated at the end of fluphenazine treatment in 73% of patients. Elevated baseline serum prolactin concentrations were significantly decreased in patients receiving quetiapine treatment compared to those receiving haloperidol (least squares mean change -601.39 mU/l and -20.54 mU/l, respectively; $P < 0.001$). At the end of quetiapine treatment, 83% (88 / 106) of patients had normal prolactin levels while only 21% (24 / 113) of patients receiving haloperidol were within the normal range (Fig. 6).

The number of patients withdrawing during the randomized phase of the trial was similar in the quetiapine ($n = 32$, 22.4%) and haloperidol ($n = 28$, 19.3%) treatment arms (Table 3). The study design allowed patients to 'withdraw their consent' at any time during the study; the proportion of patients 'withdrawing their consent' was higher in the haloperidol group (7.6%) than the quetiapine group (1.4%). The proportion of patients who withdrew because of adverse events was 8.4% in the quetiapine group compared to 3.4% in the haloperidol group. This was unexpected as quetiapine was statistically significantly superior to haloperidol for all EPS and prolactin measures.

Overall, treatment-emergent adverse events were reported in approximately half of the patients in both the quetiapine and haloperidol groups (53% and 56%, respectively). The most frequently reported adverse events in the quetiapine group were somnolence (9.8% of patients), postural hypotension / dizziness (7.7%), dry mouth (5.6%), hypertonia (5.6%) and akathisia (5.6%), the majority of which are related to the known pharmacology of the drug. In contrast, the most common adverse events experienced with haloperidol were, in general, related to EPS: tremor (11.7% of patients), akathisia (9.0%), hypertonia (6.9%), EPS syndrome (6.2%) and insomnia (6.2%).

There were no clinically important changes in clinical laboratory data, and neither treatment was associated with any clinically relevant changes in vital signs. Small increases in body weight from weeks 4-12 (or withdrawal from the trial) occurred in both treatment groups; the mean increase was 1.4 kg in the quetiapine group and 0.7 kg in the haloperidol group.

Table 3. Reasons for withdrawal from the study

Reason for withdrawal	Number (%) of patients	
	Quetiapine ($n = 143$)	Haloperidol ($n = 145$)
Death	0	0
Adverse event	12 (8.4)	5 ^a (3.4)
Non-compliance with protocol	2 (1.4)	3 (2.1)
Deterioration of condition	11 (7.7)	8 (5.5)
Informed consent withdrawn	2 (1.4)	11 ^b (7.6)
Patient lost to follow-up	3 (2.1)	0
Other	2 (1.4)	1 (0.7)
Total	32 (22.4)	28 (19.3)

^aIncludes two patients with adverse events (onset during the fluphenazine run-in phase) which led to withdrawal after randomization.

^bSee text for discussion of withdrawal of consent due to possibility of adverse events.

DISCUSSION

The results indicate that quetiapine is at least as effective as haloperidol in the treatment of schizophrenia patients with a history of, and also demonstrating as part of the clinical trial, a partial response to conventional antipsychotic treatment. For almost all of the primary and secondary efficacy endpoints, the effectiveness of quetiapine was greater than that of haloperidol, although the differences for most endpoints were not statistically significant. The decreases in PANSS total score reported here for both treatments were less than those seen elsewhere (e.g. Copolov *et al.*, 2000). These relatively small reductions in PANSS total score are not unexpected as this cohort showed previous partial responsiveness and had received 4 weeks fluphenazine treatment immediately prior to randomization. However, the proportion of patients responding to treatment was always greater in the quetiapine group than in the haloperidol group for all three definitions of response to treatment. The results of the main analysis, LVCF analysis on the ITT population, showed that the proportion of patients having a decrease of $\geq 20\%$ in PANSS total score between weeks 4 and 12 was significantly greater in the quetiapine group than the haloperidol group. For the secondary analysis, LVCF on the PP population, quetiapine was statistically superior and was associated with a higher proportion of patients responding than haloperidol for all three definitions of response.

As this patient population is likely to reflect the patients that practising psychiatrists are most likely to treat, it is possible that quetiapine may be clinically beneficial to more patients than haloperidol, especially in view of the EPS and prolactin tolerability advantages. The results from previous clinical trial populations for antipsychotic drugs may not be relevant to clinical practice and the population used in this study probably more accurately reflects real-life practice. Indeed, poor clinical improvement is observed in between 15% and 25% of patients with schizophrenia treated with antipsychotic agents (Conley and Buchanan, 1997). In clinical practice, a spectrum of patients exists, ranging from those who respond completely to treatment to those who show a partial response, and extending to those who could be classified as resistant to treatment. There are studies which show other atypical antipsychotic agents to be efficacious in the treatment of patients who are resistant or intolerant to conventional agents (Tollefson *et al.*, 1997; Bondolfi *et al.*, 1998; Flynn *et al.*, 1998; Breier and Hamilton, 1999); however, to date there have been no studies including patients who had a partial response to treatment.

When reviewing the safety results of this trial, the lack of a fluphenazine washout period in the design of this study is important to consider, as this may have artificially inflated the incidence and worsening of EPS-related adverse effects and also would have caused baseline serum prolactin levels to be elevated. Despite this limitation, these data are consistent with other reports (Arvanitis *et al.*, 1997; Copolov *et al.*, 2000) and show that quetiapine has a superior safety and tolerability profile in these respects compared to that of haloperidol, and this was particularly evident regarding motor system disturbance. The difference between treatments in a number of key measures assessing this were all statistically significant in favour of quetiapine: fewer patients receiving quetiapine required anticholinergic medication, patients receiving quetiapine had fewer EPS-related adverse events, fewer had development or worsening of EPS (increase in Simpson Scale score), and fewer had development of clinically significant EPS (increase in Simpson Scale score from week 4 and ≥ 14 at any time up to week 12).

Compared to previous controlled studies evaluating anticholinergic use during treatment with quetiapine $\leq 12\%$ versus 14% placebo, (Arvanitis *et al.*, 1997) and $\leq 12-13\%$ versus 48-49% haloperidol; (Arvanitis *et al.*, 1997; Copolov *et al.*, 2000), the use of anticholinergic medication in quetiapine patients in this study was relatively high (44%). This is very likely to be artificially high as the study did not permit a fluphenazine washout between the run-in and randomization phases. As a result, approximately 45% of patients were receiving anticholinergic medication at randomization. However, despite no washout of fluphenazine, significantly fewer patients on quetiapine required use of anticholinergic medication than

those on haloperidol ($P = 0.011$) and, of the 62 patients receiving quetiapine who required anticholinergic medication, only three (5%) were given anticholinergic therapy after week 4. Furthermore, it is also important to consider that the use of anticholinergic medication from week 4-12 reduced in patients on quetiapine (from 41% to 32%) whereas, in contrast, it increased in patients on haloperidol (from 47% to 53%). The observations from this study that quetiapine is associated with reduced onset and worsening of treatment-related EPS, compared to haloperidol, reinforces the conclusions of other reports, which have shown that the incidence of EPS with quetiapine across the full clinical dosage range of 150-750 mg/day is not significantly different from placebo (Arvanitis *et al.*, 1997; Meats, 1997) and is significantly less than haloperidol (Arvanitis *et al.*, 1997; Copolov *et al.*, 2000).

It is recognized that conventional antipsychotic-induced hyperprolactinaemia may lead to unwelcome side-effects, such as sexual dysfunction (Sullivan and Lukoff, 1990; Ghadirian *et al.*, 1992), amenorrhoea and galactorrhoea. Quetiapine does not cause a sustained elevation in plasma prolactin concentration (Saller and Salama, 1993; Hamner *et al.*, 1998). Over the 8-week treatment period of this study, the elevated serum prolactin levels observed at baseline after fluphenazine treatment were dramatically reduced in patients treated with quetiapine, whereas no change was evident in the haloperidol group. The difference between treatments was highly significant.

During the course of the study, minimal increases in weight were observed in patients in both treatment groups. It is difficult to assess the nature of such small changes in weight over a short-term study. However, long-term treatment with quetiapine has been shown to have only minimal effects on weight (Rak *et al.*, 2000), confirming that little further weight increase was observed after the first 5-6 weeks of treatment.

In summary, both quetiapine and haloperidol were associated with marked improvements in patients demonstrating partial responsiveness to standard antipsychotic treatment. However, the magnitude of improvement was always greater in the quetiapine group than in the haloperidol group and a greater proportion of patients on quetiapine responded to treatment compared to those on haloperidol. Furthermore, in contrast to haloperidol, quetiapine lessened the EPS burden and facilitated normalization of previously elevated prolactin levels. These encouraging results indicate that quetiapine may make a valuable contribution to the management of patients who have a history of partial response to conventional antipsychotics.

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3.c.ix Effects of Quetiapine and Haloperidol on Body Mass Index and Glycaemic Control: a Long-Term, Randomised, Controlled Trial

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1. Abstract

The topic of antipsychotic-induced weight-gain and its relationship to glucose metabolism is understudied. We evaluated the long-term effects of a new generation antipsychotic, quetiapine and a conventional antipsychotic, haloperidol on body mass index (BMI) and glycaemic control in patients with schizophrenia previously treated with conventional antipsychotics. Forty-five clinically stable patients with schizophrenia participated in this randomised, investigator-blinded, parallel-group comparison of flexible doses of quetiapine and haloperidol treatment over 52 weeks. Primary outcome measures were change from baseline in BMI and glycosylated haemoglobin (HBA1c) levels. There were no between-group differences at any of the time points for BMI ($F=1.90$, $p=0.1$) and HBA1c ($F=1.17$, $p=0.3$) values, and there were no significant changes in BMI from baseline for either group. HBA1c levels decreased significantly at endpoint for the haloperidol group (-1.5% ; $p=0.04$), but not for the quetiapine group (-0.3% ; $p=0.5$).

Although the sample was not generally obese (mean baseline BMI 25.5 ± 6.3 Kg/m²), a large proportion exhibited evidence of abnormal glycaemic control prior to randomisation (mean HBA1c $6.7\pm 1.9\%$), with 48% having values that were at least mildly elevated (HBA1c $>6.1\%$) and 19% markedly elevated (HBA1c $>7\%$). The number of subjects with elevated HBA1c values decreased from baseline in both the haloperidol and quetiapine treatment groups. These findings suggest that switching treatment from a conventional antipsychotic to quetiapine is not associated with weight-gain or worsening of glycaemic control, even in the long-term. The study also highlights the high incidence of unrecognised glucose dysregulation in patients with schizophrenia receiving conventional antipsychotic treatment.

Introduction

Excessive body weight gain is a common side effect of some typical and atypical antipsychotic drugs. The relative risk of weight gain varies amongst antipsychotics, but particularly the low-potency phenothiazines and some of the new generation antipsychotics are associated with greater risk (Allison et al. 1999; Baptista et al. 2002). Weight gain is highly distressing to patients, and may reduce treatment adherence (Allison and Casey 2001; McIntyre et al. 2001; Weiden et al. 2004). It is also related to poorer quality of life and decreased well-being and vitality (Allison et al. 2003). Of greatest concern however, is the risk of progression to obesity-related medical conditions such as type 2 diabetes and cardiovascular disease (Tardieu et al. 2003).

The so-called metabolic syndrome, characterized by excessive visceral fat, impaired glucose tolerance, dyslipidaemia, and hypertension occurs with increased frequency in patients with schizophrenia. This is the case even before antipsychotic treatment is administered. The reasons for this are not clear, although factors such as life style, poor diet and lack of exercise

may play a role (Ryan and Thakore 2002). A recent study clearly demonstrated that first-episode, drug-naive patients with schizophrenia have impaired fasting glucose tolerance, are more insulin resistant and have higher levels of plasma glucose, insulin, and cortisol than healthy comparison subjects (Ryan et al. 2003b),

The use of antipsychotic medication further increases the likelihood of developing weight gain and disorders of glucose metabolism. The risk is greatest with some of the new generation antipsychotics, particularly clozapine and olanzapine (Lindenmayer et al. 2003d). A recently reported consensus statement warns that treatment with new-generation antipsychotics can cause a rapid increase in body weight that may not reach a plateau even after 1 year of treatment (American Diabetes Association et al. 2004). Hyperglycaemia, exacerbation of existing diabetes, treatment-emergent type 2 diabetes and even diabetic ketoacidosis have been associated with clozapine and olanzapine, and some of the other new generation antipsychotics (Newcomer et al. 2002c). The risk of hyperglycemia does not appear to be dose dependent, it is reversible on cessation of treatment, and reappears on reintroduction of these agents (Lindenmayer et al. 2001). Also, hyperglycaemia cannot be explained purely on the basis of antipsychotic-induced weight-gain (Newcomer et al. 2002b).

The topic of antipsychotic-induced weight gain and its relationship to glucose metabolism is understudied, and there are few well-controlled trials in the literature. The purpose of our study was to compare the long-term effects of a new generation antipsychotic, quetiapine and a conventional antipsychotic, haloperidol on body weight and glycaemic control in patients with schizophrenia. While weight gain and glucose intolerance appear to be more common with olanzapine and clozapine, the risk in patients taking quetiapine is less clear (American Diabetes Association et al. 2004). There is little published information on the effect of quetiapine on weight and glucose metabolism, and results have been conflicting. The Canadian National Outcomes Measurement Study in Schizophrenia reported that weight gain (i.e. > 7% of baseline weight) was observed in 55.6% of patients treated with quetiapine, compared with 24.1% of olanzapine and 23.7% of risperidone-treated patients (McIntyre et al. 2003). This contrasts with a cross-sectional study in outpatients receiving risperidone, olanzapine, quetiapine or haloperidol for at least 4 weeks, where the proportion of patients with clinically relevant ($\geq 7\%$) weight gain was highest with olanzapine (45.7%) followed by risperidone (30.6%) and haloperidol (22.4%). Five quetiapine treated patients (13.5%) had some degree of weight gain, although this was not clinically relevant. However, data for quetiapine were not conclusive because of the short duration of treatment (Bobes et al. 2003b). In a long-term, open label extension trial in 10 adolescents, quetiapine treatment was associated with a non-significant increase in mean weight and body mass index after 64 weeks (McConville et al. 2003). Haloperidol has not generally been associated with excessive weight gain, although it may have a direct effect on glucose metabolism (Lindenmayer et al. 2003c).

Method

Participants

The sample comprised in- and out-patients aged 18 - 65 years with a diagnosis of schizophrenia or schizo-affective disorder according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) (American Psychiatric Association 1994), whose psychiatric condition was judged to be clinically stable. All participants had received a stable dose of antipsychotic medication for at least 30 days before entry. They also had tardive dyskinesia, as this formed an additional part of the study (Emsley et al. 2004). Exclusion criteria included another Axis I DSM-IV diagnosis, significant or unstable general medical condition, and patients currently receiving clozapine. The University of Stellenbosch Ethics Committee approved the study protocol, patient information and consent procedures. All of the subjects provided written, informed consent to participate. The study adhered to International Conference on Harmonisation Guidelines for Good Clinical Practice (International Conference on Harmonization 1996).

Study design

This was a randomised, investigator-blinded, parallel-group comparison of flexible doses of quetiapine and haloperidol. After an initial screening visit, subjects were tapered from all psychotropic medication over a 2 week period (although a shorter time was allowed if there was concern regarding the clinical status of the patient during this period). They were then randomised to receive either quetiapine or haloperidol for a 52-week treatment period. The dose of medication was titrated over seven days to the starting dose (haloperidol 10 mg/day, quetiapine 400 mg/day). Thereafter, flexible dose adjustment was allowed at the discretion of the investigator, up to a maximum dose of haloperidol 20mg/day and quetiapine 800mg/day. Haloperidol was adjusted in 2.5mg increments and quetiapine in 100mg increments. Medication compliance was assessed by 'pill counts' at each visit. Concomitant benzodiazepines were allowed for agitation or insomnia, and anticholinergic agents for extrapyramidal symptoms.

Assessments

Subjects were weighed, and blood samples were collected for glycosylated haemoglobin (HbA1c) and serum prolactin measurement at the screening visit (week 0) and at weeks 10, 22, 34, 46 and 54. A minor haemoglobin component of human red blood cell haemolysate, HbA1c is a product of the non-enzymatic reaction of glucose with the alpha-amino groups of the valine residues at the N-terminus of the beta-chains of human haemoglobin. Expressed as a percentage of total haemoglobin in whole blood, HbA1c measures average glycaemic control in individuals during the preceding 6-8 weeks (Dhatt et al. 2003). It is a highly specific and convenient alternative to fasting plasma glucose for diabetes screening (Rohlfing et al. 2000). HbA1c assays were performed on a Beckman Coulter CX-S synchron analyser. Values of $\geq 6.1\%$ are regarded as mildly abnormal and $\geq 7\%$ as severely abnormal (Davidson et al. 1999). Height was measured at the screening visit. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of height in meters. BMI is widely accepted as the 'gold standard' for determining whether a patient is underweight or overweight, and is strongly predictive of changes in glucose regulation (Resnick et al. 1998).

Clinical assessments were conducted at two-weekly intervals for the first 6 weeks, and thereafter 4 weekly, until the completion of the trial (52 weeks of active treatment). Patients were assessed by means of the Positive and Negative Syndrome Rating Scale (PANSS) (Kay et al. 1987) and Extrapyramidal Symptom Rating Scale (ESRS) (Chouinard et al. 1980).

Data analyses

The main analysis was conducted on observed cases (OC). We also performed an analysis on the intent to treat (ITT) population, using the method of last observation carried forward (LOCF) to deal with missing values due to dropouts. The *a priori* primary outcome measures were change in BMI and change in HbA1c from baseline to endpoint. Treatment groups were compared at each time point using Student's t test. Repeated measures analysis of variance (RANOVA) was performed including all of the assessment points, and because of considerable variance in the data, we also used non-parametric bootstrap re-sampling techniques to calculate confidence intervals for the means at the various time points. Bootstrap analysis makes no prior assumptions regarding the data provides less biased estimates of confidence intervals in highly skewed data (Pollack et al. 1994). To control for the effects of factors known to affect BMI and glucose metabolism, we performed an analysis of covariance with change in BMI and change in HbA1c as dependent variables (separately), treatment group, gender and race as categorical variables and age as covariate. For correlations between pairs of numeric variables we used the Pearson product moment correlation coefficient. Significance tests were performed at a two-sided alpha level of 0.05. Results are expressed as mean \pm SD. Analyses were performed with Statistica version 6 (Statsoft, Inc.) software package.

Results

Of 47 participants entered into the study, two were excluded (one withdrew before reaching the target treatment dose, and one had unrelated medical illness). The analysis was therefore conducted on 22 patients in the quetiapine group and 23 in the haloperidol group. Baseline demographic and clinical details were similar for the two treatment groups (Table 1). All of the subjects had been receiving conventional antipsychotics before entry into the study. The majority were receiving depot fluphenazine, flupenthixol or clopenthixol. Ten subjects from the quetiapine group failed to complete the study, for the following reasons: worsening of psychosis (n=7); non-compliance (n=1); withdrawal of consent (n=1); and pregnancy (n=1). Eight subjects in the haloperidol group did not complete the study, due to worsening of psychosis (n=4); non-compliance (n=1); withdrawal of consent (n=1); severe, persistent dystonia (n=1); and disallowed concomitant treatment (n=1). For the OC analysis the sample sizes for quetiapine and haloperidol were, respectively, 22 and 23 at week 10, 16 and 18 at week 22, 13 and 16 at week 34, 13 and 15 at week 46 and 12 and 15 at week 54. The mean±SD endpoint doses were 400±147.7mg/day for quetiapine and 8.5±5.6mg/day for haloperidol.

The sample was not overtly obese - the mean baseline BMI for the entire group was 25.5±6.3 kg/m² and 20 subjects (43%) had a baseline BMI > 25 kg/m² (overweight). However, there was evidence of abnormal glucose metabolism at baseline in a larger than expected proportion of the patients. The mean baseline HBA1c for the entire group was 6.7±1.9%, with 22 subjects (48%) having at least mildly elevated values (HBA1c >6.1%) and 9 (19%) markedly elevated values (HBA1c >7%) (Davidson et al. 1999).

Effect of treatment on BMI and HBA1c

Neither treatment group exhibited significant changes from baseline in BMI, and there were no between-group differences at any of the time points (Figure 1). There was a non-significant increase in BMI at 10 weeks for the quetiapine treated subjects, but this returned to below baseline values at subsequent visits. RANOVA reported a significant time-treatment current effect (F=2.64, p=0.03) but the 95% confidence interval estimated by bootstrap methods found no between group differences. HBA1c results for the two groups are given in Figure 2. There were no differences at any of the time points between the groups. Similarly, both the RANOVA and bootstrap showed no significant differences between the two groups (F=1.17, p=0.3). Both groups showed a reduction in HBA1c values from baseline to endpoint which reached significance for the haloperidol (-1.5%; p=0.04), but not for the quetiapine treated patients (-0.3%; p=0.5). The number of subjects with elevated HBA1c values (>6.1%) decreased from 12 (52%) at baseline to 7 (30%) at endpoint in the haloperidol group, and from 11 (50%) at baseline to 9 (41%) at endpoint in the quetiapine group. None of the subjects with elevated baseline HBA1c values (i.e. HBA1c >6.1%) showed deterioration of glycaemic control during the study. In fact, HBA1c values in these subjects also decreased from baseline to endpoint in both groups, with the reduction being statistically significant in the haloperidol treated patients (-1.9%, p=0.04), but not for the quetiapine group (-0.6, p=0.5). There were highly significant differences in the prolactin levels between the two groups, with quetiapine patients levels being reduced, and haloperidol treated patients levels increased from baseline (RANOVA F=7.02, p=0.00001).

There was a significant ethnic difference in baseline BMI (Caucasian 21.4±2.6 kg/m², mixed descent 26.3±6.5 kg/m², p=0.04), but not in HBA1c values or prolactin levels. There were considerable gender differences in baseline measures. Women had greater BMI's (29.3±6.8 kg/m² vs 23.3±4.7 kg/m², p=0.02), higher HBA1c levels (7.6±2.9% vs 6.3±8.2%, p=0.03) and higher prolactin levels (29.3± 25.6 ng/ml vs. 15.2±10.7ng/ml, p=0.01). Age was not significantly correlated with baseline BMI, HBA1c or prolactin levels. The analysis of covariance for the primary efficacy measures found that the change in BMI was not significantly influenced by gender, race, age or treatment group (F=3.19, p=0.08), although there was a slight trend in women of mixed descent toward increased BMI with quetiapine treatment and decreased BMI with haloperidol treatment. However, for change in HBA1c there was a significant effect for gender, race and treatment group (but not age), with haloperidol-treated Caucasian females showing the greatest HBA1c reductions (F=11.93, p=0.001).

We found a significant correlation between baseline PANSS negative subscale scores and change in BMI ($r=0.44$, $p=0.04$). There were no other significant correlations between symptoms of psychosis (PANSS total and subscale scores) or extrapyramidal symptoms (ESRS subscale and total scores) and BMI or HBA1c. There was an indication of an interaction between prolactin and HBA1c levels. Baseline prolactin levels correlated significantly with HBA1c at week 10 ($r=0.51$, $p=0.03$), and change in prolactin was negatively correlated with HBA1c at week 10 ($r= -0.55$, $p=0.02$); week 22 ($r= -0.52$, $p=0.03$); week 34 ($r= -0.58$, $p=0.02$), week 46 ($r= -0.52$, $p=0.03$); and week 54 ($r= -0.53$, $p=0.03$). i.e. Persistently high prolactin levels were associated with less reduction in HBA1c values.

Results of the ITT LOCF analyses were essentially the same as the OC analyses reported above.

Discussion

This is one of very few prospective, controlled studies comparing the effect of a new generation antipsychotic with a conventional antipsychotic on body mass and glucose metabolism. Moreover, we are not aware of other controlled studies that have investigated the *long-term* effects of antipsychotics on body mass and glucose metabolism. Our results indicate that, in stable schizophrenic patients previously on conventional antipsychotics, long term treatment with both quetiapine and haloperidol is not associated with persistently increased adiposity, or worsening of glycaemic control. Furthermore, these agents may be safe for patients with existing glucose intolerance, as the subjects with elevated HBA1c at baseline showed no evidence of exacerbation of glycaemic control with either of these treatments. Given the importance of glycosylation in the genesis and development of diabetic microvascular and neuropathic complications, (Davidson et al. 1999) these findings are of considerable clinical significance.

The absence of significant body weight gain in the quetiapine-treated patients contradicts the findings of the Canadian National Outcomes Measurement Study in Schizophrenia, (McIntyre et al. 2003) and is more in line with those of the cross-sectional study in outpatients of Bobes et al. (Bobes et al. 2003a) and the open label extension trial in adolescents of McConville et al. (McConville et al. 2003). An explanation for the greater degree of weight gain with quetiapine in the McIntyre et al study (McIntyre et al. 2003) is not immediately forthcoming, although theirs was an uncontrolled study permitting concomitant medication, the sample was diagnostically heterogeneous and the quetiapine sample was significantly smaller ($n=23$) than the other groups. The absence of a deleterious effect on glucose metabolism with haloperidol is in contrast to an earlier study reporting a significant increase in fasting blood glucose levels after 8 weeks of treatment with haloperidol (Lindenmayer et al. 2003b). One possible explanation for this discrepancy is that the effect with haloperidol could be dose related. Patients were treated with haloperidol 20mg/day in the Lindenmayer et al (Lindenmayer et al. 2003a) study, while the mean endpoint dose in our trial was considerably lower (8.5mg/day).

The high incidence of pre-existing glucose dysregulation in this relatively non-obese cohort gives cause for alarm, and once again highlights the fact that patients with schizophrenia are at high risk for developing glucose intolerance and type 2 diabetes. The fact that this occurred even in the absence of obesity, together with a lack of significant correlations between BMI and HBA1c provides further evidence that glucose intolerance is not necessarily secondary to weight-gain in antipsychotic-treated schizophrenic patients (Newcomer et al. 2002a; Ryan et al. 2003a).

Various, and possibly multiple mechanisms may be responsible for glucose intolerance with antipsychotic treatment. Weight gain is one of the mechanisms involved, and considerable evidence suggests that antipsychotic-induced weight gain is at least partly related to the blocking effects on serotonin- and histamine-mediated neurotransmission (Koponen et al. 2002) resulting in altered hunger and satiety (American Diabetes Association et al. 2004). Patients receiving an antipsychotic for the first time experience substantial deposition of both

subcutaneous and intra-abdominal fat, reflecting a loss of the normal inhibitory control of leptin on body mass. Along with fat deposition, there is an increase in the levels of fasting lipids and non-fasting glucose (Zhang et al. 2004). However, other mechanisms independent of weight gain may also lead to elevation of serum leptin and insulin resistance (Lean and Pajonk 2003). Serotonin (5-HT₂) receptor activation influences glycogenolysis and blood glucose levels (Darvesh and Gudelsky 2003) so that this may be a mechanism in the case of the new generation antipsychotics. Agents that influence monoaminergic neurotransmission have been shown to have an effect on glucose regulation. Peripheral blood glucose concentration was found to be significantly correlated with cerebrospinal fluid concentrations of dopamine and noradrenaline metabolites (Umhau et al. 2003). This may be pertinent with the conventional antipsychotics, with their more pronounced effect on dopaminergic neurotransmission (Meltzer et al. 1989). Finally, an association between glucose metabolism and prolactin has also been described. Prolactin induces glucose intolerance, hyperinsulinemia and insulin resistance (Tuzcu et al. 2003). This could be a relevant mechanism with patients receiving risperidone and the high potency conventional antipsychotics such as haloperidol. In this regard, our finding of a relationship between HBA1c and prolactin levels is of interest. The association between high baseline prolactin and high HBA1c levels at 10 weeks, as well as higher HBA1c values in patients with persistent prolactin levels is indeed what would be anticipated by the findings of Tuzcu et al (Tuzcu et al. 2003). Unlike another study investigating the relationships between prolactin and weight gain in antipsychotic-treated subjects, we did not find an association between prolactin and BMI (Baptista et al. 2001b).

The greater BMI's and higher HBA1c levels in women in our study are in keeping with a previous finding that women treated with conventional antipsychotics displayed more insulin resistance than healthy controls, thereby predisposing them to excessive weight gain (Baptista et al. 2001a), and suggests that female gender is a risk factor for diabetes in subjects treated with antipsychotic medication. Age and ethnicity were not identified as risk factors for glucose intolerance in our sample although non-caucasians had greater BMI's. The finding that patients with higher baseline negative symptom scores showed less reduction of BMI over the treatment period is of interest, in view of previous reports of an association between weight gain and treatment response. However, previous studies reported either no association, or improvement in symptoms together with weight gain (Meltzer et al. 2002). It has been suggested that the effects of the antipsychotic on neurotransmitters which influence weight gain, may also contribute to the improvement in psychopathology (Meltzer et al. 2002). Our result could be explained on the basis that subjects with negative symptoms display more sedentary behaviour.

This study is limited by its relatively small sample, and the findings cannot be generalised to other populations such as medication-naïve first-episode patients. In fact, our sample may be particularly at risk for disorders of glucose metabolism, as an association between diabetes and TD has recently been reported in elderly patients (Caligiuri and Jeste 2004). Also, while HBA1c is a useful measure, other means of assessing glucose metabolism such as fasting blood sugar and oral glucose tolerance tests were not performed on our subjects. These additional measures would be necessary in order to diagnose diabetes mellitus according to World Health Organisation criteria (World Health Organisation 1980).

This study highlights the high incidence of unrecognised glucose intolerance in patients with schizophrenia receiving antipsychotic treatment. Our findings suggest that switching from a conventional antipsychotic to quetiapine treatment does not further impair glucose metabolism, even in the long term. Quetiapine may be a relatively safe treatment option in patients at risk for diabetes mellitus. While haloperidol is also safe in this regard, its well documented neurotoxic effects would preclude its use where alternative treatment is available (Joy et al. 2001).

Acknowledgements

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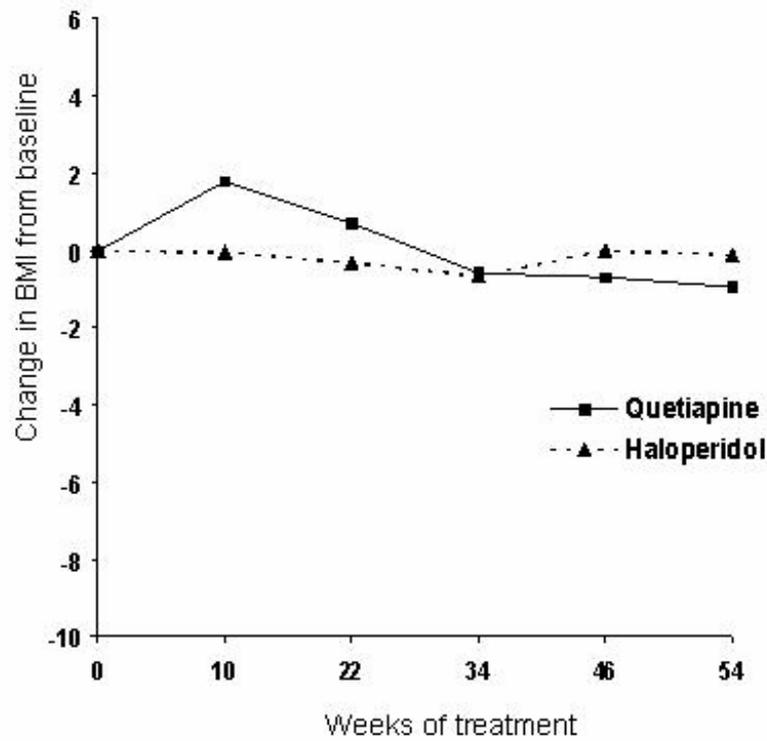
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Table 1. Baseline demographic and clinical details of the two treatment groups (mean±SD).

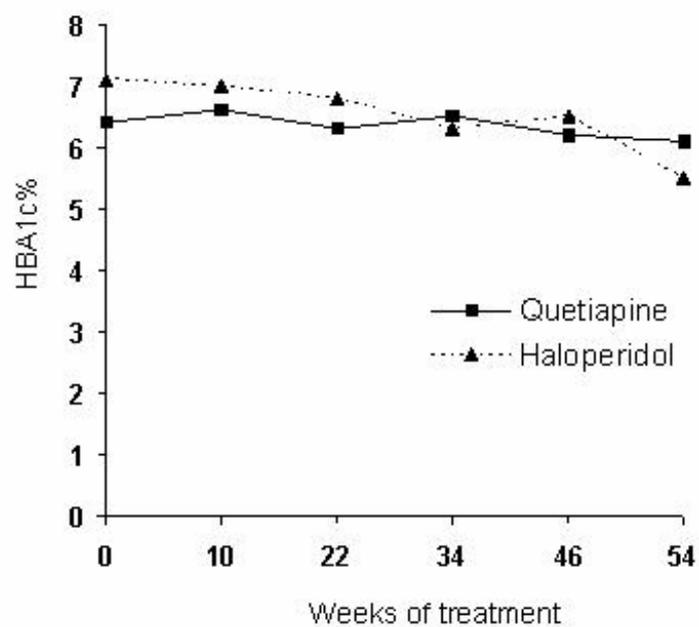
	Quetiapine (n=22)	Haloperidol (n=23)
Male : female	14:8	15:8
Age (Yrs)	49.2±14.5	50.1±8.6
Weight (Kg)	71.9±21.3	66.6±11.7
BMI (%)	26.4±7.0	24.5±5.4
HBA1c (%)	6.4±1.1	7.0±2.5
Prolactin (ng/ml)	25.4±23.3	15.2±9.2
PANSS total score	55.5±12.7	57.0±14.1

Figure 1. Change in BMI over 12 months for the two treatment groups.



Sample sizes for quetiapine and haloperidol groups were, respectively, 22 and 23 at week 22 and 23 at baseline; 10, 16 and 18 at week 22; 13 and 16 at week 34; 13 and 15 at week 46; and 12 and 15 at week 54.

Figure 2. Mean HBA1c values over 12 months for the two treatment groups.



Sample sizes for quetiapine and haloperidol groups were, respectively, 22 and 23 at week 22 and 23 at baseline; 10, 16 and 18 at week 22; 13 and 16 at week 34; 13 and 15 at week 46; and 12 and 15 at week 54.

3.c.x Cost-effectiveness of an atypical vs. conventional antipsychotic in South Africa: An Economic Evaluation of Quetiapine and Haloperidol in the Treatment of Patients Partially Responsive to Previous Antipsychotics

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Summary

Background: The introduction of a new generation of atypical antipsychotic agents has raised difficult economical and ethical questions, particularly in lower-income countries. The reported tolerability and efficacy advantages of the atypical antipsychotics over their conventional predecessors have to be weighed against their higher acquisition costs. Pharmaco-economic studies conducted in Western countries consistently report cost-advantages or cost-neutrality for these new agents. However, considerable differences in health-care service provision make it difficult to generalize these findings to South Africa.

Method: We compared the direct costs (private and public sector) of treating schizophrenia with an atypical antipsychotic quetiapine, with a conventional antipsychotic haloperidol, by adapting a decision-analytic pharmacoeconomic model for South African circumstances. The sample comprised patients partially responsive to antipsychotics, who had participated in a multinational randomized controlled trial comparing the efficacy and safety of quetiapine versus haloperidol.

Results: The estimated total direct cost for the treatment with quetiapine in South Africa was slightly less than for haloperidol for various models in both the private and the public sector.

Conclusions: Significant differences in health-care provision make pharmacoeconomic studies conducted in other countries invalid for South African circumstances. Quetiapine treatment previously did not result in direct cost savings in South Africa. However, the recently introduced legislation to establish single exit prices for medications has resulted in the cost of quetiapine treatment declining by 36.7% and that of haloperidol by 13%. This has translated into an overall direct cost-saving for quetiapine in both the private and public sector models. This, together with additional indirect advantages of the atypical antipsychotics such as improved quality of life and better social and vocational functioning, argues strongly from both an economic and ethical perspective for the use atypical antipsychotics in treating schizophrenia in South Africa.

The costs of schizophrenia

Schizophrenia is one of *the* most important diseases affecting humankind, costly in both social and financial terms.¹ It imposes a disproportionately large economic burden on patients and their families, health care systems and society, because of its early onset, devastating effects, and usually lifelong course,² and it is the most costly illness that psychiatrists treat.³ In 1993 the disease consumed an estimated \$33 billion in the United States of America (\$18 billion in direct costs and \$15 billion in indirect costs). This constituted 2.5% of the annual total health care allocations.⁴ In England, the identifiable direct and indirect costs suggest an annual total cost of £2.6 billion (this figure omitted some indirect costs).⁵ In South Africa (SA), the costs are not known. The direct costs of schizophrenia include aspects such as hospitalisation, day care, residential accommodation, medication,

special investigations and disability grant payments. Examples of indirect costs are lost employment, reduced productivity and family costs (e.g. household expenditure, travel costs, lost earnings).⁶

In the current worldwide cost-cutting climate in health services, the focus has fallen on economizing the delivery of health care. Yet decreasing expenditures on drugs for severe illnesses such as schizophrenia may be a false economy, as drugs account for only a small proportion of the total costs.¹ In the case of schizophrenia, the acquisition costs of medication comprise a very small portion of the total costs of the illness – at least in the developed world. For example, the costs of antipsychotic medication have been estimated at 4% of the direct costs in the United Kingdom (UK),⁷ 5.6% in France,⁸ and 1.1% in the Netherlands.⁹

The introduction of the atypical antipsychotics has had a major impact upon the way we treat patients with schizophrenia. Evidence is accumulating to show that these drugs hold significant advantages over their predecessors in terms of both tolerability (although other side-effect concerns have emerged) and efficacy. In particular, it has been shown that these agents have a reduced propensity to induce acute extrapyramidal symptoms (EPS),¹⁰ previously a major obstacle to the effective treatment of schizophrenia. There is now a considerable literature indicating other advantages of these drugs. These advantages include improved efficacy in treatment-refractory patients,¹¹ in patients with negative symptoms¹² and depressive symptoms,^{13;14} reduced levels of suicidality,¹⁵ less neurocognitive impairment,¹⁶ better subjective quality of life,¹⁷ reduced incidence of tardive dyskinesia,¹⁸ decreased likelihood of relapse¹⁹ and improved overall outcome.²⁰ Although often modest, these advantages often make a substantial difference to patients in terms of improved social and vocational functioning and a better quality of life. The clinical advantages of these drugs are greatest close to the onset of the illness, and they are increasingly regarded as first-choice agents.²¹ However, because of their much greater acquisition costs, their availability in lower-income countries in regions such as Africa, Latin America, Asia and the Pacific, is extremely limited.

Pharmacoeconomic studies generally show the atypical antipsychotics to be cost-effective or cost-neutral in treating schizophrenia. But it is not clear to what degree these findings (conducted in the Western world) can be generalised to other countries, where other factors need to be considered. For example, schizophrenia reportedly runs a different course in developing countries,²² and a cost-effectiveness study in Nigeria indicated that the antipsychotic drugs accounted for 52.8% of the cost of treating schizophrenia!²³ This was because most patients are cared for by their families at no direct cost to the state, and residential care, when available, had low staff and infrastructure expenditure.

The ideal pharmacoeconomic study would be a prospectively designed trial in a large sample, and conducted over a long study period. Such a study would however be very difficult to conduct, and extremely expensive. A less dependable but easier attainable alternative is to construct a pharmacoeconomic model specifically for South African conditions. This study attempts to quantify the direct costs involved in treating a large group of patients with schizophrenia in SA. It will hopefully provide guidance to clinicians and decision makers alike regarding both private and public health sector costing.

Method

This study incorporated the clinical findings of a randomized controlled trial in a pharmacoeconomic model adapted for SA circumstances. The model estimated outcomes and direct costs over 5 years for quetiapine and haloperidol in treating partially responsive patients with schizophrenia. Persistent positive symptoms occur in many patients treated with conventional antipsychotics,^{24;25} and this population has been referred to as 'partial responders'.²⁶ They are an important patient group, as they represent the majority of patients

with schizophrenia, and their treatment is problematic. Consequently, disproportionately more resources are likely to be allocated to these patients.

Patients and study design

The study that we utilized for the analysis was a multicentre, double-blind, randomised trial comparing quetiapine and haloperidol in patients with a partial response to conventional antipsychotic treatment. Although multinational, many of the participants were in SA. A detailed description of the study design, patient selection criteria, and efficacy and safety measures has been reported elsewhere,²⁷ and so will only be briefly described here. Patients meeting the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) diagnostic criteria for schizophrenia and who had a history of only partial response to conventional antipsychotics were entered into a 4-week active run-in treatment phase with fluphenazine (20 mg/day). Those patients showing either no response, or only a partial response to the fluphenazine treatment (defined as <30% reduction in the Positive and Negative Symptom Scale (PANSS) total score), were then randomised to receive either quetiapine (600 mg/day) or haloperidol (20 mg/day). As these patients were envisaged to be difficult to treat, the quetiapine and haloperidol dosages were towards the upper end of their recommended dosage ranges, namely 600 mg/day and 20 mg/day, respectively. Current clinical practice with quetiapine has moved towards the use of considerably higher doses. In fact, 600mg/day is usually the target dose for most patients, not just those considered difficult to treat. Doses were titrated over a 7-day period, and then fixed for the next 7 weeks. Key exclusion criteria included severe resistance to conventional antipsychotics, known non-responders to clozapine and an acute psychotic exacerbation within the past 3 months.

The results of the analysis of the intent-to-treat (ITT) population indicated that both quetiapine and haloperidol were associated with significant mean reductions in PANSS total scores. The reduction was numerically greater with quetiapine than that observed with haloperidol, but the difference did not reach statistical significance. However, the treatment response rate was significantly greater for quetiapine (52% vs 38%, $p=0.04$). (Treatment response was defined as a reduction in PANSS total score of $\geq 20\%$ from week 4 to week 12.) Further analysis on the ITT population indicated that a decrease in PANSS total score of $\geq 30\%$ from week 4 to week 12 was also in favour of quetiapine (29% vs 16%, $p=0.01$). This can be seen as a good level of clinical response.²⁸ The results of the safety analysis indicate that the proportion of patients who were using anticholinergic medication at the end of the trial (after eight weeks on either quetiapine or haloperidol) was significantly lower in the quetiapine group than the haloperidol group (32% vs 53%, respectively, $p = 0.001$). Other measures of EPS occurrence consistently indicated a lower incidence of EPS in the quetiapine group when compared to the haloperidol group.

The pharmaco-economic model

We adapted a study that was previously conducted on this sample for UK circumstances.²⁹ Medical resource utilisation and unit costs were obtained for SA private and public sectors. For the model, a decision-analytic model with Markov processes was constructed, incorporating the consequences of treatment with regard to both the treatment response and the incidence of EPS. The Markov model has been extensively used in pharmaco-economic studies.³⁰ Costs are computed on the basis of assumptions about service utilisation that are derived from the results of a randomized, controlled trial, the pattern of resource use assumed in SA and from information provided by SA psychiatrists. Five groups of patients are advanced through a Markov process of eleven health states in cycles of 3 months over a period of five years, based on the likely sequelae of relapse and non-response. These groups have different responses to medication and/or incidence of EPS. The sequelae for these groups are driven mainly by the probabilities of compliance to medication and relapse (determined from a literature review and advice from a panel of SA psychiatrists). The Health States of the Markov model are as follows: PANSS Improvement > 30% (without EPS); PANSS Improvement > 30% (with EPS); PANSS Improvement > 20% but < 30% (without EPS); PANSS Improvement > 20% but < 30% (with EPS); No treatment response (PANSS improvement <20%); First relapse; Post-relapse (quetiapine treatment): Response (PANSS >

30%); Post-relapse (haloperidol treatment): Response (PANSS > 30%); Post-relapse: No response (PANSS <30%); Subsequent relapse(s); Suicide.

Results

The original model for the UK found the total treatment costs of quetiapine to be lower than for haloperidol. While the cost of medication was higher for quetiapine treated patients, substantial cost savings were achieved by a reduction in the use of health care services. It cost £244 less per patient over the five year period for the quetiapine treated patients than those treated with haloperidol (£38,106 vs. £38,350).²⁹ However, these findings cannot be generalized to SA as substantial differences exist between psychiatric service delivery in the UK and both the private and public sector in SA. Health care costs obtained in August 2004 for the private and public sector in SA are provided in Tables 1 and 2, respectively. Medication costs subsequent to August 2004 in SA are provided in Table 3. Costs between countries do not only differ in terms of fee structures of specific items, but also regarding their nature. For example, general practitioners and community nurses are much less frequently involved in treating patients with schizophrenia in the private sector in SA than in the UK. Also, day-care and residential care facilities are less available in both the private and public sector. Thus, although these costs are saved in the SA system, the absence of these services increases the likelihood of relapse and lengthens the duration of hospitalization. On the basis of information obtained from a panel of SA psychiatrists from both the private and public sector, we made certain assumptions regarding these differences, and calculated the following solutions:

- (a) 'Baseline' situation: This was a direct transposition of SA private sector costs in the original model without making other assumptions about differences in health care provision between the UK and SA.
- (b) 'Private sector 1' situation: Assumed a 5% increase in hospitalization and risk of relapse for private health care services in SA
- (c) 'Private sector 2' situation: Assumed a 10% increase in hospitalization and risk of relapse for private health care services in SA.
- (d) 'Public sector 1' situation: Assumed a 5% increase in hospitalization and risk of relapse for public health care services in SA
- (e) 'Public sector 2' situation: Assumed a 10% increase in hospitalization and risk of relapse for public health care services in SA.

The results of the **cost-effectiveness analysis** for each of the five situations in terms of the main outcomes of cost-effectiveness, including the aggregate financial costs are listed in Table 4. The proportion of total direct costs for quetiapine was considerably higher in SA than in the UK. Thus, for private sector situations 1 and 2 quetiapine made up 14.2% and 13.9% of the total costs respectively, and for public sector situations 1 and 2 the figures were 16.5% and 16.2% respectively. (For private sector situations 1 and 2 haloperidol made up 1.7% and 1.7% of the total costs respectively, and for public sector situations 1 and 2 the figures were 2.1% and 2% respectively.)

The results of the sensitivity analysis (not reported here) showed that quetiapine remains less costly than haloperidol in almost all cases under the baseline and private 1 situation. In the case of situation public 1, where the cost differential was the smallest (R684 per patient over a five-year period), changes in assumptions that saw treatment costs decline in almost all cases resulted in quetiapine patients being more costly to treat than haloperidol patients. Yet, the cost differential was relatively small where quetiapine was not cost saving and ranged from R0.93 (assumed no relapse patients to be hospitalized compared to 60% in baseline situation) to R121.52 (assumed non-response and relapse health state costs to decline by 50% compared to public 1 situation) per patient per month.

The results of the conservative estimates (i.e. situation 1) for the private and public sectors are depicted graphically in Figures 1 and 2, respectively. It can be seen that, over a five year period, while the acquisition costs of the two treatments differ substantially, the *total* direct costs are very similar.

Discussion:

The results of our study show that, as in the UK, the direct costs are slightly less for quetiapine than for haloperidol for all of our situations in both the private and public sectors. Although the medication acquisition costs were higher for quetiapine, substantial savings were achieved by a reduction in the use of health care services. Cost-savings per patient over 5 years amounted to R2,641 in the baseline situation; R3,058 and R3,625 in private situations 1 and 2; and R684 and R1,197 in public situations 1 and 2, respectively. The cost differences however are not great – for the private sector models they translate into a saving of R51 (private 1) or R60 per month (private 2) for quetiapine, and for the public sector models R11 (public 1) or R20 (public 2) per month.

We conducted our initial analysis using medication prices that were in effect prior to the recently introduced legislation that has resulted in significant cost-cuts. In this analysis treatment with quetiapine did not result in cost savings compared to haloperidol. However, in view of the fact that recent legislation to introduce single exit prices has significantly cut costs of medication in South Africa,³¹ we decided to re-analyse the data using the prices introduced in August 2004. The new prices resulted in a reduction of 36.7% in the cost of quetiapine and 13% for haloperidol. As a result, quetiapine treatment is now 3.7 times more expensive than haloperidol treatment compared to the 5-fold difference in price assumed in our original model. The daily cost of the drugs used for atypical antipsychotics (15mg olanzapine and 6mg risperidone) increased marginally (1.3%), while the daily cost of anticholinergic treatment (4mg akineton) declined by 7.5%. Consequently, the results of the cost-effectiveness analysis based on these new drug prices saw quetiapine patients being less costly to treat than haloperidol patients in all five situations. Although the cost of medication was higher for quetiapine, substantial cost savings were achieved by a reduction in the use of health care services. Cost-saving over 5 years amounted to R2,889 in the baseline situation. Cost-saving for private situations one and two amounted to R3,370 and R3,981, and R2,040 and R2,579 for public situations one and two, respectively.

The analysis we used adopted a conservative approach, so that, where data were not available, it was assumed that there were no differences between the treatments. This is unlikely to be the case however, as improved side-effect profile³⁴ and better patient acceptance³² with quetiapine are likely to improve compliance and reduce the relapse rate and resource utilization in the long-term. Also, the model does not take some direct, and all indirect costs into account. These latter costs are likely to be considerable. For example, only 12% of persons with schizophrenia were found to be employed in a full-time capacity in the United States,³³ and the illness is associated with poor physical health – patients with the illness are more likely to eat poorly, smoke and drink alcohol to excess, thus necessitating additional health-resource utilisation.³⁴ Also, family members spend on average 15 hrs per week³⁵ and an estimated \$3,500 per year³⁶ looking after a family member with schizophrenia

Our findings cannot necessarily be generalized to other samples, need to be interpreted with caution, due to a number of limitations. First, the entire model is based on indirect estimates in the absence of a prospective pharmacoeconomic study. Second, the lack of good data on costs of care in both the private and public sector in SA make estimates difficult. The cost estimates employed in this study were derived from tariffs, which are unlikely to represent the true opportunity cost of resources in the absence of perfectly competitive markets³⁷ and may substantially underestimate the direct cost of treatment, thus possibly translating into greater cost savings than those reported here. Third, the inclusion in this analysis of the cost of suicide or attempted suicide (excluded here for the sake of simplicity and due to absence of good estimates of the cost of suicide in SA), which is likely to be substantial,³⁸ may also have translated into considerable resource savings, thus resulting in quetiapine being even more cost saving. Fourth, relative costs of care differ substantially in developed and developing country settings. For example, comparative costs per bed day and outpatient visit compiled by the World Health Organisation (available at <http://www.who.int/evidence/cea>) show estimates for a country such as SA to represent a quarter or less of the cost estimates for developed countries such as Canada, the US and United Kingdom.³⁹ More importantly, in terms of this

study, it shows how higher relative costs are more likely to translate into cost-effectiveness, as noted by Drummond and Pang.⁴⁰ This emphasizes how the relatively lower cost of health care in a developing country such as SA is less likely to translate into cost-effectiveness where the main cost savings result from the lower relapse rates and subsequent hospitalization and resource use under the alternative treatment. Finally, considerable variation in intensity and nature of care exists in SA in both the private and public sectors.

Notwithstanding these limitations, as far as we are aware, this study provides a first attempt at quantifying costs in treating schizophrenia in SA. Hopefully, it will focus attention on this often neglected group of patients, and encourage further research in the area. We also hope that it will provide guidance to health care costing decision makers in both the private and public domains in South Africa. While costs ultimately play a large role in deciding what medications should be made available, other considerations are no less important. Particularly, from an ethical point of view it should be argued that every individual has the right to good medical care. There is now overwhelming evidence of neurotoxic effects of haloperidol, so that even a traditionally conservative Cochrane meta-analysis recently concluded that “given no choice of drug, use of haloperidol to counter the damaging and potentially dangerous consequences of untreated schizophrenia is justified. If a choice of drug is available, however, people with schizophrenia and clinicians may wish to start another antipsychotic with less likelihood of causing parkinsonism, akathisia and acute dystonias. For countries where haloperidol is not widely used, it should not be a control drug of choice for randomised trials of new antipsychotics.”⁴¹ This study provides economic support to add to the ethical argument for more extensive use of the atypical antipsychotics in both the private and public sectors in treating schizophrenia in South Africa.

Table 1. Private Psychiatric Care Costs in South Africa.

Item	Cost per day
Hospital admission bed day (acute stay) Pr58	R 725.60
Hospital admission bed day (long stay) Pr55	R 681.10
Residential care (1 day)	R 130.00
Psychiatrist consultation (25 minutes)	R 214.10
GP consultation	R 117.20
Psychiatric nurse visit (1 hour)	R 73.40
Day care	R 486.00
Outpatient visit	R 255.90

Data provided by Old Mutual Health Group, and based on previous Board of Healthcare Funders tariffs. August, 2004

Table 2. Public psychiatric care costs in South Africa.

Item	Cost per day
Inpatient care (acute stay)	R 680.00
Inpatient care (long stay)	R 460.00
Psychiatrist visits (25 minutes)	R180
Outpatient visits	R180
Community psychiatry visits	R125
GP (clinic) visits	R125

Source: Uniform Patient Fee Schedule for externally funded patients attending public hospitals of the Provincial Administration of the Western Cape, 1 January 2004.

Table 3. Medication costs in South Africa

Product	Trade Price (ex. Vat)	Pack Size	dose/day	Cost/day
Quetiapine 300mg	R 1,017.54	60	600mg	R 33.92
Haloperidol 5mg (Serenace)	R 229.04	100	20mg	R 9.16
Olanzapine 10mg	R 965.78	28	20mg	R 68.98
Risperidone 4mg	R 928.12	30	8mg	R 61.87
Clozapine 100mg	R 682.56	100	600mg	R 40.95
Artane 2mg	R 62.28	100	2mg	R 0.62
Akineton 2mg	R 86.21	50	2mg	R 1.72
Akineton 5mg/ml	R 121.35	5	5mg/ml	R 24.27
Fluoxetine 20mg (Prozac)	R 193.85	30	20mg	R 6.46
Lilly-Fluoxetine (generic)	R 72.10	28	20mg	R 2.58

*Source: Pharmaceutical Computer Data, August 2004.
Prices are Trade Prices Excluding VAT and pharmacy costs.*

Table 4. Estimated total costs of different health care situations for SA.

AGGREGATE COSTS:	Baseline	Private 1	Private 2	Public 1	Public 2
Medical resource	Quetiapine	Quetiapine	Quetiapine	Quetiapine	Quetiapine
Total cost of study medication	28,939,380	29,152,857	29,429,104	29,152,857	29,429,104
Total cost of other medications	15,649,003	15,460,448	15,223,802	15,460,448	15,223,802
Total cost of inpatient services	117,528,542	124,027,492	129,995,166	97,955,878	103,218,503
Total cost of outpatient services	37,716,091	36,620,807	36,451,731	34,095,682	33,981,457
Total treatment costs	199,833,016	205,261,604	211,099,802	176,664,865	181,852,866
Medical resource	Haloperidol	Haloperidol	Haloperidol	Haloperidol	Haloperidol
Total cost of study medication	3,689,974	3,632,504	3,596,363	3,632,504	3,596,363
Total cost of other medications	30,884,712	31,130,841	31,312,363	31,130,841	31,312,363
Total cost of inpatient services	127,389,903	134,305,158	140,780,433	106,121,337	111,828,356
Total cost of outpatient services	40,508,846	39,251,527	39,035,591	36,465,297	36,312,806
Total treatment costs	202,473,435	208,320,030	214,724,750	177,349,978	183,049,888
Medical resource	Difference	Difference	Difference	Difference	Difference
Total cost of study medication	25,249,406	25,520,353	25,832,741	25,520,353	25,832,741
Total cost of other medications	-15,235,709	-15,670,393	-16,088,561	-15,670,393	-16,088,561
Total cost of inpatient services	-9,861,361	-10,277,666	-10,785,267	-8,165,459	-8,609,853
Total cost of outpatient services	-2,792,754	-2,630,721	-2,583,860	-2,369,615	-2,331,349
Total treatment costs	-2,640,419	-3,058,426	-3,624,947	-685,113	-1,197,022

Figure 1. Total estimated direct costs per patient treated in the Private Sector in South Africa

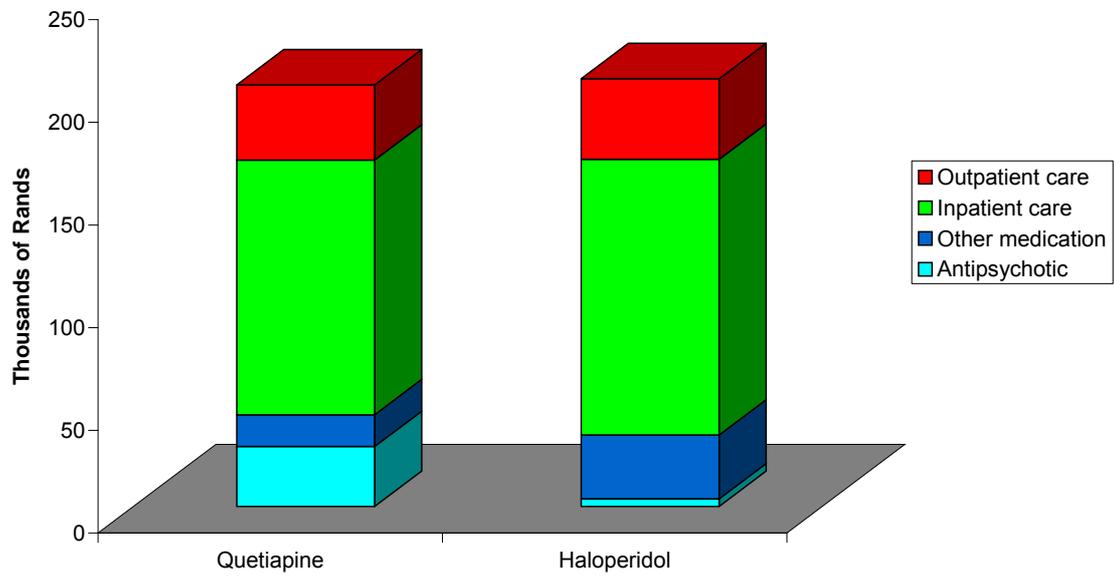
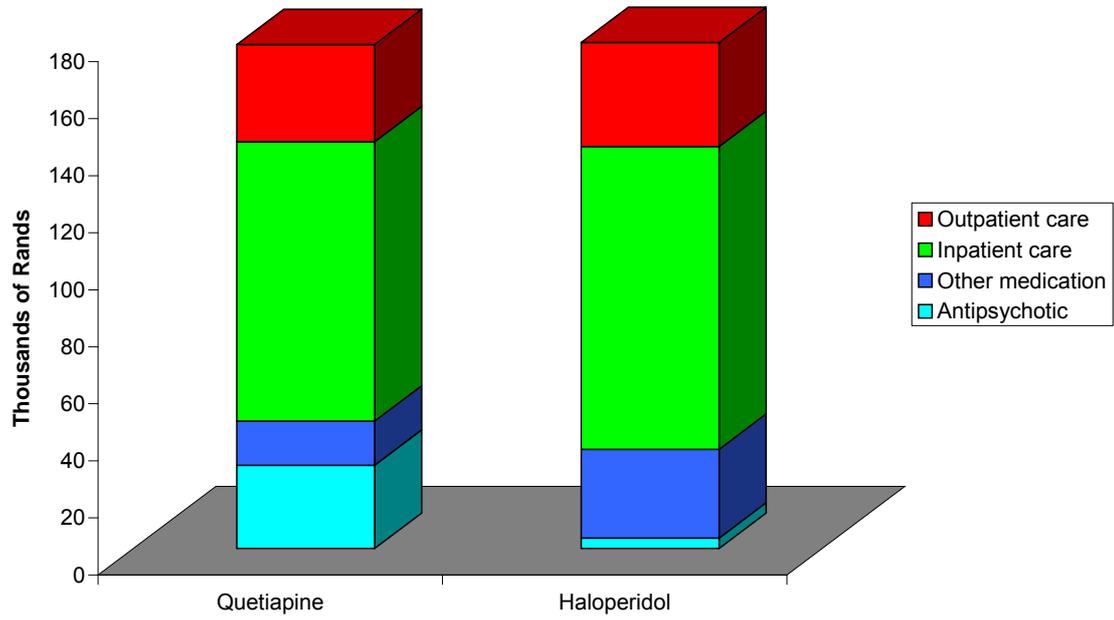


Figure 2. Total estimated direct costs per patient treated in the Public Sector in South Africa



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