Implementation of international treatment guidelines in the treatment of schizophrenia: a study of the effects of an evidence-based seminar on the knowledge and treatment habits of a sample of international psychiatrists

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Declaration

I, the undersigned, hereby declare that the work contained in this dissertation is my own original work and that I have not previously in its entirety or in part submitted it at any university for a degree.

Signature:_____ **Date: 25 September 2007**

Dedication

I would like to dedicate this thesis to all my "teachers of life":

Both my parents, my partner, my family and my friends,

Teachers, lecturers and professors,

mentors and colleagues.

Declaration of interest

The author of this dissertation is in the full-time employment of the Lundbeck Institute, where the seminars, studied in this paper, are presented.

Clinical education:
“the science, the art, and the heart of medicine”
(Atchley, 1959)

“Schizophrenia is arguably the worst disease
affecting mankind, even AIDS not excepted”
(*Nature,* 1988)

To be doctors we should be
“scientists with our brains and artists with our hearts”
(*Ancient Chinese proverb)*

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Abstract

This study reports on the effect of seminar education by studying changes in knowledge, attitude and behaviour to haloperidol prescribing patterns of psychiatrists who attended evidence-based schizophrenia seminars presented by the Lundbeck Institute in Denmark. The objectives of the study were two-fold. Firstly, it set out to determine whether changes actually occurred in the post-seminar haloperidol prescribing behaviour of participants. This was done by analysing changes in choice of optimal haloperidol dose (both in *acute* treatment i.e. most *effective* dose and *maintenance* treatment i.e. *minimum effective* dose), selected duration of treatment (for first- and multi-episode schizophrenia patients) and drug-class used (conventional versus new generation antipsychotic). The study then investigated whether these changes (if they occurred) could be ascribed wholly or in part to the effect of schizophrenia seminar attendance, or whether other factors e.g. scientific progress over time in understanding schizophrenia and its treatment ("background" knowledge) and differences between participant datasets studied (only paired pre- and post-seminar data were used in this study) also played a role. Secondly, it attempted to identify factors predictive of seminar participants changing their haloperidol prescribing behaviour post-seminar i.e. what were the factors that predisposed some attendees to change their prescribing behaviour? This was done by analysing the effect that pre-seminar prescribing behaviour, participant nationality, patient caseload, work experience and workplace environment had on post-seminar behaviour.

Results show that changes did occur in post-seminar haloperidol prescribing behaviour, but that they were not always due to an effect of seminar attendance. Only the changes in the *minimum effective haloperidol dose* and *duration of treatment for first- and multi-episode schizophrenia patients* could validly be ascribed to the effects of schizophrenia seminar attendance. Furthermore, multivariate analysis of the factors relating to these changes found that a participant was most likely to change their selected minimum effective haloperidol dose to be more in line with internationally accepted standards if they i) selected above the target dose pre-seminar, ii) had a relatively low caseload comprised mainly of schizophrenia patients and iii) came from either Greece, Germany, Britain, Spain, Italy or some other Eastern European country. The single most important factor related to *changes in duration of treatment* was found to be pre-seminar behaviour: respondents below the recommended duration of treatment increased their duration of treatment significantly.

In summary, this study demonstrated a direct relationship between seminar attendance and changes to selected minimum effective haloperidol dose and duration of treatment. However, seminar attendance did not appear to be a significant factor in changes to antipsychotic class used for treatment and changes in optimal effective haloperidol dose: rather a change in the level of "background" knowledge of participants was most likely responsible. This study also found individual participant characteristic differences in those who did change treatment duration and minimum effective dose.

In conclusion, this study showed that the successful integration of international treatment recommendations into daily psychiatric practise could be facilitated by the use of appropriate educational seminars. Not all attendees benefit i.e. "learn", but those needing to "learn" most do - i.e. those who need to change their prescribing habits most to meet internationally accepted guidelines. The peer exposure provided allows a format for informed discussion and the practise of evidence-based medicine. The judicious use of such seminars should result in better treatment options and outcomes for patients.

Abstrak

Hierdie studie beskryf die effek van seminaargerigte-onderwys deur die meting van veranderings in die kennis, gesindheid en gedrag ten opsigte van haloperidol voorskrifte van psigiaters, na bywoning van 'n bewysgebaseerde skisofrenie seminaar, aangebied deur die Lundbeck Instituut in Denemarke. Die doelwitte van hierdie studie was tweevoudig. Eerstens, om te bepaal of verandering in die haloperidol voorskrifte van deelnemers werklik plaasgevind het nadat hul die seminaar bygewoon het. Dit is bereik deur die analise van veranderings in die keuse van die optimale haloperidol dosering (beide in *akute* behandeling: mees *effektiewe* dosering, sowel as *langtermyn* behandeling: *minimum effektiewe* dosering), keuse van behandelings tydperk (in eerste- sowel as multi-episode skisofrenie pasiënte) en die klas van medikasie gebruik (konvensionele teenoor die nuwe-generasie antipsigotika). Hierna het die studie ondersoek of die veranderings (indien daar wel veranderings voorgekom het) in die geheel of slegs in 'n mate toegeskryf kon word aan die effek van die seminaar-bywoning, of dat ander faktore bv. wetenskaplike vooruitgang in skisofrenie kennis en behandeling ("agtergrond" kennis) en die veskille tussen deelnemer datastelle (slegs gepaarde voor- en na-seminaardata is in hierdie studie gebruik) ook moontlik 'n rol gespeel het. Tweedens, het die studie gepoog om faktore te identifiseer wat die veranderings in na-seminaar haloperidol-voorskrifgedrag kon voorspel: watter faktore het bygedra tot die verandering in voorskrite van sekere deelnemers? Dit is bereik deur die analise van hoe voor-seminaar voorskrifgewoontes, die deelnemer se nasionaliteit, pasiëntlading, praktykservaring en werksomgewing die na-seminaar gedrag beïnvloed het.

Uitslae toon dat veranderings wel plaasgevind het t.o.v na-seminaar haloperidol voorskrifgedrag, maar dat nie alle veranderings toegeskryf kon word aan seminaar bywoning nie. Slegs die verandering in die *minimum effektiewe dosering van haloperidol* en *behandelings termyne vir eerste- en multi-episode skisofrenie pasiënte* statisties aan die bywoning van die skisofrenie seminare toegeskryf kon word. Daar is verder bepaal, deur multi-variasie analise van bydraende faktore, dat deelnemers meer geneig was tot die aanpassing van hul voorgeskrewe haloperidol dosering tot nader aan internasionale standaarde indien hulle i) 'n te hoë dosering gebruik het voor die seminar bywoning, ii) 'n relatiewe lae pasiëntlading, bestaande uit meestal skisofrenie pasiënte, het en iii) herkoms van óf Griekeland, Duitsland, Britanje, Spanië, Italië óf 'n ander Oos-Europese land gehad het. Die belangrikste faktor wat *behandelingstermyn* verandering bepaal het was die voor-seminaar gedrag: respondente onder die aanbevole termyn van behandeling het díe behandelingstermyn betekenisvol verleng.

Ter opsomming, het hierdie studie bewys dat daar 'n direkte verhouding bestaan tussen seminaarbywoning en die verandering in die keuse van die minimum effektiewe dosering van haloperidol, asook in die duur van behandeling. Die seminaar bywoning het egter nie geblyk om die bepalende faktor te wees in die verandering van antipsigotika klas of die optimale effektiewe dosering van haloperidol nie. Díe veranderings kon eerder toegeskryf word aan die veranderings in "agtergrond" kennis van psigiaters. Die studie het wel individuele deelnemer-kenmerke identifiseer wat tot veranderings in behandeling gelei het.

Ter afsluiting, het hierdie studie bewys dat die suksesvolle integrasie van internasionale behandelingsriglyne in daaglikse psigiatriepraktyk bereik kan word deur voortgesette onderwys, deur middel van seminare. Nie alle deelnemers "leer" in sulke seminare nie, maar díe wat die meeste behoort te leer doen dit – deelnemers wie se praktykgedrag ver verwyder is van die internasionalbehandelingsriglyne. Die blootstelling aan eweknie-psigiatriese portuurgroepe skep 'n formaat vir ingeligte besprekings en die toepassing van bewysgebaseerde psigiatrie. Goed-deurdenkte toepassing van sulke seminare behoort beter behandelings opsies en uitkomste van behandeling aan pasiënte te bied.

Chapter 1 Introduction

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(*Nature*, 1988)

1.1 Schizophrenia – the illness

Schizophrenia, one of the major unsolved conditions of our time, contributes significantly to disability worldwide, ranking fourth highest as a cause of disability (Murray and Lopez, 1996; Singh, 2005). In addition to the personal tragedy it causes, the schizophrenia disease syndrome requires clinical care and living support across years of the sufferers' lives and so places a heavy social and economic burden on both sufferers and society (Davies and Drummond, 1994; De Hert et al., 1998a).

The schizophrenia syndrome is characterized by disturbing and unusual internal experiences – delusions and hallucinations, socially inappropriate behaviour, and reduced participation in social and occupational activities. Schizophrenia is generally a progressive and lifelong illness requiring on-going (possibly life-long) maintenance treatment to reduce the incidence of psychotic relapse.

Schizophrenia affects about 1% of the adult population worldwide (Torrey, 1987; Rupp and Keith, 1993). After much debate, it now seems clear that the incidence, as well as the prevalence, of schizophrenia is higher in males and in disadvantaged communities (Aleman et al., 2003; McGrath et al., 2004).

Cost of schizophrenia

Since schizophrenia is a chronic illness with frequent instances of relapse, it is not surprising that treatment costs for this condition are high: "probably the most expensive psychiatric disorder" (Andreasen, 1991).

While health care spending accounts for about 10% of GDP (Gross Domestic Product) in many developed countries (Wasylenki, 1994), the direct costs alone for the treatment of schizophrenia account for between 1.5 and 3% of the total health care budget (Rupp and Keith, 1993; Roullion et al., 1997; De Hert et al., 1998b; Meerding et al., 1998), yet the latest published data available reveal that expenditure on pharmacotherapies accounts for only 2 to 6% of the total cost of care for all psychotic illnesses in developed countries

(Salize and Rössler, 1996; Genduso and Hakey, 1997; Rouillon et al., 1997; Masand and Berry, 2000; Hansen et al., 2006).

In the United States the total estimated cost of schizophrenia was US$ 33 billion in 1990 (Rice and Miller, 1992), but by 2002 the cost of schizophrenia was estimated to be US$62.7 billion, with $22.7 billion in direct health care cost ($7.0 billion outpatient, $5.0 billion drugs, $2.8 billion inpatient, $8.0 billion long-term care). The total direct non-health care costs, including living cost offsets, were estimated to be $7.6 billion. The total indirect costs were estimated to be $32.4 billion. The indirect cost due to unemployment is the largest component of overall schizophrenia costs (Wu et al., 2005).

In Belgium, the total direct costs are estimated to account for 1.9% of national health expenditure, which means that the average expenditure on a schizophrenia patient is more than ten times the health care costs of the average citizen (De Hert et al., 1998b).

The SANE/Access Economics report into the costs of schizophrenia in Australia (Magnus et al., 2005) sets the annual direct cost at A$661 million, or A$18,000 per person with schizophrenia. The estimated transfer costs of the illness included A$190 million of lost tax revenue of patients and carers and A$274 million in welfare payments. Thus the total estimated cost to Australia of schizophrenia ranged from A$1.15 billion (Magnus et al., 2005) to A$1.44 billion (Carr et al., 2003) in 2001. These costs are heavily skewed towards acute care. However, acute care cost is under extreme pressure and the level of care offered is increasingly unacceptable. The avertable burden, although claimed to be less than in other disorders, could still be substantially addressed through improved adherence to treatment guidelines, medical accessibility and overall quality of care.

Reducing the burden

Although the acute treatment of schizophrenia is frequently favourable, the actual outcome in schizophrenia in the real world is poor with low compliance rates, frequent relapses, rehospitalisations, social and occupational impairment and a high risk of suicide (Jobe and Harrow, 2005; Leucht and Heres, 2006). This study aimed to assess whether an intensive, evidence-based seminar could successfully inform psychiatrists of the best current clinical practices and change their prescribing habits. If successful in this regard, it would contribute to reducing the burden that patients, their relatives, medical services, society and economies bear at present. By improving knowledge, attitudes and behaviour and treatment, this burden can be decreased and at the same time improve the quality of life of sufferers.

In order to meet this challenge, psychiatrists and public health organisations throughout the world have spent considerable resources on improving treatment outcomes for schizophrenia sufferers. International treatment guidelines (APA, 1997; PORT guidelines: Lehman et al., 1998; Texas Algorithm: Chiles et al., 1999; NICE, 2002; APA, 2004; Royal Australian and New Zealand College of Psychiatrists, 2005) as well as expert consensus statements (Kissling et al., 1991; Sartorius et al., 2002; Kane et al., 2003) have published recommendations on several key issues for the optimal treatment of schizophrenia.

In the age of the internet and globalisation, one would assume that since new knowledge based on recent research is rapidly disseminated, changes in clinical management incorporating new information would occur more rapidly than in the past. However, there seems to be a distinct unwillingness on the part of many clinicians to adopt new treatment guidelines. Recommendations are often applied at random or have limited effect on treatment practices (Cabana et al., 1999). According to Kissling et al. (1994), there is a lack of international or even national consensus – standards of psychiatric care vary across the world, within specific countries and even within hospital wards.

1.2 The Lundbeck Institute

The Lundbeck Institute is situated in Skodsborg, north of Copenhagen, in Denmark. Recognising the importance of psychiatric disability and the potential for vastly improved care for patients suffering from psychiatric and neurological disorders, as well as support for their relatives, the Danish pharmaceutical company H. Lundbeck A/S allocated substantial resources and personnel to found the Lundbeck International Neuroscience Foundation, which directs and monitors the activities of the Lundbeck Institute. The Lundbeck Institute is committed to improving the quality of life of patients suffering from psychiatric and neurological disorders, by increasing awareness and recognition of these disorders; and, through education, to improving the treatment of these patients by providing objective educational seminars and workshops, treatment tools and publications (Lundbeck International Neuroscience Foundation Statutes, 1998; Joubert, 1999).

All the Institute's educational activities, once approved by the Foundation, are implemented in close co-operation with the Lundbeck Institute Faculty, made up of prominent international opinion leaders within psychiatry, neurology and patient interest groups. This arrangement ensures the objectivity and quality of the education provided.

Evidence-based seminars

The main educational activity of the Lundbeck Institute is the presentation of evidence-based seminars. The seminars create a forum where psychiatrists, neurologists and other mental health workers can meet and discuss their knowledge, share experience and review relevant evidence-based literature, in plenary and groupwork sessions.

Currently the Institute presents seminars covering four main disorders: schizophrenia, mood disorders, dementia and anxiety disorders. Each seminar lasts five days with five participants from five different countries in attendance. By the end of 2006 the Institute will have presented 121 seminars in total, attended by more than 2800 psychiatrists and neurologists from 62 different countries (The Lundbeck Institute, data on file).

1.3 Schizophrenia seminars – integrating science and art

The Lundbeck Institute has presented schizophrenia seminars since August 1997. The title of the seminars is: **Evidence based medicine in schizophrenia: sharing responsibilities for improved care.** The material presented at the seminars comprises a large collection of literature related to various aspects of schizophrenia and its treatment. This literature is presented and discussed at each seminar, with the aim of reaching group consensus on diagnosis, acute and maintenance treatment, psychoeducation and the quality of care. The seminars mainly involve groupwork, where a group consists of a participant from each of the five countries attending. The rationale is that facilitating discussion on available literature, international treatment guidelines and the sharing of experience encourages consensus (Joubert, 1999) and enhances effective learning (Rutherford and Ahlgren, 1991).

For the purposes of this study data from the first 16 schizophrenia seminars, attended by 408 psychiatrists from 29 countries including Western and Central Europe, South Africa, Israel, Canada, Australia and New Zealand, were used.

Questionnaires

Two weeks prior to attending the seminars, all participants are requested to complete a pre-seminar questionnaire (see Appendix 1, page 135) to evaluate their knowledge of, and attitudes to, schizophrenia and their practice in treating schizophrenia patients. The data, collected anonymously, are retrieved and displayed on a country-by-country basis. These are used during the seminar introduction and discussions to emphasise the

differences in treatment habits in the respective countries, or even within a specific country.

Two follow-up post-seminar questionnaires are sent to the participants, the first two weeks after (see Appendix 2, page 151) and the second six months after (see Appendix 3, page 158) attending the seminar. The data presented in this paper were the accumulated data and comparative results from the pre- and post-seminar questionnaires of the participants of the first 16 schizophrenia seminars.

Each participant is also requested to complete case studies, two for the pre-seminar questionnaire and again two for the 6-month post-seminar questionnaire (see appendices 1 & 3). Examples of specific schizophrenia patients are given and the participants are asked to find similar patients in their practice and then complete the case, reporting on the actual treatment of the case.

The pre-seminar data reveal significant differences in the knowledge and attitudes of the attending psychiatrists. On a few key issues there are five- or six-fold differences between the answers given by the participants within a given group, particularly regarding optimal doses of the conventional antipsychotics and the duration of treatment for first- and multi-episode schizophrenia patients. These pre-seminar knowledge discrepancies form a starting point for the discussions in which the new literature and international treatment guidelines are discussed until the participants reach an evidence-based conclusion, preferably by consensus.

From the outset certain goals are set as measures of successful outcome for the seminars. These include a significant reduction in the dose of the conventional antipsychotics used in the treatment of the acute phase, the use of an evidence-based dose for the minimum effective dose in relapse prevention, an increase in the treatment duration for multi-episode schizophrenia patients and an increase in the overall knowledge of the psychiatrists. With a view to achieving these goals, evidence-based literature and international guidelines were selected which could be incorporated in the seminar to increase psychiatrists' awareness of and knowledge about these data.

Effective learning

The model of teaching at the Institute is designed to enhance effective learning. Teaching and learning are not the same thing, but are closely inter-related. Effective teaching takes into account the background and prior knowledge of the students, the

methods of teaching used and how to best integrates these into new thinking and behaviour.

A systematic Cochrane review on CME for medical professionals review the types of education provided and their effect on improving health care (Thomson et al., 2001). They reviewed 32 studies involving from 13 to 411 health professionals (total N= 2995) that were judged to be of moderate or high quality. For interventions that combined workshops and didactic presentations, there were moderate or moderately large effects in 12 comparisons (11 of which were statistically significant). In seven comparisons of didactic presentations, there were no statistically significant effects. They conclude that interactive workshops result in moderately large changes in professional practice while didactic sessions alone were unlikely to change professional practice. These data have been replicated showing that interactive techniques are the most effective at simultaneously changing physician knowledge and patient outcomes (Davis et al., 1992; Davis et al., 1999; Bloom, 2005). This format of education is reflected by the seminars presented by the Lundbeck Institute.

One of the cornerstones of effective education is when new knowledge is integrated into existing knowledge through understanding and deeper analysis. Therefore an understanding of the students' prior knowledge is essential. The method of delivery of the new information should be such that this encourages integration of new and older knowledge. Concrete examples may be required where after the student learns to link this information through abstract thinking to their prior knowledge.

Strategies in effective education involve creating curiosity, encouraging active participation, presenting evidence for statements, reformulating the new information, preferably in a team approach, and integration into new thinking and behaviour (Rutherford and Ahlgren, 1991).

Newly learnt information is lost very quickly with the passage of time (Andrade et al., 2003). This phenomenon is regarded as normal, but data to support this seem elusive. The Research Institute of America (RIA) has found that 33 minutes after completion of a course, students retain only 58% of the material covered in the class. By the second day, 33% is retained, and three weeks after the course, only 15% of the knowledge delivered is retained (RIA, 1990). Separate studies conducted by Neil Rackam seem to support these findings, in which he has reported that 87% of the learning from any given classroom workshop to salesmen is lost within 30 days, if not followed by a coaching intervention with the participants' manager (Rackham, 1998).

The Lundbeck Institute seminars attempt to achieve effective learning by following the strategies listed above. Prior knowledge is gathered with the pre-seminar questionnaires, showing differences in pre-seminar thinking and behaviour raises curiosity. After the evidence-based data are presented the participants work in groups to answer case-based questions with the new literature at their disposal. Each group is asked to present their answers to the full seminar group and then the new data are discussed. Once the participants return home after the seminar, they are actively encouraged to use the new-gained integrated information by doing educational workshops in their work settings.

The design of the seminars therefore takes into account background knowledge, encourages questions, debate and new thinking, attempts to integrate the new information into current thinking and then encourages further analyses and integration when the participants present their own education sessions.

Seminar content

The five-day-seminar includes presentations and discussions of most major topics of management of schizophrenia, first in a plenary discussion, followed by groupwork. Each group is assigned a task relating to the topic of the day. The group is asked to review the literature and discuss their varying experiences in the groupwork sessions. The groups then return to the plenary session where the results of each groupwork are presented to the rest of the participants. These answers are then discussed, with the aid of a moderator, to allow all participants to present their views. The moderator's task is to try to encourage the group to address unanswered questions on schizophrenia management. When the discussions or recommendations fall outside the framework of international treatment guidelines, the moderator's role is to emphasise the use of these guidelines and evidence-based medicine. If the group still wishes to recommend a treatment option outside the guidelines, they are asked to provide scientific reasons supporting the use of these treatment options.

The topics for each session during the seminar focus on the most important aspects of management: acute treatment, maintenance treatment, the new generation antipsychotic medications, psychoeducation, and the care pathway in schizophrenia and ensuring the quality of care provided. Central themes throughout the week include antipsychotic medication, side effects, remission criteria, relapse and psychotherapeutic interventions (Joubert, 1999).

The discrepancies in the data collected from the pre-seminar questionnaire are used to show differences in knowledge, attitude and behaviour of the psychiatrists present, and these form the basis of the discussions.

The treatment principles used are those set out in international treatment guidelines and expert consensus meetings. These include:

- Optimal dose of haloperidol for the treatment of psychosis
- Minimum effective dose of haloperidol in relapse prevention during long-term treatment
- Recommended treatment duration for first- and multi-episode schizophrenia.

Members of the Lundbeck Institute Faculty, including Dr Werner Kissling (München, Germany), Professor John Kane (New York, USA), Professor Nina Schooler (Washington, USA), Professor Anthony Hale (Canterbury, UK) and Professor Wolfgang Fleischhacker Innsbruck, Austria) wrote the content and approved the format of the programme. The European Committee for Accreditation (ECA) has evaluated and accredited the programme, judging it to be unbiased and of high academic standard.

Dr André Joubert (the author of this dissertation) has presented and moderated the seminars since their inception in 1997.

Psychopharmacological treatment principles

During the seminars the treatment principles of the relevant psychiatric disorders are addressed, including diagnosis, choice of pharmacotherapy, dose of medication, side effects, treatment duration, follow-up visits and all relevant psychosocial interventions such as structured psychotherapy, psychoeducation or social skills training. For the purpose of this introduction to the seminars, the treatment principles not relevant to this study will only be addressed briefly, while more detailed attention will be given to the relevant principles to highlight the topics addressed and the relevant evidence-based data presented during the seminars.

Diagnosis

In this study it was assumed that the diagnosis of schizophrenia had been confirmed, the psychiatrist had considered physical and other psychiatric comorbidity, substance abuse and suicidality. Hospital admission and the indication for ECT use should also have been considered.

Optimal treatment is important in the early phase of schizophrenia as the severity of the symptoms tend to contribute to severe deterioration in the first 5 years of the illness, contributing to sustained disability and burden (Robinson et al., 2005), and 10% of suicides by schizophrenia patients occur within the first 10 years of schizophrenia being diagnosed (Linszen et al., 1998). Once the diagnosis has been confirmed there are several decisions that need to be made concerning the treatment of the psychosis, including the choice of the class of antipsychotic, the optimal dose and the initial treatment duration.

Choice of pharmacotherapy

Psychopharmacological treatments form the cornerstone of both acute and maintenance therapy for schizophrenia. The discovery of chlorpromazine in the mid 1950s revolutionized the treatment of schizophrenia. The blockade of central D_2 receptors by the conventional antipsychotics was thought to be the key. The new generation of antipsychotics have effects on various other receptors such as those of the $5HT_{2A}$ system. However, while these other receptor binding properties may modify the side-effect profiles and possibly broaden the spectrum of efficacy, D_2 antagonism appears to remain central to antipsychotic action (Carlsson 1995; Seeman 2000), but with new evidence of extrasynaptic dopaminergic activity (Carlsson and Carlsson, 2006).

Antipsychotic drugs are effective in treating the positive symptoms of schizophrenia (hallucinations and delusions), but less effective for the negative and neurocognitive symptoms. Approximately 60% of patients treated with antipsychotic drugs achieve full or near-full remission of their positive symptoms. However, many patients continue to experience significant negative symptoms and cognitive impairment (Bilder et al., 2002; Lambert and Castle, 2003).

Several factors seem to be important in selecting a drug, such as previous response to an antipsychotic, available modes of administration (oral versus depot or long-acting), patient and relative preference, side effects and cost (APA, 2004). The preference of the psychiatrist seems to be a major factor in the selection of a drug. There are also regional differences in the availability of the new generation antipsychotics and their appropriate use (Emsley et al., 1999).

Expectations of remission, recovery, rehabilitation and reintegration are now much higher. Until recently, there was little evidence for greater efficacy of one antipsychotic

over another in schizophrenia subgroups, except for clozapine in treatment resistant schizophrenia (Kane and Marder, 1993) and also in those with active suicidal ideation (Meltzer, 2005). However, a recent important, but methodologically flawed study comparing the efficacy and safety of new generation antipsychotics found a significant advantage, in terms of lower rates of discontinuation for lack of efficacy, for olanzapine 20mg/day compared to risperidone, quetiapine, ziprasidone and perphenazine (Lieberman et al., 2005).

Choice of medication in the acute treatment phase

For several years there has been debate on whether conventional or novel antipsychotic drugs should be used as first-line treatment in first-episode psychosis or in continuing care of multi-episode patients (Geddes et al., 2000; Kapur and Remington, 2000; Lieberman et al., 2003). On the one hand, some suggested that new generation antipsychotics might be no more effective and only marginally better tolerated than haloperidol (Geddes et al., 2000) when control for the effect of the often excessively high dose of haloperidol is exercised. Others believed that efficacy and tolerability are clearly different (Davis et al., 2003).

A Cochrane Review found haloperidol to be effective – however, so toxic that "given the choice, people with schizophrenia may wish to start another antipsychotic with less likelihood of causing parkinsonism, akathisia and acute dystonias" (Joy et al., 2001).

Until recently most definitive meta-analyses favour new generation drugs over conventional antipsychotics on efficacy and tolerability grounds (Davis et al., 2003), though other authors remain somewhat more sceptical (Geddes, 2004) or reported modest superiority (Leucht et al., 2003).

In the past two years new data have been published which, for the first time, have compared the efficacy and tolerability of the newer and older antipsychotic drugs, namely the CATIE (Lieberman et al., 2005), SOHO (Haro and Salvador-Carulla, 2006) and CUtLASS (Jones et al., 2006) studies. These studies have been keenly anticipated and have been widely publicised. From subsequently published commentaries, their data have unfortunate flaws, which have not produced convincing outcomes, but have led to strong opinions being penned in the scientific and commercial press.

The CATIE study (Lieberman et al., 2005) produced advantages for the new generation antipsychotic olanzapine, but was prescribed at unusually high doses. Perfenazine, a

conventional antipsychotic seemed to produce good efficacy and comparable side effects, even EPS. However, patients with current or a history of EPS, often considered to be a "more difficult to treat" sub-population of schizophrenia patient were not "randomised" to this drug. There is evidence that patients with TD may represent a subgroup with a more severe and refractory course of illness (Ascher-Svanum et al., 2006). Patients with TD were excluded from any analysis involving perphenazine, potentially eliminating an important subset of patients. Furthermore, a significant disconnect appears between the low rating scale scores and the high patients' discontinuation due to EPS.

The SOHO study (Haro and Salvador-Carulla, 2006) showed an advantage for the new generation drugs olanzapine and clozapine over other drugs. The new generation antipsychotics were associated with a lower frequency of EPS and anticholinergic use than conventional antipsychotics, with the lowest frequency for clozapine-, quetiapine- and olanzapine-treated patients, at around 10%. The new generation antipsychotics exhibited a lower risk for tardive dyskinesia than the conventional antipsychotics.

In contract the CUtLASS study (Jones et al., 2006) seemed to show no advantage for the new generation drugs, based on the primary outcome of Quality of Life. Patient randomisation was not blinded and the number of patients on individual drugs resulted in an underpowered analysis.

Neither overly broad generalization nor wholesale rejection (or worse, cherry-picking) of study findings is helpful. Each study is a piece of the puzzle that answers a clinical question. As we try to develop more effective treatments for tomorrow (CATIE and CUtLASS reinforce the urgent need to do so), only a balanced understanding and individualized application of our data repository on existing treatments can optimize outcomes for persons with schizophrenia today (Tandon et al., 2006).

However, the CATIE and CUtLASS studies reinforce several points of agreement (Tandon et al., 2007):

- Actual benefits of new generation antipsychotics over conventional antipsychotics may be exaggerated; all new generation antipsychotics are not uniformly more effective and/or safer than conventional antipsychotics;
- Clozapine is more efficacious than other agents in otherwise treatment-refractory patients;
- Non-clozapine new generation antipsychotics provide a modest and inconsistent greater efficacy than conventional antipsychotics with reference to negative symptoms, cognition, and mood; differential EPS and related neuroleptic adverse

effects (dysphoria, neuroleptic-induced deficit syndrome, bradyphrenia) substantially explain such differences; and new generation antipsychotics generally have a lower liability than conventional antipsychotics to cause EPS;

- Different antipsychotic agents present different challenges in terms of balancing efficacy and safety/tolerability and there is considerable individual variability in antipsychotic response and vulnerability to specific adverse effects.
- Given broadly similar efficacy but significantly different adverse-effect profiles, it is important to use an effective antipsychotic that does not cause a significant adverse effect in each patient; "significant adverse effect" is determined by patient vulnerability, preference, and ultimately by which adverse effect the patient develops.

The expert guidelines (Kane et al., 2003) suggest tailoring the choice of antipsychotics to primary symptoms of the psychosis. In the case of a first-episode psychosis patient with predominantly positive symptoms, they recommend the use of risperidone, while they recommend either risperidone or aripiprazole for patients with predominantly negative symptoms.

There may still be a place for conventional antipsychotic drugs when all newer options have failed, especially in cases where long-acting (depot) use is justified. However, this is debatable as a long-acting new generation agent is now available. The better-tolerated new generation antipsychotics seem fully justified as first line treatment on clinical and humane grounds, despite their higher cost (Sartorius et al., 2002; Royal Australian and New Zealand College of Psychiatrists, 2005), particularly so in first-episode psychosis, where the patient's first experience with an antipsychotic may have a profound impact on his/her attitude towards medication use in the future (McGorry, 2002). However, a new profile of side effects has now emerged with the new generation antipsychotics. Referred to as the "Metabolic Syndrome", these effects are on weight gain, glucose dysregulation and dyslipidaemia and have now been recognised as serious clinical problems, particularly with olanzapine and clozapine, and to a lesser extent with risperidone and quetiapine (Lieberman et al, 2005).

The 2004 American Psychiatric Association (APA) guidelines suggest the following principles in deciding between conventional and new generation antipsychotic drugs:

- Consider second-generation antipsychotics as first-line medications because of the decreased risk for extrapyramidal side effects and tardive dyskinesia

- For patients who have had prior treatment success or who prefer conventional agents, these medications are useful and for specific patients may be the first choice
- New generation antipsychotics may have superior efficacy in treating global psychopathology and cognitive, negative, and mood symptoms
- With the possible exception of clozapine for patients with treatment-resistant symptoms, antipsychotics generally have similar efficacy in treating positive symptoms.

Few international treatment guidelines discuss the choice of medication. The Royal Australian and New Zealand College of Psychiatrists schizophrenia guidelines (2005) suggest the first line use of atypical antipsychotic medication on the basis of better tolerability and reduced risk of tardive dyskinesia. This is particularly strongly recommended for first-episode patients where the superior tolerability makes the new generation agents the first, second and third line choice. However, the guidelines warn against the associated potential of serious medium to long-term side effects for which patients must be carefully monitored.

The UK's NICE guidelines also recommend the use of new generation antipsychotic medication on the basis of better tolerability and reduced risk of tardive dyskinesia (NICE, 2002).

The most comprehensive review, by the World Psychiatric Association (WPA), highlights all published data providing evidence for the use of the new generation antipsychotics (Sartorius et al., 2002).

The Hungarian guidelines (1996) emphasise the importance of monotherapy.

Choice of medication in the maintenance treatment phase

The choice of antipsychotic for the maintenance phase of treatment is linked to several factors, predominantly the availability of the medication in depot- or long-acting form, and patient preferences and compliance.

Compliance (adherence/concordance) is of major concern, especially in the maintenance phase of schizophrenia management. Previously the depot conventional antipsychotics were seen as the solution to the lack of compliance to oral medications.

Even though there is little evidence that the new generation antipsychotics are more efficacious than the conventional antipsychotic medications in the acute treatment of positive symptoms, they seem to be more effective in relapse prevention (Csernansky, 2002). Also, the new generation antipsychotics demonstrate a clear advantage over the conventional antipsychotic agents because of the decreased risk of potentially serious side effects (Kapur et al., 2004; Gaebel et al., 2005). Furthermore, data have suggested greater efficacy for negative and cognitive symptoms (Purdon, 1999; Bilder et al., 2002).

Recent expert guidelines (Kane et al., 2003) suggest the use of most of the new generation antipsychotics in the maintenance phase of treatment, as well as any long-acting medication.

The Australian guidelines mention the option of conventional antipsychotic medications for relapse prevention only in low doses, where they may still have a role in an ever smaller proportion of patients (Royal Australian and New Zealand College of Psychiatrists, 2005).

It needs to be remembered that, for many countries across the globe, access to the new generation antipsychotics is restricted. In these countries, judicious use of the older agents may also provide a better outcome for patients (Emsley et al., 1999).

The dose of antipsychotic medication

Over the past 50 years there has been a worldwide trend for markedly excessive antipsychotic doses to be used both in the acute and maintenance phases, and also as a behavioural control measure. This trend has contributed to a great deal of unnecessary suffering and avoidable burden on individuals.

Establishing the optimal dose for the treatment of acute psychosis is important, as there is a dose-response curve up to a maximum response for antipsychotics (Davis et al., 1989). After this point, higher doses afford no further improvement and may even decrease response efficacy (Baldessarini et al., 1988).

Functional neuro-imaging with Positron Emission Tomography (PET) studies with haloperidol have shown a direct association between striatal D_2-receptor occupancy and antipsychotic efficacy, hyperprolactinaemia and the emergence of extrapyramidal side effects (EPS) (Farde et al., 1992). This suggests a haloperidol therapeutic window linked to D_2-receptor occupancy, with antipsychotic response starting at 60% occupancy and

EPS emerging at occupancy levels above 80% (Kapur et al., 2000). Therefore, careful titration of the haloperidol dose may achieve an antipsychotic effect without the emergence of EPS side effects. The McEvoy et al. (1991) "neuroleptic threshold" study found an effective dose of haloperidol to be 3.7 mg/day. This was in line with an earlier report by Farde et al. (1992) that a dose of 2 mg of haloperidol resulted in 70% D_2-receptor occupancy, suggesting that this could be the optimal dose. These data are consistent with the results of the Zimbroff et al. study (1997), which reported modest efficacy, yet significant EPS in the 4mg haloperidol arm of the study.

These and other data support the more recent trend to use lower doses of haloperidol, including acute phase trials (van Putten et al., 1990; McEvoy et al., 1991; Zimbroff et al., 1997; Emsley et al., 1999; Zhang-Wong et al., 1999; Oosthuizen et al., 2001, McEvoy, personal communication, 2006), maintenance phase studies (Eklund and Forsman, 1991), blood level monitoring (Coryell et al., 1998) and neuro-imaging studies (Kapur et al., 1996a and 1996b; Remington and Kapur, 1999; Kapur et al., 2000).

However, not all the evidence supports the use of low-dose conventional antipsychotics, with some suggesting poorer efficacy for low-dose oral (Zimbroff et al., 1997) or depot medication (Kane and Marder, 1983; Marder et al., 1996). An optimum dosage range of 10-15 mg/day haloperidol has been proposed (Baldessarini, 1988).

A Cochrane meta-analysis (Waraich et al., 2002) found that low doses of haloperidol (3-7.5 mg/day) "did not clearly result in loss of efficacy" and had a lower rate of development of clinically significant extrapyramidal adverse effects than at higher doses of >7.5-15 mg/day.

An evidence-based review of randomised antipsychotic trials, (Davis and Chen, 2004) found no evidence that higher doses of antipsychotics were more effective than low doses, suggesting that doses as low as 3.3 mg of haloperidol could be an effective dose.

Several recommendations suggest using conventional antipsychotics at a dose close to the "EPS threshold" (i.e. the dose that will induce extrapyramidal side effects with minimal rigidity detectable on physical examination) (APA 2004). Expert consensus suggests a haloperidol dose as low as 2.5 mg/day (Kissling et al., 1991).

The recommended optimal dose of haloperidol for the treatment of acute psychosis in schizophrenia varies from 3-20 mg/day (Hungary), 5-14 mg/day (Baldessarini et al., 1988), 11-19 mg/day (Davis et al., 1989), 6-15 mg/day (Dixon et al., 1995), 5-20

mg/day in the PORT and other guidelines (Marder, 1996; APA, 1997; Lehman et al., 1998; APA, 2004; Netherlands), and "not higher than 20 mg/day" (Denmark). Other studies suggest ultra-low doses of 1-2 mg/day (McEvoy et al., 1991; Oosthuizen et al., 2001; Oosthuizen et al., 2004) while others have until relatively recently studied doses as high as 60 mg/day (Rifkin et al., 1991) and even 200 mg/day (Chang et al., 1994).

However, all haloperidol data should be seen in light of the warning from Oosthuizen et al. (2004) on the use of low dose haloperidol in first-episode psychosis. They reported an incidence of probable or persistent tardive dyskinesia of 12.3% (n=57), despite a mean dose of haloperidol of 1.68 mg/day.

The results of the CATIE study where the conventional antipsychotic perphenazine was compared to several other new generation antipsychotics (Lieberman et al., 2005) have contributed to the debate. Although efficacy was broadly similar, perphenazine was associated with increased, but not significant, discontinuation due to EPS (it should be remembered that patients with tardive dyskinesia at baseline were not randomised to the perphenazine group). A recent meta-analysis showed insignificant differences in EPS between new generation antipsychotics, other than clozapine, and low potency conventional comparators (Leucht et al., 2003). The CATIE study results confirmed this.

The high-potency antipsychotics such as haloperidol are known to cause more EPS than the low-potency drugs such as chlorpromazine (Leucht et al., 2003). In the haloperidol versus new generation antipsychotic studies, the use of higher haloperidol doses may have lead to a bias that favours the newer drugs due to haloperidol-induced EPS (Haddad and Dursun, 2006). Further research is required to study low dose, low potency conventional antipsychotics such as chlorpromazine or even perphenazine, rather than haloperidol, as the comparator versus new generation antipsychotics.

The recommended doses for the new generation antipsychotics range as follows: aripiprazole 10–30 mg/day, clozapine 150–600 mg/day, olanzapine 5–30 mg/day, quetiapine 300–800 mg/day, risperidone 2–8 mg/day, and ziprasidone 120–200 mg/day (PORT, Lehman, 1998; Stein et al., 1999) while the APA guidelines recommend clozapine 300-400 mg/day, risperidone 4-6 mg/day, olanzapine 10-20 mg/day and quetiapine 150-750 mg/day (APA, 1997).

Minimum effective antipsychotic dose in relapse prevention

The principle of the "minimum effective dose" of an antipsychotic is the lowest dose of a drug at which there is no significant increase in the risk of relapse, and the risk of side effects is minimal. This is usually applied during the maintenance phase of treatment.

A Cochrane review (Bollini et al., 1994) of the antipsychotic neuroleptic dose for maintenance management of schizophrenia concluded that there was no benefit from doses higher than 375 mg/day of chlorpromazine or the equivalent of such a dose in the case of other antipsychotics (7.5 mg/day of haloperidol). It should be noted that adequate studies on lower doses could not be found.

Few guidelines recommend haloperidol doses for maintenance treatment. Those that do have suggested not more than 5 mg/day (Danish Psychiatry Association, 1989), or 2.5-10 mg/day (Netherlands Schizophrenia Foundation, 1996).

Antipsychotic side effects

The risk of side effects seems to drive the choice of medication. Intolerable side effects can lead to the premature discontinuation of drugs and result in an increase in potentially damaging relapses of acute symptoms of schizophrenia (Marder, 1998). As concluded in the CATIE study: "Selecting an antipsychotic involves a trade-off between efficacy and a range of side effects, the relative importance of which are likely to vary in different consultations" (Haddad and Dursun, 2006; Lieberman et al., 2005).

PET studies have shown haloperidol D_2-receptor occupancy of over 80% using 4 and 6 mg/day, which is associated with significant EPS-side effects (Farde et al., 1992).

The risk of tardive dyskinesia is significantly higher when conventional drugs are used and the levels of extrapyramidal symptoms (EPS) remain high, even with low dose conventional agents such as haloperidol (Oosthuizen et al., 2004). The new generation antipsychotic drugs are better tolerated and produce fewer motor side effects, including tardive dyskinesia – a definite advantage.

However, some of the newer drugs have potentially serious side effects of their own, such as hypotension and seizures (clozapine), prolactin elevation (risperidone, amisulpride), sedation (quetiapine, olanzapine, clozapine) and perhaps more importantly weight gain (olanzapine and clozapine) (Singh, 2005). The emergence of endocrine and cardiovascular side-effects, called the Metabolic Syndrome, characterized by weight gain,

increased triglycerides and total cholesterol and impaired glucose tolerance (Meyer, 2001), could restrict the long-term use of certain new generation antipsychotics (McEvoy et al, 2005). In the recently published CATIE study, olanzapine was associated with significantly greater increases in glycosylated haemoglobin, cholesterol and triglycerides than the other drugs even after adjustment for treatment duration, with ziprasidone being associated with an improvement on all three parameters (Lieberman et al., 2005; McEvoy et al., 2005; Haddad and Dursun, 2006).

Duration of antipsychotic treatment

Treatment duration usually refers to the duration of treatment once the patient's symptoms are in remission. Another important duration is the time one should wait to notice a response after starting an antipsychotic drug, as well as how long to wait before deciding that a drug has insufficient or no effect.

Time to antipsychotic treatment response

The criteria that should be reviewed prior to judging that there has been non-response to a specific drug are an adequate dose and adequate treatment duration, with confirmed compliance. It had long been assumed that the onset of antipsychotic action is delayed, and that these agents take several weeks to exhibit an effect. In their review of the literature, Keck et al. (1989) reported that the effects of most drugs are only significantly superior to a placebo after 3 weeks of treatment (Abse et al., 1960; Schooler et al., 1976; Johnstone et al., 1978). However, this result is usually a mean of all the different response times in the study subjects, and thus includes the patients who will not respond at all. If non-responders were removed from the dataset and another retrospective analysis performed the mean response time would be significantly shorter – as demonstrated in depression studies (Parker et al., 2000; Posternak and Zimmerman, 2005; Mitchell, 2006; Robinson, 2007). Recently, evidence has emerged showing in fact that the onset of antipsychotic action is rapid, with most of the antipsychotic effect occurring within the first few weeks of treatment (Agid et al., 2003; Kapur et al., 2005; Leucht et al., 2005; Li et al., 2006), with more improvement occurring in the first few days than in any other later period of equal duration and producing 68% of total annual improvement achieved within the first four weeks (Leucht et al., 2005). This relates particularly to multi-episode patients, while in first-episode psychosis some patients may take much longer to respond to treatment (Emsley et al., 2006).

One set of guidelines (Kane et al., 2003) considered 3–6 weeks an adequate antipsychotic trial, but suggested waiting until 4–10 weeks before making a major change in treatment regimen if there was a partial response. They recommended trying to improve response by increasing the dose of the medication before switching to a different agent.

The conclusion can be made that patients respond within days, although full remission of schizophrenia symptoms usually occurs slowly over many weeks. Guidelines still suggest that treatment with a specific antipsychotic agent should be continued for at least four to six weeks before concluding that there has been non-response to the drug, but as seen in the depression and schizophrenia data above, this guideline may soon change. Leucht et al. (2007) has just completed a review of antipsychotic trials showing that continuing treatment for four to six weeks seems to delay effective outcomes. They conclude that patients with no improvement of symptoms during the first 2 weeks of treatment are unlikely to respond at week 4 and may benefit from a change of treatment (Leucht et al., 2007).

Relapse prevention

Long-term maintenance treatment, or relapse prevention, encompasses the topics of indications for maintenance treatment, oral versus depot/long-acting administration of the drugs, minimum effective dose and treatment duration for first- and multi-episode patients.

Treatment duration after remission for first-episode psychosis

For first-episode psychosis the treatment guidelines vary from 2-3 months in Denmark, to 6 months in Sweden, to at least two years in the Netherlands. Most suggest 1 to 2 years of antipsychotic treatment before considering reducing the dose (Kissling et al., 1991; Texas Algorithm: Chiles et al., 1999; APA practice guidelines, 2004; Practice guidelines for Sweden, France, Hungary, Denmark and the Netherlands).

The latest guidelines from the United Kingdom suggest that if a patient is in full remission and remission is sustained for 12 months the medication may be stopped gradually, with close follow up (NICE, 2002).

The guidelines from Australia for first-episode psychosis patients suggest that sustained and comprehensive intervention should be provided for the initial 3-5 years (Royal Australian and New Zealand College of Psychiatry treatment guidelines, 2005).

However, there are clear data that stopping treatment even after one year of maintenance treatment in first episode patients leads to symptom re-emergence in 78% of patients in the first year and 96% within two years after discontinuation (Gitlin et al., 2001).

These data should provide strong evidence for significantly longer maintenance treatment durations in schizophrenia than the current guidelines, possibly advocating unlimited treatment duration (Zipursky, 2002).

Treatment duration after remission for multi-episode schizophrenia

In this instance the recommended treatment duration is at least 5 years (Kissling et al., 1991; APA, 1997 and 2004; France; the Netherlands). For patients with severe relapses, histories of violence and/or aggression and/or suicide the recommendation is for life-long continuous antipsychotic relapse prevention. The Danish guidelines (1996) suggest 3-5 years of sustained remission before the dose is reduced.

However, due to the lower incidence of EPS side effects with the use of the new generation antipsychotic drugs, the abandonment of the differentiated treatment duration for first- and multi-episode patients has been suggested (Robinson et al., 2005). The potential irreversible loss of functional impairment associated with the first relapse, possibly outweighs the risk of long-term side effects with the new generation antipsychotic drugs. However, this risk-benefit decision should, on one hand consider, EPS, in particular the high-potency conventional antipsychotics, but also, on the other, the Metabolic Syndrome with the long-term use of some of the new generation antipsychotics (McEvoy et al., 2005).

Psychosocial interventions

While the focus of this thesis is on pharmacological interventions, it needs to be remembered that an holistic approach to treatment is recommended as prescribing medication alone is not likely to achieve the best outcome. Other psychosocial interventions play a critical role in the management of schizophrenia. Under-development of quality systems of care and failure to provide intensive and

comprehensive psychosocial interventions to complement drug treatment have resulted in limited improvement in functioning and quality of life for schizophrenia patients, while predicting and preventing suicide remains poor (Roos et al., 1992).

Psychoeducation

The use of psychosocial interventions, such as psychoeducation, and drug management programmes, in addition to maintenance antipsychotic medication, reduces the risk of psychotic relapse (Linszen et al., 1998). The value of psychoeducational psychotherapy in the optimal treatment of schizophrenia has been shown (Kissling et al., 1996; Buchkremer et al., 1997), as have the principles of "Shared Decision Making" (Hamman et al., 2003)

A Cochrane review of studies employing psychoeducation found that compared to standard care alone, the addition of psychoeducation improved outcome and compliance (Pekkala and Merinder, 2004). The number needed to treat (NNT) with psychoeducation in addition to standard care was 9. However, while still supporting psychoeducation as good clinical practice, the recent National Institute for Clinical Excellence guidelines were ambiguous in their evaluation of the evidence, (NICE, 2002).

1.4 Haloperidol – historic rise and fall in dose

Haloperidol (initially known as R1625) was synthesized by Bert Hermans at the Janssen Laboratories, in Belgium, on 11 February 1958. Animal tests, started two days later, suggested to Paul Janssen and his colleagues that this butyrophenone drug would be of great interest as its action was similar to, but much more powerful, than that of chlorpromazine.

Five weeks after its synthesis, haloperidol was provided to a psychiatrist, Dr C. Bloch, in Brussels. He gave an intravenous injection of two milligrams of haloperidol to a few patients suffering from delirium tremens (Janssen, 1989; Niemegeers, 1989). In a letter Bloch described his first patient as "a young woman of 25 years old with a good physical condition who presented an emotional crisis (hypermotricity). A slow injection of 1ml was immediately followed by a slight sedation and three minutes later by drowsiness. Three hours later, the sedative reaction was still present, but to a lesser extent. Her blood pressure decreased from 120/70 to 95/70 mmHg while her heartbeat went from 25X4 (excitation) to 19x4 (sedation)" (Granger and Albu, 2005).

The first article on R1625, originating in Liège, was published in Acta Neurologica et Psychiatrica Belgica, and entitled "R1625: a new symptomatic treatment of psychomotor agitation" (Divry et al., 1958). In this study of 18 agitated patients, the authors concluded that haloperidol was a "powerful sedative of agitation" and "the excellence of the sedative action of R1625 upon psychomotor agitation is such that this drug has become of common usage (in the same year as its synthesis!) in our hospital department". There was no mention of neurological effects.

In their second publication (Divry et al., 1959), entitled: "Study and clinical experimentation of R1625 or haloperidol, a new neuroleptic and neurodysleptic", they reported "the brilliant effects obtained intravenously in the symptomatic treatment of agitation have led us to continue the experiment … The first results published here are enough to show, as we had guessed during episodic injections, that R1625 is not a basic sedative but a genuine neuroleptic" (Granger and Albu, 2005).

The subsequent clinical studies confirmed that this new agent was particularly effective in the treatment of delusions and hallucinations. In 1960, 15 reports were published in Acta Neurologica and Psychiatrica Belgica. Since those initial experiments hundreds of studies have followed.

In a review of haloperidol efficacy the randomised studies showed a clinically significant reduction in psychotic symptoms over placebo after 6 months of treatment when compared to placebo (Joy et al., 2001).

Of interest to the present study are the varying dosages of haloperidol that have been prescribed over the decades. Dosing seemed to have started very low (Divry, 1958 and 1959;), peaked at 100mg/day or more and now returned to the initial doses of 2-4 mg (seminar data).

Several studies have reported the use of very high haloperidol doses of 75 mg (Paquay and Brasseur, 1976) and 60 mg per day, where the 'tolerance was always good' (Lavagna et al., 1976). McCreadie and McDonald (1977) reported in the British Journal of Psychiatry on a 3-month, double-blind, chlorpromazine-controlled trial, high dosage haloperidol study using 100 mg haloperidol daily in drug resistant schizophrenia in-patients. "Serious extrapyramidal side effects were not seen at high doses. However,

the majority of patients on haloperidol showed deterioration in ward behaviour, possibly related to drowsiness".[1]

Meanwhile, across the Atlantic, rapid neuroleptization was rampant with doses of 1-30mg being used, with a maximum daily dosage of 100 mg (Donlon et al., 1979).

In a randomised study comparing haloperidol low dose (mean: 20 mg/day) to high dose (mean: 58 mg/day) the authors reported no difference in efficacy or side effects and concluded "Administration of higher oral haloperidol doses cannot be recommended as a standard procedure" (Modestin et al., 1983).

As recently as 1989, a Greek study reported the effective use of haloperidol doses up to 60 mg per day, which were associated with a significant decrease in serum testosterone levels in 15 male patients (Rinieris et al., 1989).

In 1991 Rifkin et al. reported a 6-week study where 87 patients were randomized to receive 10, 30 or 80 mg/day of haloperidol. Survival analysis showed no differences among the three treatments, side effects were minimal in all three treatment groups with no differences among the groups. They suggested that haloperidol dosages higher than 10 mg/day for most patients have no additional beneficial effect in the treatment of acute or exacerbated schizophrenia (Rifkin et al., 1991).

By 1993 there was a "trend towards lower neuroleptic dosing in the treatment of psychosis" but there were still patients receiving doses of 40-80 mg/day. In their study Remington et al. (1993), reported on a successful dose-lowering study. A similar study in Canada saw mean doses successfully reduced from 62 to 30 mg/day (Leblanc et al., 1994). Similar results were later reported by Volavka et al. (2000).

However, in 1994, a study in Taiwan (Chang et al., 1994) reported on the treatment of 60 schizophrenia patients with high to very high doses of 40-200 mg/day haloperidol. The researchers noted, "All patients safely tolerated the high haloperidol dosages and only five patients had extrapyramidal side effects that were unresponsive to anticholinergic medication". They also added that therapeutic improvement was not observed in each patient.

[1] A personal observation: The highest reported dose of haloperidol suggested by a seminar participant was in 1998, from a British psychiatrist who surprised us all by stating that he routinely used 150 mg/day of haloperidol for his acutely psychotic patients, without serious side effects.

Illustrating the dangers of excessively high doses of haloperidol, a case report described a severely agitated patient who received 80 mg of intravenous haloperidol: "The results of the electrocardiogram were consistent with torsade de pointes and showed a prolonged QTc interval of 610 milliseconds. Magnesium sulphate controlled the arrhythmia, … but bravery and persistence prevailed and the patient received one additional 80 mg haloperidol dose six hours after the arrhythmia-triggering dose, without reoccurrence of torsade de pointes (total dosage 915 mg over 7 days). Haloperidol was then discontinued" (O'Brien et al., 1999).

In a sudden turn around, a dose of 4 mg/day of haloperidol was found to be as effective as a dose of 10 and 40 mg (Stone et al., 1995). In 1997 Zimbroff et al. published a sertindole versus haloperidol versus placebo-controlled study. This study has been called "the haloperidol dose finding study" because doses of 4, 8 and 16 mg of haloperidol were randomly assigned. Efficacy was similar for the three groups, although side effects were significantly reduced in the 4 mg group, but this group still had significantly more side effects than the placebo group (Zimbroff et al., 1997). This raised the question of whether there is an effective yet EPS-free haloperidol dose.

In contrast to most earlier studies, Oosthuizen et al. (2001) from South Africa reported an open label, dose-finding study in 35 patients with first-episode psychosis, employing ultra-low haloperidol doses. After 12 weeks, 16 patients (55%) had stabilized on 1 mg/day or less, and 29 (83%) were stable on a mean dose of 1.78 mg/day. There were no significant differences in mean EPS ratings between baseline and 12 weeks. Ultra-low doses of haloperidol were found to be effective and well tolerated in first-episode psychosis. This study replicated one of the core messages from McEvoy et al. (1991), that low dose haloperidol can be effective if the initial dose is maintained for a sufficient period of time to allow the medication to take full effect. In a further randomised, double-blinded study Oosthuizen et al. compared 20 patients treated with 2 mg/day haloperidol against 20 patients treated with 8 mg/day haloperidol. There were no differences in efficacy between the groups, while there were significantly fewer EPS in the 2 mg/day group (Oosthuizen et al., 2004).

The first dose of haloperidol given in 1958 was 1 mg. In the subsequent years the dose gradually increased to exceed 100 and 150 mg per day, but was also studied in a dose as high as 200 mg per day. Since the beginning of the 1990s the dose has rapidly declined again to the latest studies showing significant effect with a low level of side effects at approximately 1-2 mg per day.

In short, lower haloperidol doses may be as effective as the higher dose ranges and result in fewer adverse effects (Waraich et al., 2002).

1.5 Evidence-based medical education

Psychiatry, as with other branches of medicine, has changed profoundly over the last few decades, with continual advances and changes in available information in the field of schizophrenia.

The rate of change in medical technology is now so fast that it is estimated that 50% of all knowledge is out of date within 5 years; therefore, the need for doctors and allied professionals to remain informed about the latest management techniques is greater than ever (Souery and Mendlewicz, 1995).

These changes include the new data on the epidemiology of disorders, adaptation of diagnostic criteria, refinement of diagnostic categories, aetiological changes, recent attention to early intervention strategies in prodromal stages of the disease, replacement of the conventional antipsychotics with the new generation drugs as well as the re-introduction of clozapine for treatment resistant cases. Regular introduction of new antipsychotics, changes in dosing recommendations, the mass discharge of many patients from long-term in-patient care, the greater recognition of the need to supplement physical treatment with more active psychosocial interventions for both the patient and particularly for the family (Singh, 2005), and then publication and updating of international treatment guidelines have also occurred. All these factors make it essential that psychiatrists be kept informed of updates and changes, preferably from scientifically reliable sources.

Evidence-based medicine (EBM) is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients, which implies clinicians integrate individual clinical expertise with the best available external clinical evidence from systematic research (Sackett et al., 1996).

In recent years there has been an understandable and growing focus on the importance of Evidence-based Medicine (EBM). Clinicians still fail to adequately recognise that in the case of burdensome psychiatric disorders they should practise high quality medicine; they should be able to justify their decision-making under all (or nearly all) circumstances, while still applying judicious economic efficiency (Stein et al., 2002).

Goldner and Bilsker described evidence-based medicine, and its role in education, in their seminal paper in 1995 (Goldner and Bilsker, 1995). Evidence-based psychiatry requires that psychiatrists base their clinical decision-making not so much on lecture-styled training or traditional treatment practice (which is not necessarily the same as clinical experience) as on high-quality research evidence.

However, in psychiatry there are still large knowledge caveats creating important residual clinical uncertainties. Among these is the role of new generation antipsychotics, the duration of treatment before a patient is considered non-responsive and the prioritisation of strategies when non-response occurs. However, answers to any of the questions regarding optimal treatment in psychiatry require several large, but simple, randomized trials.

Implementing EBM primarily requires a practical, problem-based method of learning that allows clinicians to keep up with the ever-increasing research data and new literature to ensure that important research findings can be integrated into clinical practice so that patients benefit from the best possible care (Geddes and Carney, 2001). The successful introduction of evidence-based practice into psychiatry will require the acquisition and sustained application of new skills. These include the ability to read and select credible research results, grasp basic standard statistical methods and understand the applicability of these data to their practise of psychiatry.

Psychiatrists seem to recognise the need for EBM. In a survey of psychiatrists in Scotland (Lawrie et al., 2000), only 40% of respondents thought their practice was evidence-based. They contended that a lack of time was the greatest barrier to implementing evidence-based psychiatry. As many as 70% of psychiatrists and General Practitioners (GPs) in South Africa felt there was a need for regular EBM updates in psychiatry (Siegfried et al., 2003). It also seems there is increasing acceptance of EBM amongst psychiatrists and GPs alike (Geddes and Carney, 2001).

Policy makers should be using EBM in compiling clinical practice guidelines, to assist, not to enforce, clinical decision-making. In the UK, the National Institute of Clinical Excellence (www.nice.org.uk) has been charged with this task.

It is also vital to understand that EBM is an evolutionary and dynamic process. Many current EBM guidelines are based on relatively old data and outdated methods of consensus development. Continual review and updating are required, as well as local

adaptation prior to implementation. Stein et al. (2002) highlighted potential pitfalls of applying guidelines from developed countries in developing countries.

Keeping abreast of change in a world of increasing information is difficult in itself. In psychiatry we are fortunate to be in an exciting field with rapid advances in our understanding of psychiatric disorders and the possible underlying mechanisms in the brain. Coupled to that is an expectation that we are able to deliver improved, and often more rapid, outcomes, with improved quality of life for our patients. To achieve this, psychiatrists need to be able to evaluate, select and implement best-practice principles in the care of their patients through continual education that draws on the latest research and most recent publications. Evidence-based medicine is vital.

1.6 Current literature on the effects of Continued Medical Education

Clinical education:
"the science, the art, and the heart of medicine"
(Atchley, 1959)

"Hippocrates (b. c. 460 BC, island of Cos, Greece — d. c. 377, Larissa, Thessaly) appears to have travelled extensively in Greece and parts of Asia Minor practicing his art and teaching his pupils" (Atchley, 1959). This description possibly illustrates the separation on the one hand between the art and practice of medicine, and on the other hand, the science and teaching of medicine. Medical education with its clinical decision-making is no doubt one of the areas where science and art are intricately interwoven. Atchley (1959) describes clinical teaching as a synthesis of "the science, the art" which then becomes "the heart of medicine".

The conflict between the art and science of medical practice has always posed problems for medical education (Weatherall, 2006). Medical curricula have changed radically in an attempt to develop the best students into the best doctors they can be. When the great English physician, Thomas Sydenham, returned to England after the Civil War to study medicine at Oxford, he was not impressed with what he saw. He is believed to have said that "It was better to send a man to Oxford to learn shoe-making than to practise medicine!" (Weatherall, 2006).

The question is how science, medicine and medical practice integration are related to the crucial issue of the character of medicine (Labisch, 2000), particularly as a result of the

explosion of medical information and the changes brought about in international medical curricula in the past 20 years. Since the beginning of the previous century there have been several major changes in the way medicine is taught, from a basic science approach in the early 20th century, to organ-based approach started at Case Western Reserve University and, more recently, a problem-based approach, first started at McMaster University in Montréal, Canada.

During the recent decades of development it has become clear that medicine will never become a pure science, not even an applied science (Labisch, 2000), despite the tremendous increase in our scientific understanding of the biological underpinning of psychiatric disorders. To benefit from expanding scientific data, however, further education has become necessary to keep clinicians up to date. Continued Medical Education (CME) was formalised as a method to maintain or even improve trained clinicians' knowledge and skills.

Changes resulting from CME have been studied in various settings. The attitudes to and participation in CME activities, for GPs and psychiatrists, as well as the effect or result of CME are of particular interest to this study.

Two Danish groups have reported on attitudes to, and participation in, CME activities in General Practice in Denmark. The first publication was an audit of 369 GPs who were asked to record their perceived need for training in relation to individual consultations. They identified a need for further education in 16% of all consultations. Psychiatry, community medicine and musculoskeletal diseases were the areas of medicine where the greatest need was identified (Hansen et al., 1999).

The second paper reported on participation in CME activities by GPs. The audit found that GPs spent approximately 96 hours per year on CME. In addition they spent 90 hours per year reading textbooks, journals and the Internet, and also 12 hours per year in small group-based CME. The nearly 200 hours per year spent on education exceeded the requirements of their medical organisation (Nielsen et al., 2002).

A similarly positive attitude to implementing continuing medical education (CME) was reported from a survey of psychiatrists in southern Transvaal (a region in the Transvaal province in the pre-1994 South Africa). Sixteen of the 40 psychiatrists in the survey responded. All 16 felt CME was necessary, and most favoured symposia, lectures and congresses activities. While nearly everyone read journals in psychiatric and non-psychiatric fields, group journal reviews, as a form of CME, were categorically rejected.

Most respondents were, however, prepared to contribute time and effort to earn CME accreditation (Freed and Miller, 1979).

The real effects of education have often been discussed and remain highly emotive and controversial. The Internet, international medical journals, congresses and symposia offer a wealth of educational possibilities for psychiatrists and other clinicians after their initial training. However, this field remains difficult to research comprehensively, and few attempts at doing so have been published.

Recognising that depression is frequently unrecognised and under-treated, and there is a need to increase the knowledge and skills of primary care physicians regarding management of depression, Kutcher et al. (2003) initiated a brief educational intervention. They evaluated 68 GPs pre- and post- educational programme where the doctors were trained in depression and its management. In their study doctors demonstrated high baseline knowledge of depression, yet 75% of them still had better scores following the programme. Their study demonstrated that a short, simple educational programme could enhance the participants' knowledge of depression. However, an increase in knowledge alone did not necessarily translate into a change in practice behaviour.

Updating knowledge will not ensure improved treatment. This will happen only if the clinicians put the new information into practice and follow the recommended treatment guidelines. A study was undertaken in the Texas public mental health system of psychiatrists' adherence to depression medication algorithms after being educated on the algorithm with regard to outcome measures, prescribing patterns (correct medications, therapeutic dosing, dosage increases and appropriate medication changes), and visit frequency (Bettinger et al., 2004). The results showed consistently high adherence to appropriate drug regimens at appropriate dosages. Although there was extensive variation in many other outcome measures, it appeared possible to implement medication algorithms in the mental health services that could improve the quality of care provided.

Finally, a study of the effect of psychiatry residency training demonstrated changes in knowledge and measured change in prescribing habits. Alexander et al. (1983) studied the effects of pharmacology education in psychiatry services at a Veterans Administration centre. They conducted a retrospective prescription review of psychopharmacologic treatment methods, before and after education, related to multiple daily dosages, polypharmacy, prophylactic anticholinergic use, and drug use in alcohol

withdrawal. They found that teaching resulted in the use of psychotropic medications that were more in line with recommendations in the literature presented. It appears that education can lead to improved treatment planning and prescription.

From these studies it is possible to conclude that GPs and psychiatrists generally seem to exhibit a positive attitude towards CME, participate at least as well as is required, often apply the new information to their practice, and that the education does in fact change their prescribing habits.

1.7 Study objectives

The overall objective of this study was to understand the effect of education in changing treatment habits, attitudes and behaviour among participants attending schizophrenia seminars presented by the Lundbeck Institute in Denmark. In this respect, the study was descriptive in nature. Explanations of the changes, or lack of changes, in behaviour are also presented. What was of particular interest was whether variation existed in these changes in different seminar participants and why some participants changed their behaviour and others did not.

To summarise: the question was firstly whether knowledge, attitudes and behaviour were affected by the seminar, and secondly, to explore variation/differences in changes among participants.

The study focused on the three domains of change in knowledge, attitude and behaviour. These three areas were studied by means of measuring change in the following topics within schizophrenia treatment:

- Haloperidol doses prescribed
    - Effective dose in the acute treatment of psychosis
    - Minimum effective dose in the relapse prevention phase
- Duration of treatment
    - First-episode patients
    - Multi-episode patients
- Drug-class used
    - Conventional versus new generation antipsychotic drugs

The domains of change were studied by analysing the effects of the seminar using participant questionnaires, two weeks before the seminar, compared with two weeks and six months after the seminar. The three areas were primarily analysed by looking at the

changes between the pre-questionnaire and the 6-months questionnaire for each variable.

Additionally, it was important to be aware that change in behaviour was not always needed. For example, learning was not needed where the psychiatrist treated patients within the desired ranges before the seminar. Therefore, the focus on change was not an entirely valid reflection of the success of the seminar. This was a major reason for focusing on variation in results, by identifying the effect of the seminar on those participants who needed to change behaviour versus those who did not need to change.

Structure

The structure of this study follows the two-fold purpose of description and explanation.

- Chapter 3 presents the results in the key areas of learning.
- Chapter 4 reports on the changes in behaviour, together with a short discussion of the relevant test-statistics and whether the changes in knowledge, attitude and behaviour could be attributed to the seminar.
- Chapter 5 addresses the variables that could influence learning.
- Chapter 6 tries to explain the changes described in chapters 3 and 4.
- Chapter 7 performs bi-variate and multivariate tests of the different explanations.

Overall the study focused on changes in knowledge, attitude and, ultimately, reported behaviour after participation in the seminars, and how these changes could be explained. In order to measure these changes the questionnaire data were used. The assumption was that changes in answers from the pre-seminar questionnaire to the 6-months questionnaire could be ascribed to the seminar.

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Chapter 2 Methods

2.1 Subjects – recruitment and selection

2.2 Demographics

2.3 Assessment measures and questionnaires

2.4 Ethical considerations

2.5 Statistical methods

Chapter 2 Methods

2.1 Subjects – recruitment and selection

This study measured data collected prospectively from 408 psychiatrists from 29 countries who attended the first 16 schizophrenia seminars. The Lundbeck Institute in Denmark from August 1997 hosted these seminars until October 2001.

The sample of participating countries and psychiatrists was neither random nor representative. There was no standard recruitment process in place; the psychiatrists were selected to attend the seminars in different ways in various countries and each country used different criteria in their selection/invitation procedure. In some countries psychiatrists were invited by the local Lundbeck office, in other countries a local psychiatric organisation or representative office selected the participants, while in yet other countries participants were nominated or they applied personally to a selection committee. The selection process of the attendees is clearly a significant limitation in the design of the study.

The number of psychiatrists from each country was also not a representative sample of the country's psychiatry specialists. This represents a major limitation to the study data, particularly that the data cannot be extrapolated to reflect the standard and quality of care in the different countries.

However, it is possible to assume that those who attended these "evidence-based medicine" seminars were psychiatrists more interested in benefiting from further education in their field, or in education as a whole. Were this the case, this fact may indeed strengthen the results of this study, since these psychiatrists, already interested in evidence-based education, may be following these principles closely and therefore be less likely to learn and change practise due to the seminar.

2.2 Demographics

The pre-seminar questionnaire collected data about participants' demographics. Not all participants answered the questionnaire, nor did all who responded answer all questions. However, 95.5% (390 of the 408) did supply at least some of their demographic data.

The demographics-Table 1 lists the number of participants from the different countries.

Demographics-Table 1:
Country of origin of seminar participants

	Seminar participants (n=408)	
Australia	15	3.7%
Austria	20	5.0%
Belgium	26	6.4%
Canada	5	1.2%
Czech republic	10	2.5%
Denmark	25	6.0%
Estonia	5	1.2%
Finland	15	3.7%
France	20	5.0%
Germany	30	7.4%
Greece	18	4.4%
Hungary	15	3.7%
Ireland	3	0.7%
Israel	5	1.2%
Italy	29	7.1%
Luxembourg	1	0.3%
Macedonian	2	0.5%
Netherlands	22	5.4%
New Zealand	17	4.2%
Norway	23	5.6%
Poland	15	3.7%
Russia	5	1.2%
Slovakia	5	1.2%
Slovenia	5	1.2%
South Africa	15	3.7%
Spain	20	5.0%
Sweden	10	2.5%
Switzerland	15	3.7%
United Kingdom	12	3.0%
Total	**408**	(100%)

The pre-seminar questionnaire asked participants about their primary place of work. The results are presented in Table 2.

Demographics-Table 2:
Workplace of respondents in pre-seminar dataset

	Pre-dataset (n=386)	
University Hospital	140	36.3%
District or General Hospital	93	24.1%
Private Practice	7	1.8%
Specialised Psychiatric Hospital	132	34.2%
Other	14	3.6%

Other demographic data collected included years of experience in psychiatry, number of patients seen per month and the percentage of those patients who had been diagnosed with schizophrenia. Again, not all seminar participants returned the questionnaire, or answered all questions.

Demographics-Table 3:
Other demographics of pre-seminar dataset

Pre-seminar dataset		Mean	Std. Deviation
Years of experience in psychiatry	(n=390)	13.3 years	7.42
Number of patients seen per month	(n=390)	79.0 patients	67.80
Percentage of patients with schizophrenia	(n=229)	37.3%	24.24

The available demographic data of the seminar participants was limited to the information deemed important to measuring the effect of education. We did not collect data on other traditional study demographics such as age, gender, social or financial background. Although one cannot assume that these factors do not have an effect on education, it should be borne in mind that this was a population of psychiatrists where these factors *should not* influence the standard of knowledge or the quality of care provided to schizophrenia patients. However, this may not be true, and should be seen as a limitation in the design and interpretation of this study.

Only the **paired data** was used for analyses. i.e. only the data of the respondents who returned *both* the pre-seminar questionnaire and the 6-month post-seminar questionnaire. The respondent numbers and the validity of the paired respondents' data are addressed in Chapter 4, section 4.

2.3 Assessment measures and questionnaires

Participants attending the seminars were sent a pre-seminar questionnaire (Appendix 1, page 135) in the month preceding their attendance. This questionnaire elicited the psychiatrist's baseline knowledge and attitude, as well as their treatment practice in two case studies. The two cases are used to differentiate the "intended behaviour", as measured by the questions, from the "actual behaviour", which is recorded in the case studies of two patients. After attending the seminar, the participants were first sent a 2-week follow-up questionnaire (Appendix 2, page 151) and then a 6-month post-seminar questionnaire (Appendix 3, page 158). The data for this study were collected from the returned questionnaires.

The questionnaires were designed to collect many different data, including participant demographics (years of experience in psychiatry, practice setting, patient load), knowledge questions relating to schizophrenia (relapse rates, suicide rates), and its treatment (optimal doses, treatment duration, choice of drug), as well as questions aimed at evaluating attitudes to the disease and its diagnosis and treatment (duration before a non-response judgement, psychoeducation, and quality management). These data were collected anonymously but could be linked to a participant's number or nationality. The differences in treatment habits and attitudes in the various countries, or even within a specific country formed the basis for the discussions at the seminars.

2.4 Ethical considerations

Ethical approval was not sought for this study. According to the regulations of the Office for Human Research Protection in the United States (with which the Committee for Human Research of the Faculty of Health Sciences, University of Stellenbosch is registered), retrospective studies such as this one are exempt from full ethics review, as long as they involve the study of existing records, and the information was collected and recorded in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

Written informed consent was not obtained from the participants in this study. However, before participants were asked to complete the questionnaires they were fully informed of the nature of the questionnaire and the fact that the information obtained was to be used to assess the effectiveness of the seminar in a later analysis. They were also informed that their responses would remain anonymous. Care was taken to preserve the anonymity of the participants. No identifying details were requested in the questionnaire. Details were entered into the database according to a participant number.

2.5 Statistical methods

All statistical analyses were conducted with the help of a biostatistician. Differences between the pre-seminar dataset and the 6-months post-seminar dataset were analysed by using either a paired samples t-test or cross-tabulation and McNemar test.

The two datasets (the pre-seminar and the 6-months post-seminar) may be described as dependent because the respondents of the 6-months and pre-seminar questionnaire were theoretically the same, even though not everybody who filled in the pre-seminar

questionnaire filled in the 6-months post-seminar questionnaire. The paired samples t-test was therefore adequate because the test is designed to take account of the dependency between the groups.

The paired t-test was approached circumspectly because the 6-month dataset might not have the same distribution of respondents as the pre-seminar dataset. There could be a problem if, for instance only the "good learners" filled in the 6-months post-seminar questionnaire (see below). However, as the next sections show, this was not the case, so the paired samples t-test could be used. The test compares the means on a given variable e.g. duration of treatment.

Furthermore, this study also included variables that cannot be quantified, e.g. the factors influencing the selection of the antipsychotic drug-class used. In order to analyse changes in the drug-class used, cross-tabulation tables were made of the class of drug in the pre-seminar and the 6-months post-seminar dataset. A test was also performed to determine whether respondents' changed answers, i.e. determining whether "learning" had occurred (meaning the seminar had an effect). To ascertain whether the differences in the cross-tabulation tables or between the binary categorical variables were significant, McNemar's test was used. This test determines whether the answers in the pre-dataset equal the answers in the 6-months dataset. The test is especially good at detecting changes in answers due to experimental intervention (e.g. a seminar) in a before-and-after design.

The changes in haloperidol prescribing behaviour were investigated using multivariate-dummy-regression (see chapters 6 and 7).

Regression analysis investigates the relationship between a single dependent variable e.g. change in haloperidol dose, and several independent variables e.g. nationality, years of experience, caseload, workplace. The objective is to use the independent variable(s), whose values are known, to predict a single specified dependent variable.

Dummy variables are a way of adding the values of a nominal or ordinal variable to a regression equation. The value of each categorical independent variable with the exception of one is entered as a dichotomy. For instance, to test whether a difference exists between Norway, Denmark and Sweden, the nominal variable "Country" creates a set of dummy variables. (Denmark = 1 if the unit is from Denmark, otherwise 0; Norway = 1 if the unit is from Norway, otherwise 0) One class must be left out to prevent perfect multicolinearity in the model (in our example Sweden is left out).

In these analyses the dummy variable was given the value 1 if the respondent was on the outside of the target before the course. For example, a respondent might recommend 10 months treatment of first-episode schizophrenia before the course. This respondent's recommendation is below the internationally recommended target. If the dummy variable was significant, the duration of treatment recommended by participants would change in a significantly different way from those whose recommendations were above the target. However, it would still not be clear whether the change was in the intended direction. When the dummy is positive, it indicates that those who were below the target before the seminar increased the duration of their treatment after the seminar.

Chapter 3 Results

Chapter 3 Results

3.1 Haloperidol doses

The haloperidol dose was analysed in respect of both the most *effective haloperidol dose* to treat acute episodes of schizophrenia and the *minimum effective haloperidol dose* that could be prescribed without increasing the relapse risk.

Table 1: Mean of respondents' selected effective haloperidol dose to treat acute schizophrenia, before and 6 months after attending the schizophrenia seminar

	Mean	Std. Deviation
Before the seminar	8.6 mg/day	5.3
6-months after the seminar	7.4 mg/day	3.6

n=122, paired samples t-test: t=3.03; p=0.003

The results in Table 1 indicate a difference in the selected effective haloperidol dose by respondents before the seminar and 6-months after the seminar i.e. it dropped from 8.6 mg/day to 7.4 mg/day, more in line with the internationally recommended effective haloperidol dose of approximately 5 mg/day. Despite a big standard deviation, the difference is statistically significant (p=0.003).

The large standard deviation indicated a degree of variation amongst respondents. Also, many respondents recommended the internationally accepted effective dose before the seminar and therefore did not need to change ("learn"). Thus it was more useful to evaluate the change in dosing regime of participants who recommended a haloperidol dose above 5 mg/day i.e. needed to "learn". Such an analysis focused more directly on the learning effect of the seminar, removing the effect of those who were already using the recommended dose beforehand. The analysis, which allows isolation of the behaviour of the participants using a dose above 5 mg/day before the seminar, is a simple cross-tabulation of the dose before the seminar and 6-months after the seminar.

Table 2: Effective haloperidol dose to treat acute schizophrenia: actual numbers and percentage of total respondents above or below 5 mg/day pre- and post-seminar

		Use of haloperidol 6-months after the seminar	
		Above 5 mg/day	**Below 5 mg/day**
Use of haloperidol	**Above 5 mg/day**	59* (49.6%)**	22 (18.5%)
before seminar	**Below 5 mg/day**	13 (10.9%)	25 (21.0%)

n=119, * *number of respondents*, ** *percentage of total respondents*
McNemar test of changes p = 0.176

Table 2 shows that 49.6% of the respondents selected a dose above 5 mg/day before the seminar and after the seminar, 21% chose below 5 mg/day before and after the seminar, while 18.5% chose above 5 mg/day before the seminar and below 5 mg/day after 6 months. However, 10.9% moved in the other direction - from below 5 mg/day before the seminar, to above 5 mg/day after the seminar. Therefore, even though significant change in the "magnitude" of pre- and post-seminar dosing behaviour occurred, the "direction" of these changes was not statistically significant.

Of interest is that close to half the psychiatrists knew the "correct" dose before the seminar - therefore not needing to "learn", whereas 50% did need to "learn". More interestingly, 18.5% who selected above 5 mg/day before the seminar chose below 5 mg/day after the seminar ("learned"), whereas 10.9% moved in the opposite direction i.e. "unlearned".

These results indicate that the seminar did not have a uniform effect on the participants. (i.e. changes did not all occur in the one direction; some went from above 5 mg/day to below and vice versa, while others did not change at all). The McNemar test of changes yielded a p-value of 0.176 indicating that the changes in effective haloperidol dose to the internationally recommended dose of below 5 mg/day were not significant. This is somewhat surprising because Table 1 shows that the haloperidol dose was significantly reduced on average from before the seminar to after the seminar. Consequently, it seems as if the knowledge of participants changed in the intended direction, though the change was not statistically significant in respect of the below 5 mg/day target.

Table 3: Mean of respondents' selected minimum effective haloperidol dose for schizophrenia relapse prevention, before and 6-months after attending the seminar

	Mean	Std. deviation
Before the seminar	4.9 mg/day	3.9
6-months-after the seminar	4.1 mg/day	2.9

n=96, paired samples t-test: t = 1.79; p=0.076

The internationally accepted recommended minimum effective haloperidol dose is approximately 2-3 mg/day. Results in Table 3 show that the average minimum effective dose selected by respondents before the seminar was 4.9 mg/day, and after the seminar 4.1 mg/day; this was not considered a statistically significant change (p=0.076). However, there was wide variability in responses, as evidenced by the substantial standard deviation and may explain why this difference was not considered significant.

The factors behind the apparent variation in learning among participants are analysed in Chapter 5.

Since many psychiatrists knew the minimum effective dose before the seminar, it was therefore again useful to evaluate behaviour of the participants who recommended a haloperidol dose above 3 mg/day before the seminar.

Table 4: Minimum effective haloperidol dose in schizophrenia relapse prevention: numbers and percentage of total respondents above or below 3 mg/day before and 6-months after the seminar

		Haloperidol dose 6-months after the seminar	
		Above 3 mg/day	**Below 3 mg/day**
Haloperidol dose before the seminar	**Above 3 mg/day**	37* (39.8%)**	19 (20.4%)
	Below 3 mg/day	7 (7.5%)	30 (32.3%)

n=93; * *number of respondents*, ** *percentage of total respondents*
McNemar test of changes p = 0.031

Table 4 shows that 39.8% of the respondents were above 3 mg/day before the seminar and 6-months after the seminar, while 32.3% recommended 3 mg/day or less both before the seminar and 6-months after the seminar. More interestingly, 20.4% who were above 3 mg/day before the seminar were below after the seminar, whereas only 7.5% moved in the opposite direction. Note that before the seminar nearly 40% of the psychiatrists were using the recommended minimum effective dose of haloperidol, therefore not needing to "learn", whereas 60% did need to "learn". Of importance was that 20.4% of the participants moved ("learned") in the intended direction. This change was statistically significant. Analysed in terms of the 3 mg/day target, significant changes occurred in the behaviour of the participants. However, the change was not necessarily due solely to effects of the seminar – as explained in Chapter 4.

To conclude, significant changes occurred with regard to both the selected effective dose and the selected minimum effective dose of haloperidol, 6-months after the seminar. However, establishing that changes in haloperidol dosing behaviour pre- and post-seminar occurred is not evidence that the seminar was responsible for these changes. This is examined in the following chapters.

3.2 Duration of treatment

The internationally accepted recommended minimum duration of treatment for first-episode schizophrenia patients is 18 months.

Table 5: Mean selected duration of treatment before the seminar and 6-months after the seminar, for first-episode schizophrenia patients

	Mean	Std. deviation
Before seminar	16.7 months	10.9
6-months-after the seminar	17.5 months	7.9

n=124, paired samples t-test: t = 0.86; p=0.39

The selected duration of treatment for first-episode schizophrenia patients increased after the seminar towards the recommended minimum treatment period of 18 months. However, the magnitude of the change was not statistically significant.

The wide variation in the answers, reflected in the large standard deviation, could indicate that the effect of the seminar (change in knowledge and behaviour) was influenced by certain characteristics of the respondents. Changes in behaviour may be due to specific characteristics of the psychiatrists. One hypothesis is that the effect of the seminar was different for psychiatrists with few years of experience compared with those of many years experience. Potentially, psychiatrists with less experience can learn more than psychiatrists with many years of experience i.e. who have entrenched treatment practices. This hypothesis is tested in Chapter 6. Other variables that may affect the influence of the seminar are described in Chapter 5.

The internationally recommended minimum duration of treatment of multi-episode schizophrenia patients is 60 months.

Table 6: Mean selected duration of treatment before the seminar and 6-months after the seminar, for multi-episode schizophrenia patients

	Mean	Std. Deviation
Before the seminar	38.7 months	19.4
6-months-after the seminar	45.9 months	17.8

n=120, paired samples t-test: t = 4.81; p < 0.0001

Table 6 indicates that treatment behaviour had altered significantly 6-months after the seminar ($p < 0.0001$), increasing from 38.7 months pre-seminar to 45.9 months post seminar. However, there was considerable variation in the responses after the seminar (sd = 17.8).

It is not immediately apparent why the selected duration of treatment of multi-episode patients changed significantly 6-months after the seminar, whereas the selected treatment duration for first-episode schizophrenia patients did not change significantly. However, the substantial variation in the answers after the seminar suggests that there

may be subsets of participants who changed their prescribing habits significantly. Further understanding of this variation is explored in Chapter 6 by analysing respondent characteristics to explain the differences in learning of the psychiatrists.

3.3 Drug-class used

The last of the three areas of interest concerns the selected antipsychotic drug-class. In this study, antipsychotics were categorised into two groups: conventional and new generation. The conventional antipsychotics included haloperidol, flupenthixol, zuclopenthixol, perphenazine, trifloperazine and sulpride. The new generation antipsychotics included risperidone, olanzapine, quetiapine, ziprasidone, amisulpiride, clozapine and sertindole.

Two different types of behaviour were analysed concerning the drug-class - *intended* (i.e. as measured by the differences in knowledge in the pre-seminar questionnaire and the post-seminar questionnaire) and *actual* (i.e. as measured by the differences in treatment options chosen in the *case reports* in the pre-seminar and post-seminar questionnaires). The interest was in determining firstly whether a difference existed in the *intended* drug-class used before and after the seminar, and secondly, whether the *actual* drug-class used also changed after the seminar. Finally, the correlation between the intended and actual drug-class used was investigated.

3.3.1 Intended drug-class used before and 6-months after the seminar

The intended drug-class was analysed in respect of both first-episode and multi-episode schizophrenia patients.

Table 7: "Intended" drug-class used before and 6-months after the seminar for first-episode schizophrenia patients: total number and (percentage of total)

		Drug-class used 6-months after the seminar			
		New Generation		**Conventional**	
Drug-class used before the seminar	**New Generation**	55*	(55%)**	6	(6%)
	Conventional	23	(23%)	16	(16%)

n=100, * *number of respondents, ** percentage of total respondents*
McNemar test of changes p = 0.003

Table 7 shows that 55% of the participants intended to use new generation antipsychotics before the seminar and 6-months after the seminar and 16% used conventional antipsychotics before the seminar and 6-months after the seminar. In total 71% of the participants did not change their preferred drug-class. Of the remaining 29%, 23% substituted conventional with new generation antipsychotics, while 6%

intended to swap from new generation antipsychotics before the seminar to conventional 6-months after.

These changes in intended drug-class for treatment of first-episode schizophrenia patients were significant (p=0.003). However, they were not necessarily due to the effects of the seminar. Chapter 4 analyses whether certain pre-conditions are fulfilled.

Table 8: "Intended" drug-class used before and 6-months after the seminar for multi-episode schizophrenia patients: total number and (percentage of total)

		Drug-class used 6 months after the Seminar	
		New Generation	**Conventional**
Drug-class used before the seminar	**New Generation**	48* (50.5%)**	5 (5.3%)
	Conventional	21 (22.1%)	21 (22.1%)

n=95, * *number of respondents, ** percentage of total respondents*
McNemar test of changes p = 0.003

Table 8 shows that 72.6% of the respondents did not change their intended behaviour 6-months after the seminar when treating multi-episode schizophrenia patients; 50.5% used new generation both prior to and 6-months after the seminar and 22.1% used conventional drugs prior to and 6-months after the seminar. The remaining 27.4% changed their behaviour: 22.1% moved from conventional drugs to new generation drugs, while 5.3% changed in the opposite direction.

These changes in intended drug-class for treatment of multi-episode schizophrenia patients 6-months after the seminar were highly statistically significant (p=0.003).

3.3.2 Actual drug-class used before and after the seminar

Actual changes in drug-class used were assessed by asking the delegates how they would manage an acute patient (see appendices 1 & 3, patient case 1, pages 147 & 166) and a chronic (multi-episode) patient (patient case 2, pages 149 & 168).

Table 9: Actual drug-class used before and 6-months after the seminar for acute phase of schizophrenia: total numbers and (percentage of total)

		Drug-class used 6-months after the seminar	
		New Generation	**Conventional**
Drug-class used before the seminar	**New Generation**	22* (45.8%)**	6 (12.5%)
	Conventional	10 (20.8%)	10 (20.8%)

n=48, * *number of respondents, ** percentage of total respondents*
McNemar test of changes p = 0.45

Table 9 shows that two-thirds of the psychiatrists did not change the drug they used (45.8% and 20.8%), while 20.8% changed from a conventional to a new generation drug, and 12.5% changed from a new generation to a conventional drug. It is important to note that the changes were not only in the direction of new generation drugs as was the case of intended behaviour towards first-episode patients (see Table 7, page 62).

Only 48 respondents completed the information about patient 1 before the seminar and after the seminar. Consequently conclusions derived from Table 9 need to be interpreted with caution.

Table 10: Actual drug-class used before and 6-months after the seminar for the treatment of chronic schizophrenia patients: total number and (percentage of total)

		Drug-class used 6-months after the seminar	
		New Generation	**Conventional**
Drug-class used before the seminar	**New Generation**	12* (47.7%)**	5 (7.7%)
	Conventional	8 (30.8%)	1 (3.8%)

n=26, * *number of respondents*, ** *percentage of total respondents*
McNemar test of changes p = 0.109

Table 10 shows more consistency in the changes compared with Table 9. Approximately 50% of the respondents did not change behaviour, 30.8% changed from conventional to a new generation drug, while 7.7% changed from conventional to a new generation drug. Overall there was a clear trend towards the new generation drugs. However, the differences did not meet statistical significance, possibly due to the low number of respondents.

The results indicated that no statistically significant change occurred in the ***actual*** drug-class used from before to after the seminar, as assessed by case report responses. This contrasts with the analysis of the intended drug-class; a significant number of respondents ***intended*** to use new generation antipsychotics 6-months after the seminar. Therefore a difference seems to exist between intended and actual behaviour, indicating actual use does not always follow intention. To test this assumption, Table 11 compared the intended versus actual selected antipsychotic for treating a multi-episode schizophrenia patient (patient 1).

If there were no difference in intended and actual behaviour, 100% of the cases would be in either the cell "new generation/new generation" or in the cell "conventional/conventional".

Table 11: Intended drug-class and actual drug-class used for case "Patient 1" before the seminars: total number and (percentage of total).

		Drug-class intended	
		New Generation	**Conventional**
Drug-class used for patient 1	**New Generation**	47* (40.2%)**	11 (9.7%)
	Conventional	31 (26.2%)	28 (23.9%)

n=117, * *number of respondents, ** percentage of total respondents*
Chi-square test of independence: p = 0.004

The analysis in Table 11 confirms that the intended medication choice was not necessarily the same as the actual choice; approximately 37% of the respondents exhibited inconsistent behaviour. However, these differences are not significant. In statistical terms the actual behaviour is dependent upon the intended behaviour because the Chi-square is below 0.05. In other words the null hypothesis (H_0) assuming independence between intended and actual behaviour is rejected.

(The McNemar test of difference was not used in this instance, as the test compares whether the difference is significant in a particular direction and not whether differences exist overall. The latter is the most relevant when consistency is analysed, whereas the former is relevant when the effect of a seminar is analysed.)

3.4 Summarising changes in selected haloperidol dose, duration of treatment and antipsychotic class used

The preceding sections have analysed the changes in behaviour before the seminar and 6-months after the seminar concerning haloperidol dose prescribed, duration of treatment and drug-class used. In all three areas some, but not all of the prescribing behaviour changed significantly 6-months after the seminar compared with the situation before the seminar. Respondents' selected duration of treatment of first-episode schizophrenia patients did not change significantly 6-months after the seminar. The same was to a certain extent the case with the effective haloperidol dose. Furthermore, and perhaps more interestingly, the actual drug-class used did not change significantly from before the seminar to 6-months after the seminar despite the significant change occurring in the intended drug-class (bearing in mind the small sample size used for the analysis). If the significant change in the intended drug-class was due to the seminar, it would appear that the seminar had more effect on the intended behaviour than on the actual behaviour.

Although significant changes in haloperidol prescribing behaviour were observed, factors other than Institute seminar attendance may be responsible. These factors are discussed in the next chapter.

Chapter 4 Changes in prescribing behaviour due to evolving knowledge over time

Chapter 4 Changes in prescribing behaviour due to evolving knowledge over time

The main purpose of this study was to research changes in knowledge, attitude and prescribing behaviour after participation in an educational seminar. The descriptive part of this study was presented in Chapter 3, where it was determined that changes in haloperidol prescribing behaviour did actually occur. The important question yet to be addressed was whether the changed behaviour, 6-months after the seminar, could be attributed wholly or partly to seminar learning. Several factors other than the seminar may be responsible for these changes.

In order to conclude that the seminar had an effect, a *necessary* condition was that a difference existed between the answers given before the seminar and the answers given after the seminar. However a difference is not a *sufficient* condition for concluding that the seminar had an effect. For example, changes in policies, international treatment guidelines and marketing might occur and influence the psychiatrists' knowledge and attitudes. It would be incorrect to ascribe such changes to the effects of the seminar if this proved to be the case.

Accordingly, two factors of importance concerning the responses before the seminar and 6-months after the seminar were analysed in this chapter. These were the changes in the background knowledge of the psychiatrists over time, and dataset differences between respondents of the pre-questionnaire and the 6-month-questionnaire.

Development in knowledge

It is a fair assumption that the knowledge of participants concerning the treatment of schizophrenia might change over time. In this section the possible effect of changes in background knowledge from August 1997 (when the first seminars were presented) until 2001 (when the last of the seminars included in this study was presented) were studied. A significant difference between delegate responses over time regarding the pre-seminar dataset and the 6-months dataset would suggest that the changes in haloperidol prescribing behaviour described in Chapter 3 were not necessarily a direct result of the seminar, but were due, at least in part, to changes in background knowledge. In order to test this, two analyses were performed.

One analysis compared the mean pre-seminar questionnaire responses of each seminar group over the time course of the seminars i.e. from 1997 to 2001. If there were no

differences between the first eight and the last eight seminars, then it could be concluded that the participants' background knowledge did not change over the years of the seminars.

As there was no control group in this study, the pre-seminar data of the participants in the later seminars will be regarded as the control group for the participants in the earlier seminars (in other words, the pre-seminar data of the 1999 seminar participants acted as the control group for those who participated in 1998. Hence most pre-seminar datasets containing data from the first 18 pre-seminar questionnaires act as the control for the last seminar in this study.) Thus, background changes in treatment principles were evaluated by comparing the pre-seminar data of the earlier participants with the pre-seminar data of later participants.

The second analysis compared the knowledge of delegates 2-weeks and 6-months after the seminar. This test also focused on the development in background knowledge among the participants. However, this analysis used only the data of those participants' who filled in both the 2-week and the 6-months post-seminar questionnaires. One would expect that the effect of learning derived from a seminar declined after 6 months. Bearing this in mind, if knowledge remained unchanged or even increased, this could indicate changes in background knowledge. These changes in knowledge could, in turn, change behaviour. Both analyses tested whether any changes occurred in the key areas of interest: haloperidol dose prescribed, duration of treatment and drug-class used.

4.1 Haloperidol doses

Analysis of pre-seminar questionnaire responses over time

In figures 1 and 2 the variation in the average effective haloperidol dose and the average minimum effective dose, respectively, before the seminars, was plotted.

While Figures 1 and 2 indicate the trend of a slight decrease in the mean haloperidol dose chosen by each seminar group over time (suggesting small changes in general background learning took place), the scatter of results makes this interpretation tenuous.

Figure 1: Variation in the average effective haloperidol dose for treating acute schizophrenia, before the various seminars

The mean result for the pre-seminar selected effective haloperidol dose for each seminar group was plotted against sequential seminars (i.e. from earliest to latest). The line of best fit for individual points was determined using the method of least squares

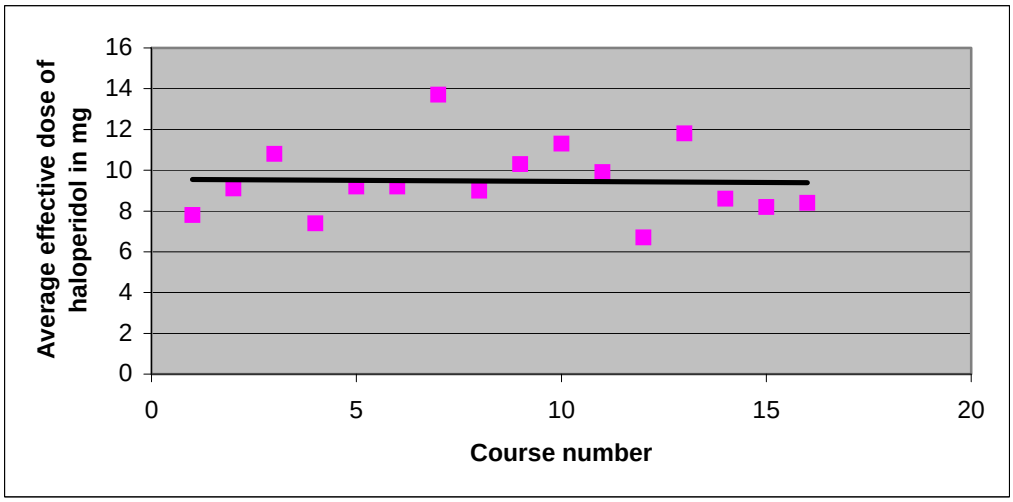
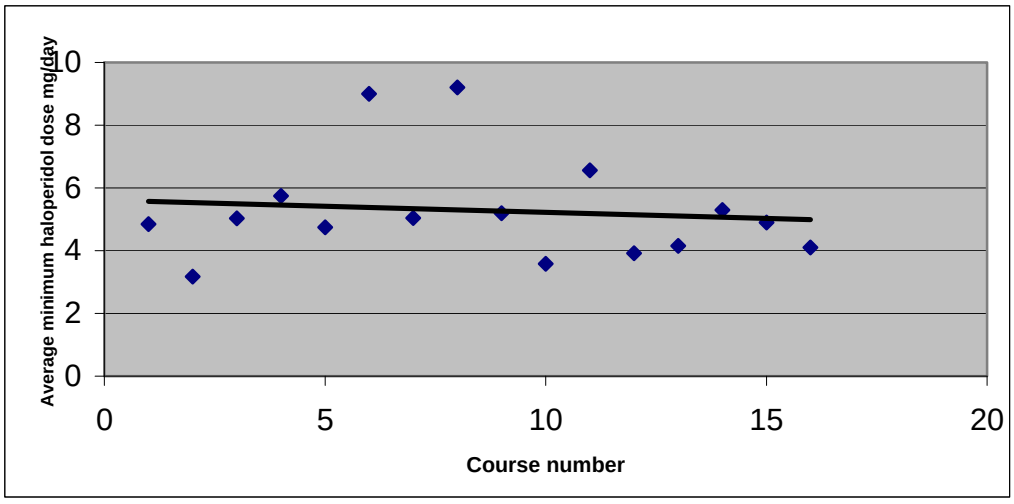


Figure 2: Variation in average minimum effective haloperidol dose for schizophrenia relapse prevention, before the various seminars

The mean result for the pre-seminar selected minimum effective haloperidol dose for each seminar group was plotted against sequential seminars (i.e. from earliest to latest). The line of best fit for individual points was determined using method of least squares.



Further investigation was performed by comparing the average pre-seminar haloperidol dose selected by delegates attending the first 8 seminars conducted ("earlier" seminars) and those attending the last 8 seminars conducted ("later" seminars) – see Tables 12 and 13.

Table 12: Mean selected effective haloperidol dose before the seminar for the "earlier" seminars and the " later" seminars

	Mean	Std. Deviation
Earlier seminars	9.6 mg/day	6.9
Later seminars	9.2 mg/day	6.3

n=377, Independent samples t-test: t=0.59; p=0.556

Table 13: Mean selected minimum effective haloperidol dose before the seminar for the " earlier" seminars and the" later" seminars

	Mean	Std. Deviation
Earlier seminars	5.4 mg/day	5.9
Later seminars	5.3 mg/day	5.9

n=294, Independent samples t-test: t=0.23; p=0.82

Results shown in Tables 12 and 13 confirm there were no statistically significant differences between earlier and later seminars in the pre-seminar average selected effective haloperidol dose (p=0.556), or in the pre-seminar average selected minimum effective haloperidol dose (p=0.82).

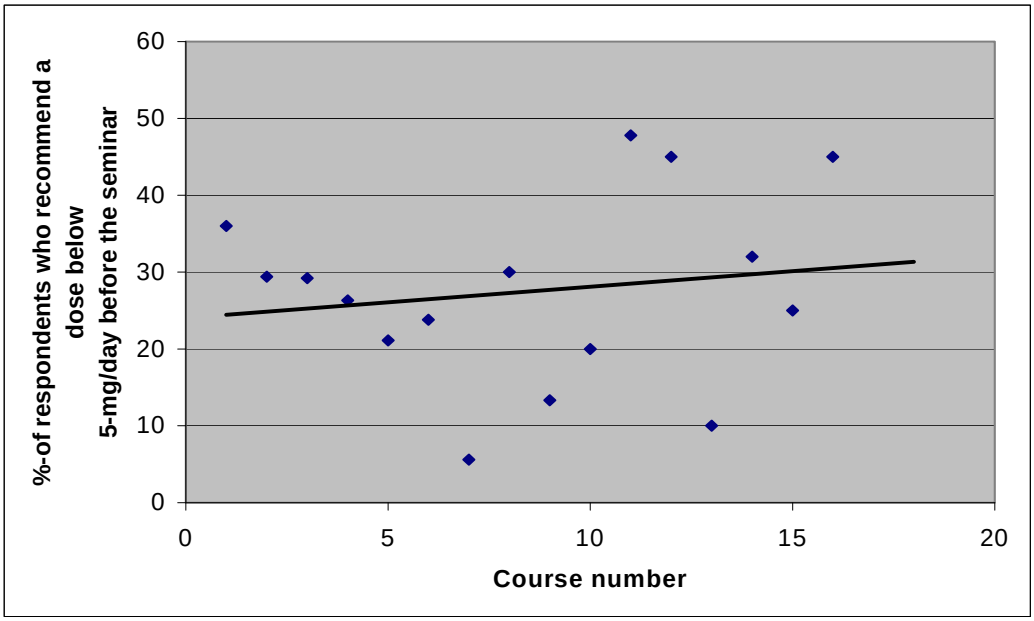
Therefore, no significant systematic difference in effective or minimum effective haloperidol dose selected pre-seminar occurred during the time period over which the seminars were conducted. Therefore, according to these results the changes both in effective haloperidol dose and the minimum effective dose from before the seminar to 6-months after the seminar were not likely due to changes in the background knowledge of psychiatrists.

However, the result was slightly different when the percentage of psychiatrists selecting a dose below the recommended target of 5 mg/day before the seminars were compared.

Figure 3 shows that the percentage of seminar respondents who selected a dose of haloperidol below the 5 mg/day target for the effective haloperidol dose was influenced by the number of the seminar, i.e. when the seminar was held.

Figure 3: Variation in the percentage of respondents who recommended a haloperidol dose below 5 mg/day, before the seminar

Plot of the percentage of pre-seminar respondents who selected an effective haloperidol dose below 5mg/day versus sequential seminars, earliest to latest. The line of best fit for individual points was determined using method of least squares.



The trend-line indicates that the percentage of psychiatrists who selected a haloperidol dose below 5 mg/day, increased over time. These data could therefore explain why the mean effective haloperidol dose was significantly lower 6-months after the seminar, even though the shift towards the recommended target of below 5mg/day was insignificant (see Chapter 3, Tables 1 & 2, page 58).

Table 14: Effective haloperidol dose selected before the seminar (earlier and later seminars)

		Seminar time	
		Earlier seminars	**Later seminars**
Use of haloperidol dose before the seminar	**Above 5 mg/day**	75.3%	66.8%
	Below 5 mg/day	24.7%	33.2%
		(100%)	(100%)

n=377, Chi-square test of independence p = 0.045

Table 14 analyses the data to determine whether there was a systematic difference between the earlier seminars and the later seminars concerning respondents who viewed less than 5 mg/day of haloperidol as the effective dose. In the earlier seminars, 75.3% of respondents were above the target compared with 66.8% in the later seminars. This difference is statistically significant (p=0.045). It indicates that changes in knowledge about the effective haloperidol dose took place over time. It then follows that the

significant change in the average effective haloperidol dose (see Table 1, page 58) could be attributed to a higher percentage of participants in later seminars already selecting less than 5 mg/day pre-seminar i.e. a change in background knowledge and not necessarily a change due to the effect of the seminar.

Figure 4 relates to the minimum effective haloperidol dose. It plots the change in the percentage of respondents who were below the 3 mg/day target (the recommended minimum effective dose discussed at the seminars), pre-seminar.

Figure 4: Variation in the percentage of respondents that recommended a minimum effective haloperidol dose below 3 mg/day, pre-seminar in the various seminars

Plot of the percentage of pre-seminar respondents who selected a minimum effective haloperidol dose below 3mg/day versus sequential seminars, earliest to latest. The line of best fit for individual points was determined using method of least squares.

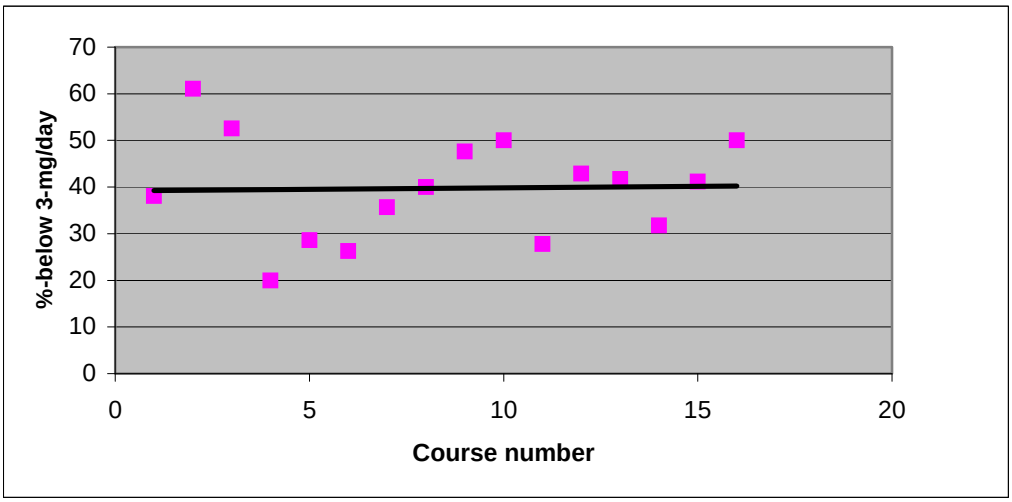


Figure 4 demonstrates there was no systematic change over time in the percentage of those who prescribed below 3 mg/day: the trend-line is almost horizontal. The results in Table 15 confirm this i.e. there was no statistically significant difference found between the pre-seminar minimum effective haloperidol dose selected by "earlier" versus "later" seminar attendees, indicating no significant "background" learning took place.

Table 15: Pre-seminar selected minimum effective haloperidol dose for "earlier" and "later" seminar groups

		Seminar time	
		Earlier seminars	**Later seminars**
Use of haloperidol dose before the seminar	**Above 3 mg/day**	62.4%	59.2%
	Below 3 mg/day	37.6%	40.8%
		(100%)	(100%)

n=294, Chi-square test of independence p = 0.331

To summarise, it seems that the ***effective haloperidol dose*** changes related to the time when the seminar course was given. However, this conclusion did not hold true for the ***minimum effective haloperidol dose***. Therefore, the overall change in the selected effective haloperidol dose was most likely due to changes in background knowledge rather than an effect of the seminar, whereas change in the selected minimum effective dose after the seminar was probably *not* due to changes in background knowledge.

Analysis of changes in responses from 2-weeks after to 6-months after seminar attendance

This section analyses whether changes occurred in responses between 2-weeks after and 6-months after the seminar.

Table 16: Mean selected effective haloperidol dose 2-weeks and 6-months after seminar attendance

	Mean	Std. deviation
2-week post-seminar	7.51 mg/day	5.08
6-months post-seminar	7.27 mg/day	3.55

n=115, Paired samples t-test: t=0.50; p=0.616

Table 16 shows that there was no statistically significant change in the mean selected effective dose between 2-weeks and 6-months after the seminar (p=0.616). General background learning cannot be said to take place in this respect.

Table 17: Mean selected minimum effective haloperidol dose 2-weeks and 6-months after seminar attendance

	Mean	Std. deviation
2-week-post-seminar	4.13 mg/day	2.5
6-months-post-seminar	4.14 mg/day	2.9

n=106, paired samples t-test: t=0.004; p=0.997

Results in Table 17 indicate no significant difference in the mean selected minimum effective haloperidol dose from 2-weeks after to 6-months after the seminar (p=0.997) i.e. general background learning does not seem to take place. Accordingly, this indicates that the changes in selected minimum effective dose from before the seminar to 6-months after the seminar were most likely due to the seminar itself, and not to the effects of "background" learning.

The seminars recommended an effective dose of haloperidol of 5 mg/day and a minimum effective dose of 3 mg/day. It is therefore of interest to know whether changes occurred in respect of this target during the period from 2-weeks after the seminar to 6-months after the seminar.

Table 18: Selected effective haloperidol dose 2-weeks after and 6-months after the seminar: total number and (percentage of total)

		Use of haloperidol 6-months after the Seminar	
		Above 5 mg/day	**Below 5 mg/day**
Use of haloperidol 2-weeks after the seminar	**Above 5 mg/day**	128* (43.5%)**	31 (10.4%)
	Below 5 mg/day	33 (11.3%)	102 (34.8%)

n=294, * *number of respondents, ** percentage of total respondents*
McNemar test of changes p = 0.841

Table 19: Selected minimum effective haloperidol dose 2-weeks after and 6-months after the seminar: total number and (percentage of total)

		Use of haloperidol 6-months after the Seminar	
		Above 3 mg/day	**Below 3 mg/day**
Use of haloperidol 2-weeks after the seminar	**Above 3 mg/day**	114* (38.7%)**	50 (17.0%)
	Below 3 mg/day	30 (10.4%)	100 (34.0%)

n=294, * *number of respondents, ** percentage of total respondents*
McNemar test of changes = 0.194

Results in Tables 18 and 19 indicate no significant systematic changes occurred with respect to selected effective and minimum effective haloperidol doses in the period 2 weeks post to 6 months post the seminar (p=0.841 and p=0.194 respectively).

To summarise: analysis of questionnaire responses for selected effective haloperidol dose over the time course seminars have been held indicated that background learning or changes in knowledge occurred; later seminar participants tended to recommend a lower effective dose. However, no change occurred in the selected effective dose during the period from 2-weeks after the seminar to 6-months after the seminar. Despite this, a general learning process seems to take place over time. Therefore, the change in the magnitude of selected effective haloperidol dose before and after the seminar (from 8.6mg/day to 7.4mg/day, described in Chapter 3) were probably not due to effects of the seminar, but to general "background" learning. The opposite conclusion was reached when considering the selected minimum effective dose where general learning did not seem to occur. This was confirmed by an absence of changes between the groups before the seminar, as well as by comparing the change 2-weeks after the seminar with the change 6-months after the seminar. The finding is similar for both measures –

average dose or dichotomised between below or above 5 mg/day. These findings suggest that the seminars change participants' knowledge on minimum effective haloperidol dose.

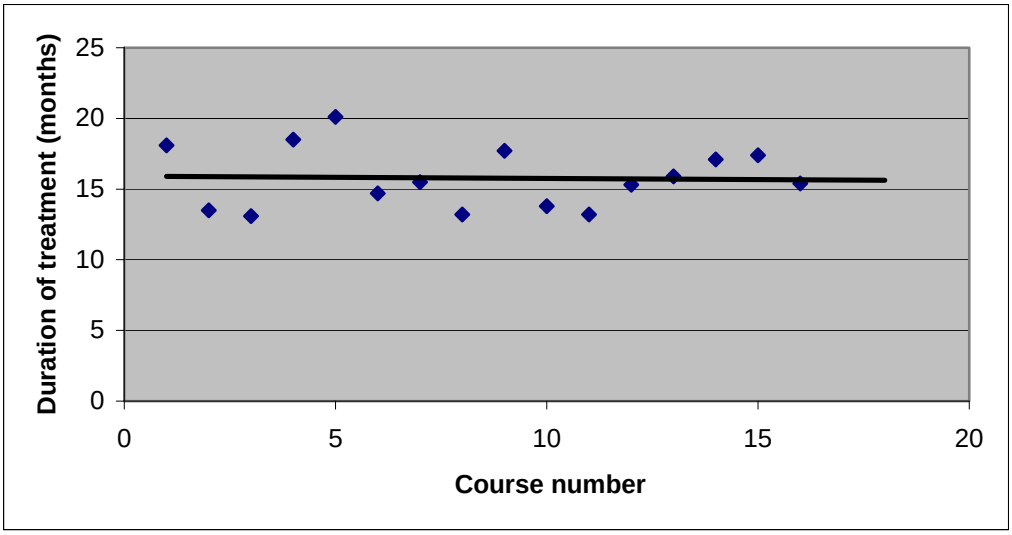
In conclusion, the above analyses lend validity to ascribing the changes in selected minimum effective haloperidol dose 6-months after the seminar, to the seminar itself. The significant change in the magnitude of the selected effective haloperidol dose was unlikely due to effects of the seminar alone; instead general background learning seemed to take place, which could in part account for this change.

4.2 Duration of treatment

Analysis of pre-seminar questionnaire responses

Figure 5: Variation in average selected duration of treatment before the seminar for first- episode schizophrenia patients

Plot of mean pre-seminar average duration of treatment (in months) for first-episode schizophrenia patients by each seminar group versus seminar course number over time (earliest to latest). The line of best fit for individual points was determined using method of least squares.



Results in Figure 5 indicate that no systematic learning took place; the trend-line is horizontal. The lack of "background" learning was confirmed when the average duration of treatment for the first 8 seminars (earlier seminars) and the last 8 seminars (later seminars) was compared. In Table 20, the difference between the two groups of seminars is reported.

Table 20: Mean selected duration of treatment for first-episode schizophrenia patients ("earlier" and "later" seminars)

	Mean	Std. deviation
Earlier seminars	16.03 months	9.46
Later seminars	15.87 months	11.24

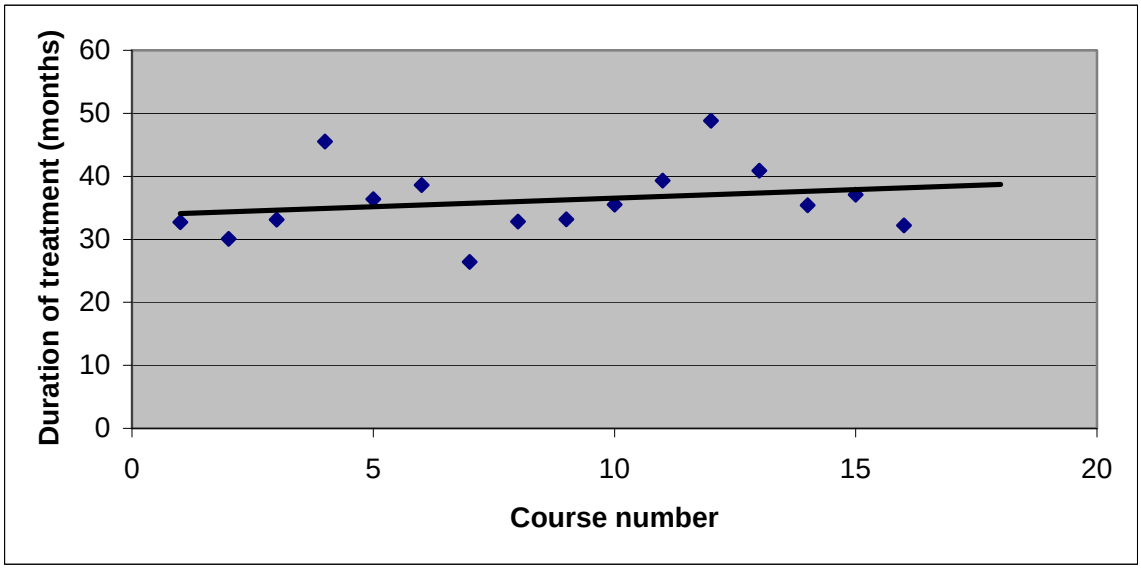
n=351, Independent samples t-test: t=0.25; p=0.80

Results in Table 20 indicated that no statistically significant difference existed between the mean selected duration of treatment for first episode schizophrenia patients for "earlier" versus "later" seminar attendees (p=0.80).

The same conclusion was reached when results for selected duration of treatment for multi-episode patients were analysed. From Figure 6 it can be seen that no significant systematic learning appeared to take place. The trend-line had a minimally positive skew. A substantial amount of variation exists between the groups.

Figure 6: Variation in average duration of treatment for multi-episode schizophrenia patients, before the seminar

Plot of mean pre-seminar duration of treatment (in months) for multi-episode schizophrenia patients by each seminar group versus seminar course number over time (earliest to latest). The line of best fit for individual points was determined using method of least squares.



The lack of learning was confirmed when a comparison was made of the average selected duration of treatment of the first 8 seminars (earlier seminars) and the last 8 seminars (later seminars). Table 21 reports the difference between the two groups of seminars.

Table 21: Mean selected duration of treatment for multi-episode schizophrenia patients, "earlier" and "later" seminars

	Mean	Std. Deviation
Earlier seminars	34.47 months	19.42
Later seminars	38.22 months	19.78

n=340, Independent samples t-test: t=1.76; p=0.08

The difference in the selected duration of treatment between later and earlier seminars was approximately 4 months. Despite this rather large change, the difference between the groups was not considered statistically significant (p=0.08). There was substantial variation within the groups (refer to respective standard deviations).

In summary, the analyses of responses provided before the seminars showed that no systematic difference existed between the earlier seminars and the later seminars concerning the selected duration of treatment. In this respect the difference in duration of treatment from before the seminar to 6-months after the seminar was probably not due to development in background knowledge.

Analysis of changes in responses from 2-weeks after to 6-months after seminar attendance

The above conclusion was re-confirmed when the responses 2-weeks after the seminar and 6-months after the seminar were analysed.

Table 22: Mean selected duration of treatment for first-episode schizophrenia patients, 2 weeks and 6-months after the seminar

	Mean	Std. Deviation
2-weeks-dataset – Duration of treatment	17.94 months	8.93
6-months-dataset – Duration of treatment	17.80 months	9.10

n=117, paired samples t-test: t=0.22; p=0.83

Table 22 shows that no significant difference existed between the 2-week dataset and the 6-months dataset concerning recommended duration of treatment for first-episode schizophrenia patients (p=0.83).

Table 23: Mean selected duration of treatment for multi-episode schizophrenia patients, 2 weeks and 6 months after the seminar

	Mean	Std. Deviation
2-weeks-dataset - Duration of treatment	48.17 months	17.45
6-months-dataset - Duration of treatment	47.47 months	17.50

n=113, paired samples t-test: t=0.47; p=0.64

Table 23 also shows that no significant change occurred in the recommended duration of treatment for multi-episode patients, in the period from 2 weeks to 6 month after the seminar (p=0.64).

To summarise, no learning or changes in knowledge seemed to take place regarding selected duration of treatment, either when pre-seminar questionnaire responses were analysed or when questionnaire responses from 2-weeks after and 6-months after the seminar were analysed. This conclusion is independent of the schizophrenia subtype: first-episode or multi-episode.

In conclusion, these results support the hypothesis that the significant changes in respondents' selected duration of haloperidol treatment 6-months after the seminar can be ascribed to the effects of the seminar.

4.3 Drug-class selected

New Generation versus Conventional antipsychotic

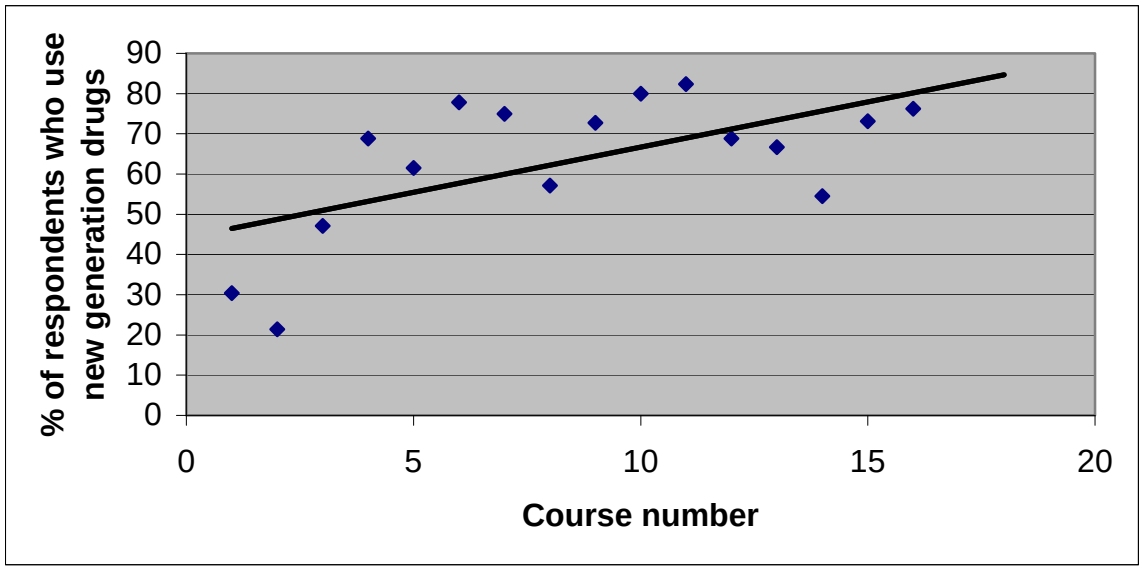
The emergence of the new generation of antipsychotic drugs from the early 1990s and during the early stages of seminar presentation clearly led to significant knowledge changes occurring apart from the seminars. It was therefore necessary to assess whether the changes in choice of drug-class 6 months after the seminar could be ascribed to the seminars.

Analysis of questionnaire responses pre-seminar

Figure 7 reports the average percentage of respondents before each seminar who intended to use new generation drugs treating first-episode schizophrenia patients. This figure shows a clear upward trend over time.

Figure 7: Variation in the percentage of respondents who used new generation drugs for treating first-episode schizophrenia patients, before the seminar

Plot of the percentage of each seminar group who chose new generation antipsychotics for treating first-episode schizophrenia patients pre seminar versus seminar course number over time (earliest to latest). The line of best fit for individual points was determined using method of least squares.



The positive skew of the trend line in Figure 7 clearly indicates an increase in the percentage of respondents choosing new generation antipsychotics.

This trend was confirmed when the difference between earlier and later seminars was analysed. Table 24 reports the comparison of drug-class between earlier and later seminar attendees.

Table 24: Pre-seminar selected antipsychotic drug-class used for first-episode schizophrenia patients by "earlier" (first 8) vs "later" (last 8) seminar attendees

	Seminar time		
Drug-class used for first-episode patients	n= 304	**Earlier seminars**	**Later seminars**
	New Generation	55.1%	74.1%
	Conventional	44.9%	25.9%
		(100%)	(100%)

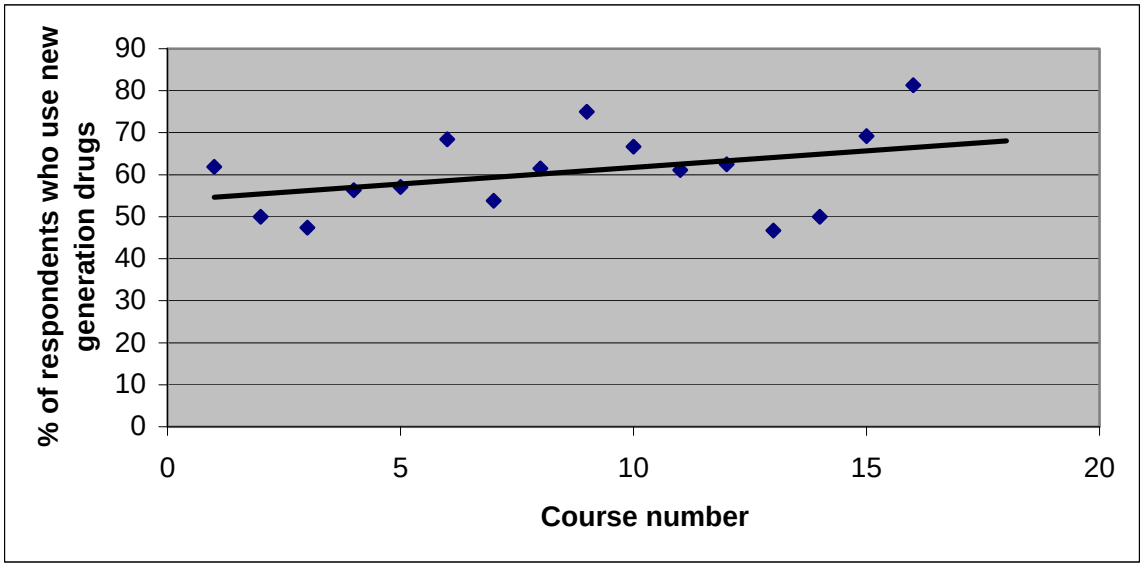
n=304, Chi-square test p = 0.001

In the earlier seminars 55.1% used new generation drugs, whereas 74.1% used new generation drugs in the later seminars. This result is highly significant (p = 0.001) and suggests that the changes in drug-class selected before the seminar to 6-months after the seminar were due to developments in the background knowledge and behaviour of psychiatrists.

Figure 8 indicates that the selection of new generation drugs for treating multi-episode schizophrenia patients also increased over time.

Figure 8: Variation in the percentage of respondents who chose new generation drugs for treating multi-episode schizophrenia patients, before the seminar

Plot of the percentage of each seminar group who used new generation antipsychotics to treat multi-episode schizophrenia patients pre seminar attendance versus seminar course number over time (earliest to latest). The line of best fit for individual points was determined using method of least squares.



While the tendency is less marked than was the case for first-episode patients (Fig 7), the differences between earlier and later seminars seem to be considerable.

Table 25: Pre-seminar selected drug-class used for multi-episode schizophrenia patients by "earlier" versus "later" seminar attendees

		Seminar time	
		Earlier seminars	**Later seminars**
Drug-class used for multi-episode patients	**New Generation**	59.0%	67.1%
	Conventional	41.0%	32.9%
		(100%)	(100%)

n=300, Chi-square test = 0.09

While the percentage of respondents choosing the new generation drugs in multi-episode patients increased from 59% in the earlier seminars to 67.1% in the later seminars, this did not reach statistical significance. The possibility of a type II error here (concluding that no difference exists between earlier seminars and later seminars when in fact there is a difference) needs to be kept in mind, as the p value is close to significant. Considering the difference in the numbers of respondents selecting the new generation drugs at earlier and later seminars, and the probability of conducting a type II error, it is reasonable to conclude that a difference exists between earlier and later seminars

regarding the drug-class i.e. in spite of background changes in the choice of antipsychotic over time, there is still evidence to suggest that the seminars had a significant effect in changing the antipsychotic choice.

In summary, the analysis of questionnaire responses completed before the seminars has shown that changes occurred over time concerning chosen antipsychotic drug-class for both first- and multi- episode schizophrenia patients, with the selection of the new generation antipsychotics becoming more common. This was most likely due to general background knowledge developments rather than to effects of the seminar.

Analysis of response changes from 2-weeks after to 6-months after seminar attendance

However, the above conclusion was not supported by the analysis of the changes in response from 2-weeks to 6-months post-seminar for first- and multi-episode schizophrenia patients.

Table 26 shows the respondents' selection of drug-class used for first-episode schizophrenia patients 2-weeks after and 6-months after the seminar.

Table 26: Drug-class (conventional or new generation) selected for first-episode schizophrenia patients by delegates 2 weeks and 6 months after the seminar: total number and (percentage of total)

		Drug-class used 6-months after the Seminar	
		New Generation	**Conventional**
Drug-class used 2-weeks after seminar	**New Generation**	75* (73.5%)**	5 (4.9%)
	Conventional	6 (5.9%)	16 (15.7%)

n=102, * *number of respondents*, ** *percentage of total respondents*
McNemar test of changes p = 1.0

As can be seen from Table 26, 73.5% of the psychiatrists chose new generation drugs both 2-weeks and 6-months after the seminar, and 15.7% used conventional drugs 2-weeks and 6-months after. Therefore, 89.2% of the respondents did not change their opinions regarding drug-class for treating first-episode schizophrenia patients. In general the behaviours seem to have stayed the same.

Table 27: Drug-class (conventional or new generation) selected 2 weeks and 6 months after the seminar for multi-episode schizophrenia patients: total number and (percentage of total)

		Drug-class used 6-months after the Seminar	
		New Generation	**Conventional**
Drug-class used 2-weeks after seminar	**New Generation**	61* (61.0%)**	7 (7.0%)
	Conventional	15 (15.0%)	17 (17.0%)

n=100, * *number of respondents*, ** *percentage of total respondents*
McNemar test of changes p = 0.134

Table 27 shows that 78% did not change drug-class between the 2-week and the 6-months-questionnaire when treating multi-episode schizophrenia patients, while 15% moved from conventional to new generation drugs and 7% moved from new generation to conventional drugs. Compared to Table 26, slightly more psychiatrists seem to have changed behaviour, but this result was not statistically significant. It would appear, therefore, that the behaviour of respondents in terms of drug-class selected 2 weeks after the seminar and 6 months after the seminar did not change significantly.

In contrast to the analysis performed on pre-seminar data, no change in background knowledge seemed to take place from 2-weeks after to 6-months after the seminar. This difference in results between the analysis comparing earlier and later participants and the above analysis might be due to at least two factors. Firstly, only participants who answered *both* the 2-week *and* the 6-months questionnaire were included in the analysis. The dataset of answers 2-weeks after and 6-months after the seminar were subsets of the pre-seminar dataset i.e. not all participants who filled in the pre-seminar questionnaire completed either the 2-week post or 6-month post questionnaires. Secondly, the learning from a seminar usually declines over time, but the opposite seems to be the case in Tables 26 and 27. The reason could be that there was still a general learning process taking place, which could cancel out the decline in the effect of the learning, thereby preventing the decline in knowledge after the seminar.

The conclusion was that the background knowledge and behaviour of psychiatrists changed significantly over the time that elapsed before the different groups attended the seminars. The consequence was that the differences in the drug-class selected before the seminar and 6-months after the seminar could not be ascribed purely to the effect of the seminar.

Choice of antipsychotic agent before and 2-weeks after the later seminars

The above results suggest that the effect of the seminar only partially explained the observed changes in preference of antipsychotic class used for treatment. This section examined whether the seminars played a role in the changes at all; specifically whether there was a significant difference in the drug-class selected pre- and 2-weeks post seminar, using only the data for the "later" (last 8) seminars. If a difference existed, it might indicate that the seminars had some effect on the psychiatrists' knowledge, behaviour and attitude to the new generation drugs. The analysis of the previous data indicated that the participants at later seminars possibly experienced "background" learning about the use of new generation drugs to a greater extent than the earlier participants. If there were a difference in drug-class used after later seminars, this would indicate that the seminar did have an effect, despite changes occurring in background knowledge). Changes between the pre-seminar dataset and the 2-week post-seminar dataset were compared because this provided the best chance to detect direct effects of the seminar for the following reasons: firstly, the amount of background-learning change that could happen in the period of a month (2 weeks before the seminar and 2 weeks after the seminar) would be minimal, and secondly, the effect of a seminar normally declines rapidly. If there was no significant difference in the selected drug-class used 2-weeks post-seminar compared with the selected drug-class used 2-weeks pre-seminar, there would probably be no significant difference 6-months post seminar.

Table 28 represents the change in responses for selected drug-class used for first-episode schizophrenia patients from 2-weeks pre-seminar to 2-weeks post-seminar as analysed for the "*later*" i.e. last 8 seminars only.

Table 28: Selected drug-class (conventional or new generation) used for first-episode schizophrenia patients before and 2-weeks after the seminar, using only responses from the last 8 seminars

		Drug-class used 2-weeks after the Seminar	
		New Generation	**Conventional**
Drug-class used before the seminar	**New Generation**	62* (72.1%)**	6 (7.0%)
	Conventional	10 (11.6%)	8 (9.3%)

n=86, * number of respondents, ** percentage of total respondents
McNemar test of changes p = 0.45

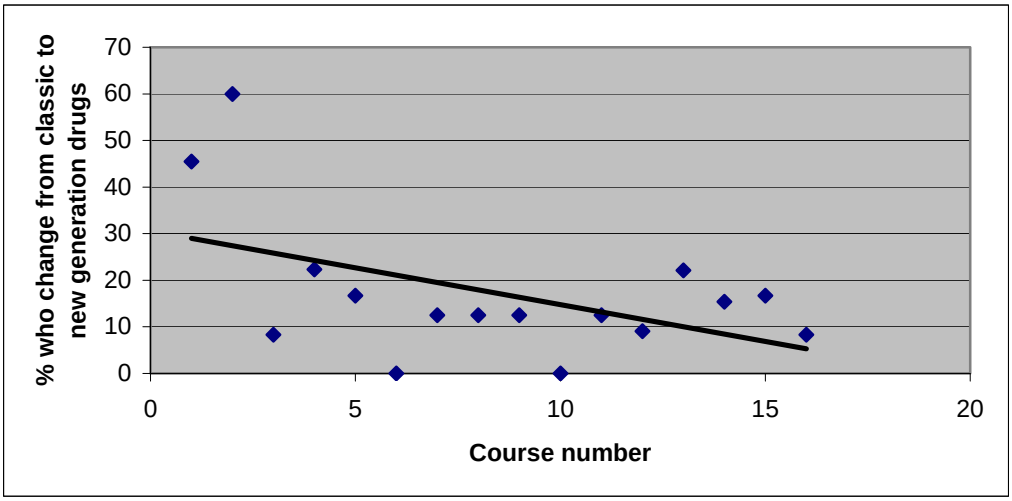
The results of Table 28 indicate that 18.6% of the respondents changed their behaviour, of whom 11.6% changed from a conventional drug to a new generation drug. This

indicates that the drug-class selected did not change significantly as a result of the later seminars.

In comparison, when the results of the earlier seminars are included, about 30% had changed drug-class after 6-months (see Table 7, page 62), of whom 23% had changed from conventional to new generation antipsychotics. These figures indicate that change to new generation agents decreased over time i.e. over time, more and more respondents used new generation antipsychotics prior to attending the seminars.

Figure 9 plots the percentage of participants who changed from selecting conventional to new generation antipsychotics for first-episode patients 2-weeks after the seminar.

Figure 9: Variation in the percentage of respondents over the time course of seminars who changed from selecting conventional antipsychotics before the seminar to new generation antipsychotics 2 weeks after the seminar (for first-episode patients)

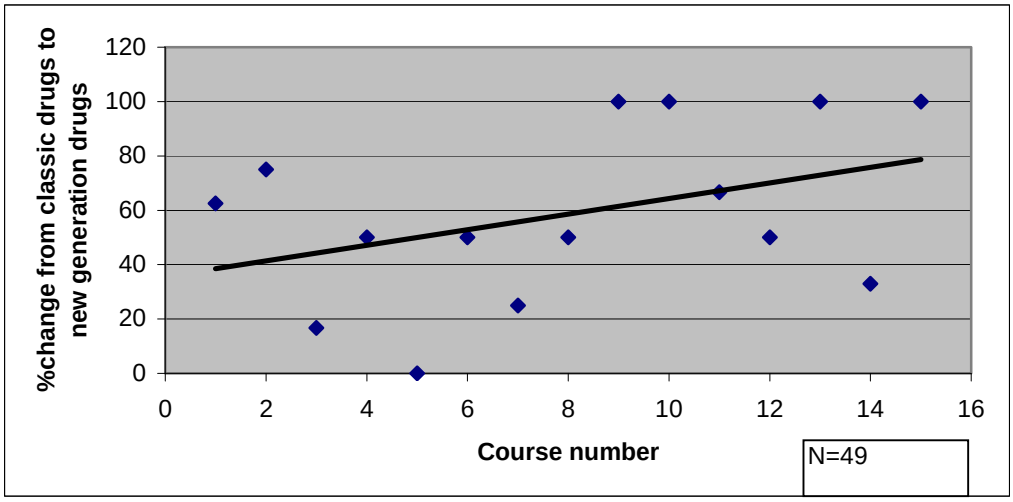


The trend-line indicates that the percentage change from conventional to new generation antipsychotics decreased as the seminar-number increased, i.e. as time passed. However, results from the first two seminars seem to account for most of the variation. It could also be that the percentage change from conventional to new generation drugs was fairly stable across the period. To better investigate whether the seminars had the desired effect of increasing the percentage of new generation antipsychotics chosen, it would be more correct to examine the effect of the seminar by separately analysing those respondents who used conventional drugs before the seminar.

Figure 10 shows the percentage of respondents at each seminar included in this study who changed from conventional to new-generation anti-psychotics. It is important to

note that the percentages may not be valid as the number of respondents from which the percentages are derived is small (n=49).

Figure 10: Variation in the percentage of respondents that change from conventional to new generation drugs at various seminars for treating first-episode schizophrenia patients, from before the seminar and 2 weeks after the seminar



In Table 29 the drug-class used for multi-episode schizophrenia patients was reported before the seminar and 2-weeks after the *later* seminars.

Table 29: Drug-class (conventional or new generation) used before the seminar and 2-weeks after the seminar for multi-episode schizophrenia patients (Percentage of later seminar answers)

		Drug-class used 2-weeks after the Seminar	
		New Generation	**Conventional**
Drug-class used before the seminar	**New Generation**	73,5% (58)	4,9% (4)
	Conventional	5,9% (5)	15,7% (12)

n=79, McNemar test of changes = 0.65

Only 5.9% changed from conventional to new generation drugs. As was seen with the drug-class for first-episode schizophrenia patients, the drug-class used for multi-episode schizophrenia patients did not change either when the later seminars were analysed.

By comparison, from before the seminar to 6-months after the seminar, when all seminars were included, about 22.1% of the participants changed from conventional to new generation drugs (see Table 8, page 63).

Figure 11 shows the average percentage of participants at different seminars who changed from conventional drugs to new generation drugs 2-weeks after the seminar in cases where multi-episode schizophrenia patients are treated.

Figure 11: Variation in the percentage of respondents at different seminars who changed drug-class from conventional to new generation drugs

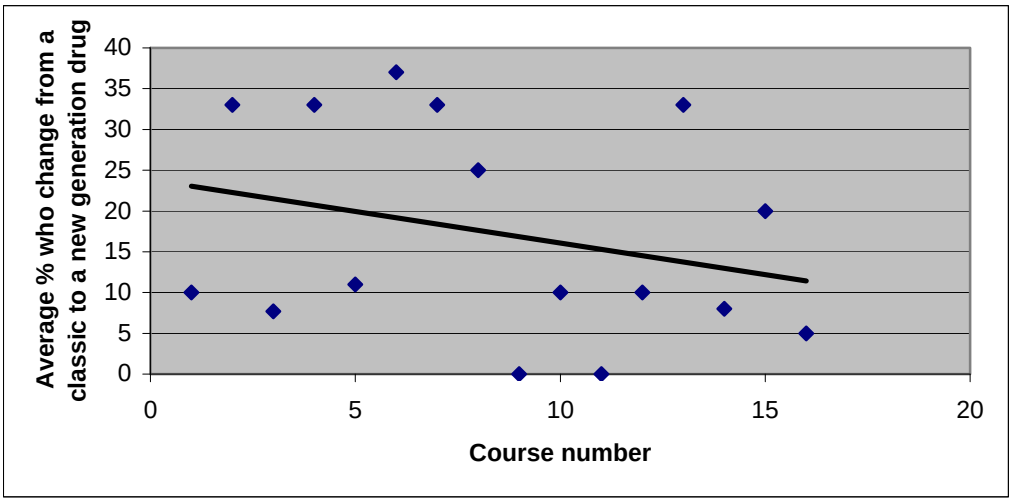


Figure 11 shows there was a great deal of variation between seminars in the average percentage of respondents who changed from conventional to new generation drugs. Despite this, the trend-line seems to indicate that the percentage who changed to new generation drugs became progressively smaller as time passed, i.e. the effect of the seminars became progressively less and less.

To conclude, the seminars did *not* seem to have any significant effect on the drug-class used in the short-term when the "later" seminars were analysed; hence the change in drug-class from before the seminar to 6-months after *all* the seminars could not be attributed to the effects of the seminar. The reasons are, firstly, that differences occurred in the drug-class used over time; participants at "later" seminars tended to use more new generation drugs before the seminar compared to those at "earlier" seminars. This indicated that a change towards new generation drugs was a general feature and did not result from effects of the seminar itself. Secondly, there was no significant change in drug-class from before to 2-weeks after the "later" seminars. Further, a lower percentage of psychiatrists changed to new generation drugs in the "later" seminars compared with the "earlier" seminars. Given these data it seemed many participants (72% used new generation drugs before the seminar) had already made the change to new generation drugs before the "later" seminars. Therefore the seminar could not have had a significant effect on the drug-class used. However, based on the significant effect

that could be demonstrated, changes in the drug-class used did seem to occur as a result of attendance at the "earlier" seminars.

4.4 Number of study respondents completing questionnaires

Even though the level of knowledge concerning duration of treatment and haloperidol dose seems to be more or less identical during the period of investigation, the number of respondents in the different datasets might influence the results.

Not all of the 408 seminar participants answered to all questionnaires. Furthermore, the number of participants who filled in the pre-questionnaire and the 6-months questionnaire differed: 386 participants filled in the pre-questionnaire and 139 filled in the 6-months questionnaire. The participants who completed the questionnaires may not have been representative of the entire sample. For example, it may be possible that only the general hospital employed psychiatrists filled in the 6-months questionnaire. Let us assume that general hospital employed psychiatrists are better learners compared to those employed in a university hospital. Therefore, it would mean that only the good learners (i.e. those from the general hospitals) filled in the 6-months-questionnaire. This would bias results in favour of seminar learning having a greater effect on changes to haloperidol prescribing behaviour than were the case. Therefore, a paired comparison, where only responses of participants who filled in *both* questionnaires (pre- and 6-months post-seminar), was used in this study. Therefore, if learning ability or willingness to learn was connected to certain characteristics of the psychiatrist, it was important to make sure that the characteristics of respondents who filled in *both* questionnaires also reflected the characteristics of those who only filled in the pre-seminar questionnaire i.e. it was important to determine whether there were any data-set differences. Otherwise, the conclusions of the paired analyses might prove invalid.

Characteristics of respondents used to detect differences between the two-datasets were workplace, years of experience, number of patients and country of origin (see tables 31-34). If no differences were detected between the two datasets, then differences in knowledge and behaviour, before the seminar and 6-months after the seminar, could not be due to specific characteristics of the psychiatrists comprising each dataset.

Table 30: Workplace of pre-seminar and 6-months post-seminar respondents

	Pre-dataset (n=386)	6-months-dataset (n=139)
University Hospital	36.3%	37.4%
District or General Hospital	24.1%	25.9%
Private Practice	1.8%	1.4%
Specialised Psychiatric Hospital	34.2%	30.9%
Other	3.6%	4.3%

Chi-square test = 0.95

As can be seen from Table 30, no significant difference between the two datasets existed in terms of the workplace of the respondents.

Clinical experience is perhaps a doctor's most trusted tool. This certainly could influence knowledge and clinical care. Table 31 compares the clinical experience of participants in the pre-seminar dataset and the 6-month post-seminar dataset.

Table 31: Years of experience practising psychiatry for respondents in the pre-seminar and 6-monthpost-seminar dataset

		Mean	Std. Deviation
Pre-dataset	(n=390)	13.3 years	7.42
6-months-dataset	(n=144)	14.5 years	7.46

Independent samples t-test: t=1.64; p=0.09

Results in Table 31 indicate no significant difference in the average years of psychiatric experience among respondents of the pre-seminar and 6-months post-seminar dataset.

Workload (patient numbers per month) determines the time a doctor can spend with a patient, in turn influencing the quality of care and treatment practises. Table 32 explores this.

Table 32: Number of patients treated per month by respondents in the pre-seminar and 6-month post-seminar dataset

		Mean	Std. deviation
Pre-dataset	(n=390)	79.0 patients	67.8
6-months-dataset	(n=144)	80.6 patients	70.9

Independent samples t-test: t=0.17; p=0.82

No significant difference in the average number of patients seen per month by respondents of the pre-seminar and 6-months post-seminar questionnaire was detected (p=0.82).

Psychiatrists from 29 different countries attended the seminars. It is quite possible that the two datasets exhibited a high knowledge variation in different countries of origin because not all countries have the same knowledge, training and interest in schizophrenia. Table 33 shows that similar percentages of participants from the various countries were represented in the pre-seminar dataset and the 6-months post-seminar dataset.

Table 33: Country of origin of respondents in the pre-seminar and 6-months post-seminar dataset

	Pre-seminar-dataset (n=382)		6-months-dataset (n=157)	
Australia	15	3.9%	6	3.8%
Austria	20	5.2%	7	4.5%
Belgium	23	6.0%	12	7.6%
Canada	5	1.3%	0	0%
Czech Republic	10	2.6%	6	3.8%
Denmark	23	6.0%	9	5.7%
Estonia	5	1.3%	3	1.9%
Finland	12	3.1%	7	4.5%
France	18	4.7%	9	5.7%
Germany	28	7.3%	11	7.0%
Greece	16	4.2%	4	2.5%
Hungary	15	3.9%	7	4.5%
Ireland	3	0.8%	2	1.3%
Israel	5	1.3%	0	0%
Italy	29	7.6%	10	6.4%
Luxembourg	1	0.3%	1	0.6%
Macedonian	0	0%	1	0.6%
Netherlands	20	5.2%	8	5.1%
New Zealand	17	4.5%	6	3.8%
Norway	23	6.0%	11	7.0%
Poland	12	3.1%	6	3.8%
Russia	5	1.3%	0	0%
Slovakia	5	1.3%	3	1.9%
Slovenia	3	0.8%	0	0%
South Africa	15	3.9%	6	3.8%
Spain	20	5.2%	6	3.8%
Sweden	10	2.6%	5	3.2%
Switzerland	13	3.4%	6	3.8%
United Kingdom	11	2.9%	5	3.2%
Total	**382**	(100%)	**157**	(100%)

Chi-square test = 0.976

For the analyses conducted in chapter 6, it was vitally important that the two datasets should be similar in terms of country of origin of the participants. For the purpose of analysis, participants were clustered into three groups of countries on the basis of similarity of knowledge in the pre-seminar questionnaires. The groups were arranged in

descending order i.e. Group 1 countries had the highest proportion of "correct answers" whereas the Group 3 countries had the lowest proportion.

These groups are listed below:

Table 34: Countries listed by their allocated country-groups

Group 1	Group 2	Group 3
Canada	Denmark	Greece
Australia	Sweden	Germany
South Africa	France	Britain
Netherlands	Belgium	Spain
Norway	Switzerland	Eastern-European-countries
New Zealand	Ireland	Italy
	Austria	
	Finland	

Table 35 reports the percentage representation of each country-group within the pre-seminar and the 6-months post-seminar datasets.

Table 35: Country of origin in the pre-seminar dataset and the 6-months post-seminar dataset, reported in terms of the country-groups

	Pre-dataset (n=382)	6-months-dataset (n=157)
Group 1 countries	27.5%	26.8%
Group 2 countries	30.9%	33.8%
Group 3 countries	41.6%	39.5%
	(100%)	(100%)

Chi-square test = 0.805

Table 35 shows that there were no significant differences in the country-group distribution in the two datasets (p=0.805).

4.5 Summarising the effect of developments in knowledge over time and differences between datasets - can differences observed before and after the seminar be ascribed to the beneficial effects of the seminar?

It was important to investigate whether advances occurred in the level of general schizophrenia knowledge among psychiatrists – "background" knowledge change. If knowledge advanced over time, the difference in responses of the pre-seminar questionnaire and the 6-months post-seminar questionnaire (presented in Chapter 3)

could be the result of changes in this background knowledge rather than the result of seminar attendance.

Accordingly, a comparison of the knowledge and behaviour of the participating psychiatrists (relating to the variables of most interest to the study) was made between the "earlier" and the "later" seminars and between the responses in the two-week post-seminar and 6-months post-seminar questionnaires.

Results of these analyses showed that only the **minimum effective dose** selected by psychiatrists before they attended the seminars did not change over time, indicating that changes observed after the seminar were not due to changes in background knowledge. However, the changes in the selected **effective dose of haloperidol** after the seminar were probably, at least in part, due to changes in background knowledge. The percentage of respondents prescribing below 5 mg/day pre-seminar increased over time, even though there were no changes between 2-weeks after and 6-months after the seminar.

The analyses of changes in recommended **duration of treatment** showed that no significant differences were found between "earlier" seminars and "later" seminars. Furthermore no changes occurred between 2-weeks after the seminar and 6-months after the seminar. Therefore, it was likely that changes in selected duration of treatment for first- and multi-episode schizophrenia patients pre-seminar to 6-months post-seminar were *not* due to changes in background knowledge.

Furthermore, the intended **drug-class used** changed between the earlier seminars and the later seminars. Despite the fact that the intended drug-class used was quite stable from 2-weeks after to 6-months after the seminar, substantial changes occurred in the drug-class used over time by psychiatrists before they attended i.e. new generation antipsychotics were gradually more commonly chosen as the preferred drug before the seminars. Section 4.3 (see Table 28) showed that there was no significant change in favour of the new generation antipsychotics two weeks after the later seminars. The change in favour of new generation antipsychotics, 6 months after *all* the seminars, was probably due at least partly to development in the background knowledge of psychiatrists and not solely due to the beneficial effects of the seminars. The change in *actual* antipsychotic class chosen over time was not investigated because no significant change occurred 6 months after the seminar.

The data-set comparison performed to eliminate the possibility that characteristic differences between the pre-dataset and the 6-months-datasetmight be responsible for any post-seminar haloperidol prescribing behaviour change showed there were no significant differences in the key characteristics of workplace, years experience, number of patients seen per month and country of origin. Therefore, the post-seminar changes described in Chapter 3 were unlikely a result of these factors.

Consequently, it would seem that changes in responses concerning the selected minimum effective haloperidol dose and selected duration of treatment were neither due to increases in the background knowledge of psychiatrists nor differences between the pre-seminar and 6-month post-seminar datasets used for analysis. The inference is that changes in responses concerning these two areas (minimum effective haloperidol dose and duration of treatment) could be ascribed to effects of the seminar.

Conversely, the changes in the effective haloperidol dose post seminar were probably due at least in part to changes in the background knowledge of psychiatrists. Changes in the intended drug-class used by later seminar participants seem to be minimal at best and could not be attributed to the seminars. However, these changes occurred far more significantly in earlier seminar participants, and these changes *do* seem to be an effect of attendance at the early seminars.

Chapter 5 Variables that could influence outcomes

Chapter 5 Variables that could influence outcomes

In Chapter 3, changes in haloperidol prescribing behaviour post-seminar were investigated, with significant change in several key areas noted. In Chapter 4, some of these changes in prescribing behaviour were partly attributed to respondent "background" learning (not solely an effect of seminar attendance). The likelihood of dataset differences between pre-seminar and 6-months post-seminar respondents being responsible for any change was discounted. Thus it was concluded that the changes in selected minimum effective haloperidol dose and selected duration of treatment were the only changes in haloperidol prescribing behaviour likely to be directly related to seminar attendance. The following two chapters investigate why some seminar attendees changed behaviour (i.e. what attendee traits or characteristics made them more likely to change haloperidol prescribing behaviour) by looking at the effect nationality, years of work experience, patient caseload and workplace environment had on changes in selected minimum effective dose and selected duration of treatment.

Changes were analysed only with respect to the minimum effective haloperidol dose and duration of treatment. The variation in drug-class used and effective haloperidol dose was not analysed, as these differences before and after the seminars can probably not be ascribed to an effect of the seminars.

5.1 Country of origin

It is likely that different countries have different approaches to psychiatry. This in turn might impact on the learning abilities and potential of the participants through differing knowledge levels, training provided and ethics. By way of example, a Dutch psychiatrist may be more "open" to new ideas and knowledge compared to a psychiatrist from Greece. The difference in learning – and possibly change in behaviour – may therefore be due to a difference in "learning culture". Also, the Dutch may have a "psychiatry culture" that focuses on fewer patients but higher quality treatments, whereas the Greeks may focus on more quantitative aspects. These differences in "learning-culture" and "psychiatry culture" may result in more openness to new ideas among Dutch psychiatrists. As a result the Dutch may learn more at the seminars than the Greek psychiatrists. On the other hand, the Dutch may know more than the Greeks before they attend the seminar; therefore a comparison of the changes in behaviour between Dutch and Greek psychiatrists may demonstrate that the Greeks learn more.

In order to test the hypothesis of the effect of different countries of origin/cultures, the next chapter compares changes in behaviour between different cultures of psychiatry controlled for the answers before the seminar (the knowledge before the seminar is taken into account). The countries have been categorised into groups reflecting different levels of knowledge in the pre-seminar questionnaires ("psychiatry culture") (See Table 34, page 91).

5.2 Years of experience

Other factors could possibly affect the changes in prescribing behaviour that were observed after the seminar. The number of years the psychiatrists have practised could influence their way of practice and their ability, interest, or even need, to learn. An experienced psychiatrist might be more conservative in the treatment habits compared to a younger psychiatrist. On the other hand, the more experienced psychiatrist might have greater knowledge compared to the young psychiatrist, meaning that the experienced psychiatrists could not learn as much from the seminar.

In order to take the level of knowledge into account, the pre-seminar answers are controlled for level of knowledge when changes in behaviour are analysed. As an example, if the effective haloperidol dose is given as below 5 mg/day before the seminar, it is deemed that the participant cannot "learn" much. When this is not taken into account, the result might be that number of years of experience does not influence the effect of the seminar – changes in knowledge and behaviour. The following section compares changes in behaviour between less and more experienced psychiatrists, controlling for level of knowledge in the answers before the seminar.

5.3 Workplace

The workplace setting can influence learning. By example, before attending a seminar, a psychiatrist from a specialised psychiatric hospital might have superior knowledge of schizophrenia management and may therefore have less opportunity to learn from the seminar, as compared to a psychiatrist who works at a general hospital, who perhaps does not treat schizophrenia patients on a regular basis. As in testing the previous hypotheses, the level of knowledge before the seminar needs to be taken into account.

5.4 Average number of patients treated per month

The number of patients treated by the psychiatrist may influence both the knowledge/experience of the psychiatrist as well as the time available to see each

patient. A psychiatrist with many patients might have less time for keeping up to date with the literature compared to a psychiatrist with few patients. On the other hand, psychiatrists with fewer patients might have less experience treating patients compared to psychiatrists with many patients. In this sense it is difficult to conclude *a priori* what effect having many patients might have on changes in behaviour. However, as in testing the previous three hypotheses, the level of knowledge before the seminar needs to be taken into account, as it is a fair assumption that the participants' knowledge varied before the seminar.

In the next chapter the effect of the average number of patients seen by the psychiatrist on the changes in behaviour is analysed. The number of patients was considered in terms of the total number of patients per month, the number of schizophrenia patients seen per month, and percentage of patients who have a schizophrenia diagnosis. Several indicators are used to obtain a more valid assessment of the work-load and area of specialisation of the particular psychiatrist.

5.5 Summary

Having established that i) changes in haloperidol prescribing behaviour post-seminar actually do occur ii) some of these changes are attributable to "background" learning by participating psychiatrists and iii) the pre- and post-seminar datasets used in this study are comparable, it was important to further investigate the nature of the variation in the changes in prescribing behaviour of the different participants at the seminars. The next chapter tests whether the variation can be understood with reference to: country of origin, workplace, and years of experience and number of patients seen.

Chapter 6 Exploring variations in results

Chapter 6 Exploring variations in results

The tests of the explanatory-power of the above hypotheses concerning the nature of the variation in changes to haloperidol prescribing behaviour focus on the minimum effective haloperidol dose and duration of treatment. The variations in drug-class used and effective haloperidol dose were *not* analysed because these prescribing changes post-seminar were most likely due to factors other than the learning effect of the seminar (see Chapter 4). The testing of the above explanations of change was two-tiered.

Firstly, there was a need to test whether the individual variables e.g. years of experience, caseload, nationality, or workplace could explain the variation in dependent variables e.g. duration of treatment, minimum effective dose. As an example, the association between years of experience and changes in duration of treatment was tested, controlled for by duration of treatment prescribing behaviour before the seminar. A dummy-variable[2] was constructed in order to take account of the knowledge before the seminar. Dummy variables are a way of adding the values of a nominal or ordinal variable to a regression equation. Each value of the categorical independent except one is entered as a dichotomy.

In the current analysis, the dummy variable was created in such a way that it had the value 1 if the respondent was on the wrong side of the target i.e. below the recommended duration of treatment or above the recommended minimum dosage before the seminar e.g. a respondent might recommend 10 months treatment of first-episode schizophrenia patients before the seminar. This respondent is deemed below the target of 18 months, and for the purpose of analysis is assigned the value of 1, compared with a respondent recommending a value above 18 months who is assigned the value of 0. This enables regression analysis to be performed. If, after analysis, the dummy variable then is found to be significant, the interpretation is that those selecting below the recommended target duration of treatment pre-seminar changed behaviour in a significantly different way compared to those above the target pre-seminar. The duration of treatment is said to be increased when the regression coefficient of the dummy variable is positive, indicating that those below the target pre-seminar increased

[2] A dummy-variable is a variable with 2 values: 0 or 1. In this sense the variable is on interval (numerical)-level and can consequently be used in regression-analysis. Categorical variables cannot be used in normal regression-analysis. Categorical variables like country of origin are instead often transformed into dummy-variables.

their duration of treatment in comparison to the reference group i.e. those selecting above the target pre-seminar. In other words, an important objective of the seminar has been fulfilled - a change in the prescribing behaviour of those participants below the target pre-seminar occurred, i.e. "learning" occurred where "learning" was required.

Secondly, in addition to the dummy-variable, interaction-variables were also constructed. Interaction exists when the association between e.g. changes in haloperidol dose and number of patients is altered as the haloperidol dose before the seminar changes. The number of patients and the haloperidol dose before the seminar are said to interact, which means that the association between number of patients and changes in haloperidol dose is conditioned by the haloperidol dose before the seminar. An example could be that the changes in behaviour are especially related to the situation where the psychiatrist prescribes a dose above the target dose of haloperidol (in this case higher than 5 mg/day) and has many first-episode schizophrenia patients. Put differently, the haloperidol dose changes especially among those psychiatrists who are above the target before the seminar *and* see many first-episode schizophrenia patients. If this is the case, interaction exists between the number of first-episode schizophrenia patients and the haloperidol dose before the seminar. The test described below shows that this was the case.

When the effect of the individual variables had been tested individually using simple regression analysis (through including the dummy-variables and interaction-variables) all the variables (country of origin, years of experience, workplace and number of patients) were put into a multivariate analysis. A so-called multiple-dummy-regression was performed. This implies that the effects of all the different hypotheses on changes in behaviour (e.g. duration of treatment and experience) are taken into account *at the same time.* The advantage is that a spurious[3] correlation, such as between duration of treatment and years of experience could be detected more easily. It may be that a given relationship between duration of treatment and country of origin was the effect of the numbers of years of experience. By way of example, Greek psychiatrists may have more years of experience compared to other countries, which may be why the country of origin (incorrectly) seems to explain changes in the duration of treatment, whereas years of experience offers the explanation for the change in duration of treatment.

[3] A relationship between two variables is said to be spurious if both variables are dependent on a third variable, so that the association disappears when the third variable is controlled.

6.1 Country of origin

In order to test whether the country of origin made a difference to the learning or changes in prescribing behaviour of a participant, the countries were categorised into groups the same as those used in Chapter 4 (see Table 34, page 91). A dummy-variable was constructed to control for the knowledge before the seminar. In the case of country of origin, two dummy-variables were constructed; Dummy group 1 and Dummy group 2. To make the results more readable, the interaction variables were only reported if they contributed significantly to the explanation.

6.1.1 Country of origin and changes in duration of treatment

Table 36: Regression analysis of the association between participant's country of origin and changes in the selected optimal duration of treatment for first-episode schizophrenia patients

	Regression coefficient	Beta-coefficient	Significance (T-test)
Constant	-5.624		0.002
Dummy group 1	-2.001	-0.081	0.371
Dummy group 2	1.077	0.048	0.604
Dummy below 18 months of treatment before the seminar	10.513	0.472	0.000
Explained variation R^2 = 24.1%			**n=116**

Results in Table 36 show that country of origin had neither a direct effect (see regression coefficients) nor an indirect effect through interactions with other variables on the changes in selected duration of treatment of first-episode schizophrenia patients. Instead, changes in duration of treatment post-seminar were explained with reference to the length of treatment recommended before the seminar. Respondents who selected below the target of 18 months before the seminar increased their recommended duration of treatment by approximately 5 months (i.e. 10.51 months - 5.62 months) more compared with respondents who were above 18 months before the seminar.

Table 37: Regression analysis of the relationship between changes in duration of treatment for multi-episode schizophrenia patients and country of origin

	Regression coefficient	Beta-coefficient	Significance (T-test)
Constant	-2.288		0.416
Dummy group 1	-0.155	-0.004	0.965
Dummy group 2	-0.048	-0.001	0.988
Dummy below 60 months of treatment before the seminar	16.295	0.480	0.000
Explained variation R^2 = 23.0%			**n=112**

Similar to Table 36, Table 37 shows that country of origin again had neither a direct effect (see regression coefficients and T-test significance for dummy groups 1 and 2) nor an indirect effect (interaction variables insignificant so not included) on changes to the duration of treatment of multi-episode schizophrenia patients. Instead, the changes in duration of treatment were again explained by the recommended duration of treatment selected before the seminar. Respondents below 60 months before the seminar increased their duration of treatment by 16.3 months in comparison to respondents above 60 months pre-seminar.

6.1.2 Country of origin and changes in minimum effective haloperidol dose

Table 38: Regression analysis of the relationship between changes in minimum effective haloperidol dose and country of origin

	Regression coefficient	Beta-coefficient	Significance (T-test)
Constant	0.338		0.619
Interaction dummy group 1 and above 3 mg/day of Haloperidol	2.429	0.201	0.090
Interaction dummy group 2 and above 3 mg/day of Haloperidol	4.651	0.413	0.001
Dummy above 3 mg/day of Haloperidol before the seminar	-4.266	-0.467	0.000
Explained variation R^2 = 16.5%			**n=90**

The regression model in Table 38 explains 16.5% of the variation in changes in minimum effective haloperidol dose. The recommended dose before the seminar had an effect on the changes observed: respondents above 3 mg/day pre-seminar *decreased* their dose compared with those below 3 mg/day pre-seminar.

Country of origin also had an effect. However, this effect was indirect (effects of dummy group 1 and dummy group 2 alone not significant so not included in table). The interaction between the country-groups and dummy above 3 mg/day were more or less significant. Respondents from a Group 2 country and above the target of 3 mg/day before the seminar, *increased* their haloperidol dose by 4.65 mg/day compared to respondents from a Group 3 country who were also above the target before the seminar. In other words, the net-effect of the seminar on respondents from a Group 2 country was marginal; the effect of being above 3 mg/day was cancelled out by the fact that the respondents were from a Group 2 country.

In the case of respondents from a Group 1 country, the interaction was significant on the 10%-level but not the 5%-level. Group 1 respondents who were above target before the seminar *increased* their dose, albeit only slightly. However, the increase was slightly less than Group 2 respondents, who increased their haloperidol dose by 2.4 mg/day after the seminar, compared to Group 3 respondents who were above the target. However, the general effect of being above the target was not cancelled out, as was the case with Group 2 respondents. Therefore, the seminar still had an effect on Group 1 members in the intended direction.

The greatest effect of the seminar was present among Group 3 members. Those above the target before the seminar *decreased* their haloperidol dose by 4.2 mg/day. These findings were not unexpected; as respondents from Group 3 countries seemed to have the greatest need to learn i.e. alter their minimum effective dose of haloperidol prescribing habit.

Finally, it is noteworthy that the explained amount of variation in change of minimum effective haloperidol dose was considerable when compared to Table 41 below (page 106); years of experience explained only 5.6% of change, whereas nationality explained 16.5% (see Table 38 above). In other words, nationality played a stronger role in explaining the changes in selected minimum effective haloperidol dose than psychiatrists' years of experience.

6.2 Years of experience

This section analysed the correlation between number of years of experience and the changes in both duration of treatment and haloperidol dose by performing simple

regression analyses, controlling for either the duration of treatment before the seminar or the haloperidol dose before the seminar[4].

6.2.1 Years of experience and changes in duration of treatment

Table 39 reports the association between years of experience and changes in duration of treatment for first-episode schizophrenia patients, controlled for by the selected duration of treatment before the seminars. A dummy-variable was constructed i.e. for first-episode schizophrenia patients, the recommended duration of treatment is 18 months; therefore the dummy separated the respondents into those who selected above or below 18 months pre-seminar. In order to make the results more readable, the interaction variable (i.e. effect of the interaction between years experience and pre-seminar response) was not reported[5] if it did not contribute significantly to the explanation.

Table 39: Regression analysis of the relationship between changes in duration of treatment for first-episode schizophrenia patients and years of experience, controlled for by selected haloperidol dose pre-seminar

	Regression coefficient	Beta-coefficient	Significance (T-test)
Constant	-7.798		0.000
Years of experience	0.115	0.078	0.332
Dummy below 18 months of treatment before the seminar	11.165	0.489	0.000
Explained variation R^2 = 25.5%			**n=119**

Dependent variable = duration of treatment

Independent variable = psychiatrists' years of experience

Control group = participants who selected above 18 months duration of treatment pre-seminar

Table 39 shows the interaction-variable did not contribute significantly and was not included. Equally, years of experience alone had an insignificant effect on the changes in duration of treatment. The learning concerning treatment duration was not affected by the years of experience of the psychiatrist. Instead, the treatment duration response

[4] Whether the models meet the assumptions of multiple-regression, and whether multicollinearity (the independent variables are highly correlated) could be a problem, were tested - this was not the case in any of the models presented. Visually the plot of the significant variables was tested to be linear. The conditional distribution of the dependent variable was normal. The distribution of the independent variable had constant standard deviation throughout the range of independent variables - homoscedasticity is present.

[5] The variables are removed from the model by backward selection; therefore, all the variables are entered into the model in a block and then removed one at a time. Firstly to test whether the interaction term contributes significantly to the model and thereafter the effects of the main effects are tested.

before the seminar was relevant. Respondents, who recommended less than 18 months of treatment before the seminars, increased their recommended duration of treatment by approximately 11.2 months compared to those respondents who recommended more than 18 months of treatment pre-seminar. The respondents who selected above 18 months treatment pre-seminar *decreased* their recommended duration of treatment by 7.8 months. In other words, the net-increase of those below the target was approximately 3.4 months[6].

Analysed this way, the seminar had an effect, which differed from the findings in Chapter 4. Those who selected below 18 months treatment before the seminar *increased* their duration of treatment and those who selected more than 18 months treatment pre-seminar *decreased* the duration. In short, the seminar had the intended effect on treatment duration for first-episode schizophrenia patients.

The total model – knowledge of the recommended duration of treatment before the seminar – explains a quarter (25.5%) of the differences in learning/changes in duration of treatment. This is an impressive proportion.

Table 40 reports the effect of years of experience on the change in duration of treatment when the patient is a multi-episode schizophrenia.

Table 40: Regression analysis of the relationship between changes in duration of treatment for multi-episode schizophrenia patients and years of experience, controlled for by selected duration of treatment pre-seminar

	Regression coefficient	Beta-coefficient	Significance (T-test)
Constant	-2.132		0.546
Years of experience	0.015	-0.007	0.937
Dummy below 60 months of treatment	16.074	0.470	0.000
Explained variation R^2 = 22.1%			**n=115**

Dependent variable = duration of treatment

Independent variable = psychiatrists' years of experience

Reference group = participants who selected above 60 months duration of treatment pre-seminar

[6] In this special situation, where only the dummy is significant, the constant refers to the changes in the duration of treatment of the reference-group. The constant reports that those above the target before decrease their duration of treatment by 7.8 months. The value of the dummy-variable is the ***difference*** compared to the reference-group. As those below the target increase their duration of treatment by 11 months, the net-increase in duration of treatment of those below the target is 3.4 months.

Once again, years of experience did not affect the changes in duration of treatment. Instead, those respondents who selected below 60 months treatment before the seminar, increased their duration of treatment by approximately 16.1 months on average compared to those who selected greater than 60 months duration of treatment pre-seminar (the reference group). Those who selected above 60 months of treatment pre-seminar decreased their duration of treatment by approximately 2 months (the constant). Consequently, the net-increase of those below the target was 16.1 months - 2.1 months i.e. approximately 14 months. This indicated that the seminar had an effect on the participants who were most out of line with treatment guidelines. The whole model explains 22.1% of the variation in changes between the respondents.

To summarise, the changes in duration of treatment were not explained by either the years of experience of a psychiatrist, nor the interaction between years of experience and pre-seminar questionnaire response. Instead the pre-seminar duration of treatment response alone was the best predictor of the duration of treatment after the seminar. Participants below the recommended duration of treatment before the seminar increased their duration of treatment after the seminar. Therefore, the seminar altered the prescribing behaviour of those most out of line with the recommended standards.

6.2.2 Years of experience and changes in minimum effective haloperidol dose

Table 41: Regression analysis of the relationship between changes in minimum effective haloperidol dose and years of experience, controlled for by selected pre-seminar dose

	Regression coefficient	Beta-coefficient	Significance (T-test)
Constant	-0.292		0.803
Years of experience	0.043	0.071	0.494
Dummy above 3 mg/day before the seminar	-2.011	-0.221	0.035
Explained variation R^2 = 5.6%			**n=91**

Dependent variable = minimum effective haloperidol dose

Independent variable = psychiatrists' years of experience

Reference group = participants who selected below 3 mg/day pre-seminar

Table 41 reports the association between changes in haloperidol dose and years of experience explains a total of 5.6% of the variation in changes in haloperidol dose. This is not impressive, when considering that country of origin explained 16.5% of the variation in change of minimum effective haloperidol dose (see Table 38, page 102).

Nationality plays a much stronger explanatory role with regard to changes in minimum haloperidol dose.

Furthermore, changes could not be explained by years of experience. It seems that the haloperidol dose prescribed pre-seminar best explained the changes. Respondents who were above 3 mg/day before the seminar decreased their haloperidol dose by approximately 2 mg/day in comparison to the reference group (those who selected below 3mg/day pre-seminar). The net-reduction was 2.3 mg/day since those who were below 3 mg/day pre-seminar *also* decreased their dose. This leads to the conclusion that the seminar had the intended effect – a reduction in the haloperidol dose.

6.3 Workplace

6.3.1 Workplace and changes in duration of treatment

Workplace was also analysed using regression analysis. Again dummy-variables were made: dummy university employed and dummy district-hospital employed psychiatrists. The reference category was respondents employed at specialised hospitals, private practices and other venues. Essentially though, the reference category was limited to specialised hospitals as only four respondents were employed at private hospitals or other places.

Table 42 reports on whether or not workplace influenced the changes in duration of treatment.

Table 42: Regression analysis of the relationship between changes in duration of treatment for first-episode schizophrenia patients and workplace

	Regression coefficient	Beta-coefficient	Significance (T-test)
Constant	-6.538		0.000
Dummy university Employed	0.770	0.014	0.876
Dummy district employed	0.315	0.030	0.734
Dummy below 18 months of treatment before the seminar	11.163	0.490	0.000
Explained variation R^2 = 24.3%			**n=121**

Workplace did not seem to have any effect on changes in behaviour. Neither university employed nor the district-hospital employed psychiatrists differed significantly from the reference-category (the specialised hospital employed). Instead, the variation in the

changes of duration of treatment was explained by the pre-seminar selected dose responses.

This picture was confirmed when multi-episode schizophrenia patients were analysed in Table 43.

Table 43: Regression analysis of the relationship between changes in duration of treatment for multi-episode schizophrenia patients and workplace

	Regression coefficient	Beta-coefficient	Significance (T-test)
Constant	-1.518		0.560
Dummy university Employed	-1.780	-0.050	0.771
Dummy district employed	-1.013	-0.027	0.586
Dummy below 60 months of treatment before the seminar	15.810	0.289	0.000
Explained variation R^2 = 21.2%			**n=117**

The table shows that those respondents selecting below the recommended period of 60 months before the seminar on average increased their duration of treatment by 15.81 months in comparison to those selecting above 60 months.

In summary the workplace of the respondents did not seem to have any effect on the changes in duration of treatment. This conclusion was valid when both first-episode schizophrenia patients and multi-episode schizophrenia patients were analysed.

6.3.2 Workplace and changes in minimum effective haloperidol dose

In this section relationships between workplace and changes in the haloperidol dose were analysed. The results are shown in Table 44.

Table 44: Regression analysis of the relationship between changes in minimum effective haloperidol dose and workplace

	Regression coefficient	Beta-coefficient	Significance (T-test)
Constant	0.138		0.807
Interaction district employed and above 3 mg/day before the seminar	-3.432	-0.299	0.005
Interaction university employed and above 3 mg/day before the seminar	-1.999	-0.178	0.088
Explained variation R^2 = 9.6%			**n=92**

Neither the haloperidol dose before the seminar nor the workplace had any direct effects on the changes in the haloperidol dose, so results were not included in Table 44. Instead, the interaction between workplace and haloperidol dose before the seminar explained 9.6% of the changes in the haloperidol dose.

Table 44 shows that respondents who were above 3 mg/day before the seminar and were employed at a district hospital reduced their haloperidol dose by 3.4 mg/day more than the reference group. Put differently, a psychiatrist employed at a district hospital who selected above the target of 3 mg/day before the seminar reduced the haloperidol dose significantly more compared with a respondent at a specialised hospital who was above the target. Therefore, it seems, a district-employed psychiatrist may be a better learner than a psychiatrist employed at a specialised hospital.

Also, university-employed psychiatrists above the target of 3 mg/day pre-seminar also reduced the dose of haloperidol more than the respondents in the reference-group ("specialised" hospital employed above 3 mg/day pre-seminar). However, this conclusion was less certain ($p=0.088$) but may suggest that the behaviour of university-employed psychiatrists did differ from that of the reference-group.

Compared with Table 38 (page 102), where the changes in haloperidol dose were explained solely with reference to the responses before the seminar, more change in the haloperidol dose is explained in Table 44; in total 9.6% of the change in behaviour was understandable in terms of workplace and selected haloperidol dose pre-seminar. The model in Table 44 contributes to a better understanding of the changes in the haloperidol dose.

6.4 Estimated number of patients seen per month

This section analyses the correlations between estimated number of number of patients seen by respondents per month and the changes in both the selected duration of treatment and haloperidol dose. A simple regression analysis was performed and controlled for either the duration of treatment before the seminar or the haloperidol dose before the seminar.

6.4.1 Number of patients seen and changes in duration of treatment selected

In Table 45 the association between the changes in the duration of treatment selected and the estimated number of patients seen per month is reported with a differentiation between the total number of patients and the number of new schizophrenia patients.

Table 45: Regression analysis of the association between changes in duration of treatment for first-episode schizophrenia patients and estimated number of patient seen per month/number and percentage of schizophrenia patients

	Regression coefficient	Beta-coefficient	Significance (T-test)
Constant	-3.254		0.061
Number of patients in general per month	0.003	0.025	0.786
Number of schizophrenia patients per year	-0.017	-0.051	0.580
Percentage of patients who have schizophrenia	0.007	0.019	0.838
Dummy below 18 months of treatment before the seminar	8.463	0.446	0.000
Explained variation R^2 = 20.4%			**n=104**

Table 45 shows that neither the total number of patients per month nor the number or percentage of schizophrenia patients affected the changes in duration of treatment. Again, the reported duration of treatment in the pre-seminar questionnaire explained the changes in behaviour. Respondents below the 18 months target before the seminar increased the duration of their treatment by approximately 8.5 months compared to the reference group (respondents selecting above 18 months treatment pre-seminar), who in this model *decreased* their duration of treatment by approximately 3.3 months.

Table 46 shows the same result; neither the estimated number of patients per month nor the number or percentage of schizophrenia patients seen showed any association with changes in duration of treatment of multi-episode schizophrenia patients.

Table 46: Regression analysis of the association between changes in duration of treatment of multi-episode schizophrenia patients and estimated number of patients seen per month/number and percentage of schizophrenia patients

	Regression coefficient	Beta-coefficient	Significance (T-test)
Constant	-0.301		0.927
Number of patients in general per month	-0.009	-0.042	0.650
Number of schizophrenia patients per year	-0.024	-0.038	0.680
Percentage of patients who have schizophrenia	0.016	0.023	0.817
Dummy below 60 months of treatment before the seminar	15.786	0.454	0.000
Explained variation R^2 = 22.1%			**n=101**

As can be seen, a selected duration of treatment below 60 months before the seminar resulted in an average increase of 15.8 months of treatment compared with the reference-group (respondents selecting above 60 months pre-seminar).

To summarise, neither the total number, nor type of patients seen by a psychiatrist, nor the interaction between many patients and a low duration of treatment before the seminar, influenced changes in behaviour. Once again, the pre-seminar selected duration of treatment response was the best predictor of how the participant changed prescribing behaviour after the seminar.

6.4.2 Number of patients and changes in haloperidol dose

Table 47 shows the changes in haloperidol dose as influenced by the number of patients, differentiated into total number of patients and number of new schizophrenia patients.

Table 47: Regression analysis of the association between changes in minimum effective haloperidol dose and number of patients (total and percentage with schizophrenia)

	Regression coefficient	Beta-coefficient	Significance (T-test)
Constant	-0.122		0.840
Interaction total number of patients per month and above 3 mg/day before the seminar	0.023	0.389	0.000
Interaction number of schizophrenia patients per year and above 3 mg/day before the seminar	-0.080	-0.372	0.001
Interaction percentage who have schizophrenia and dummy above 3 mg/day before the seminar	-0.049	-0.309	0.004
Explained variation R^2 = 29.4%			**n=85**

The model in Table 47 explained 29.4% of the changes observed in haloperidol dose prescribing post-seminar. The haloperidol dose selected before the seminar was no longer significantly associated with the changes in dose selected after the seminar, and results were not included in Table 47. Furthermore, a three-way interaction term was also tested: interaction between the number of patients, percentage schizophrenia patients and dummy below 3 mg/day before the seminar. This interaction term did not contribute significantly to the model, so also was not included in the table. However, despite the fact that no direct effect was apparent from the dose of haloperidol before

the seminar, the variable was still important because it interacted with some of the other tested variables.

When the beta-coefficients were compared, the most important variables in terms of explaining the changes in the haloperidol dose were the interaction between total number of patients and haloperidol dose before the seminar. If the psychiatrist had many patients (not only schizophrenia patients) *and* was above the target before the seminar, the participant ***increased*** the haloperidol dose after the seminar compared to a participant who had fewer total patients and was above the target. Therefore, the number of general patients had a *negative* effect on the learning of the participants - the expectation would be that those above the 3 mg/day target would reduce their dose.

However, the number of patients did not necessarily cause a net increase in the haloperidol dose. The haloperidol dose was ***reduced*** by participants who, pre-seminar, were above the 3mg/day target, *and* concurrently had a high percentage or high number of schizophrenia patients. In fact, the higher the percentage of schizophrenia patients a participant selecting above 3/mg/day pre-seminar had, the greater the *reduction* in the haloperidol dose. Similarly, the reduction in haloperidol dose was even greater when a participant selecting above 3 mg/day saw a high number of schizophrenia patients, regardless of percentage.

To summarise, the seminar *would* have had a direct effect on participants who were above the target haloperidol dose before the seminar, if these participants reduced the dose after the seminar independently of their number of schizophrenia patients or percentage of schizophrenia patients in general. However, the effect was not direct. Instead, the seminar had a positive learning effect on those participants who were above the target before the seminar and *either* saw many schizophrenia patients in total *or* had a high percentage of schizophrenia patients. Put differently, the *decreased* dose change in haloperidol was dependent upon whether the participant firstly, selected above the target dose of 3 mg/day pre-seminar, and secondly had a high number or percentage of *schizophrenia* patients i.e. psychiatrists who selected above the target before the seminar, and either had many schizophrenia patients or a high percentage of schizophrenia patients, reduced the haloperidol dose they prescribed.

Also, the haloperidol dose was *increased* by participants selecting above the 3 mg/day target before the seminar but had many patients in total (not specifically schizophrenia patients), compared with the participants who were also above the target but saw fewer patients.

Therefore, the number of patients seen had a *negative* learning effect in general, but a *positive* learning effect if the patients were predominantly schizophrenia patients.

Finally, a note on the "level of explanation". Table 47 (number of patients) explains five times as much of the change in the minimum effective haloperidol dose compared to the model presented in Table 38 (page 102) (country of origin). If the workplace of the respondents were included as well, the amount of explained variation could perhaps increase further - as long as the variables were not highly related. Inclusion of workplace in the model is presented in the multivariate analysis in Chapter 7.

6.5 The association between the individual variables and changes in behaviour - tentative explanation of changes

The previous sections have analysed changes in both duration of treatment and changes in the minimum effective haloperidol dose. The effect of one explanatory variable (e.g. years of experience), the behaviour before the seminar (e.g. selecting above or below 3 mg/day haloperidol) and the interaction variables (e.g. interaction between selecting above 3 mg/day pre-seminar and nationality) were tested. However, all explanatory variables, the relevant dummy and the interaction variables were not tested at the same time. The analyses performed thus far can be said to be partial, therefore conclusions derived from the analyses are only tentative.

6.5.1 Haloperidol doses - what explains the changes?

Changes in the haloperidol dose were more complex compared with the changes in duration of treatment; more factors were associated with changes in haloperidol dose prescribing than just the level of the dose selected before the seminar.

The pre-seminar selected minimum effective dose seems to explain some of the changes in haloperidol dosage. A dose above 3 mg/day before the seminar resulted in a reduction of the level after the seminar, accounting for about 6% of the changes in the doses. The equivalent degree of explanation concerning the responses before the seminars and changes in duration of treatment was 25%. Thus, in comparison to the explanation of changes in duration of treatment, pre-seminar prescribing behaviour was not as important when the changes in haloperidol dose were examined. Other factors were also important.

Country of origin, in combination with the minimum effective haloperidol dose before the seminars, had an effect on the changes in haloperidol dose. Respondents from Group 2 countries, who were above the target, increased the haloperidol dose compared to respondents from Group 3 countries who were above the target. The same was true, but to a lesser extent, for respondents from Group 1 countries.

Workplace of the respondents contributed to the understanding of the haloperidol dose changes as well. The effect of workplace interacted with the haloperidol dose selected pre-seminar. District-hospital employed psychiatrists, who were above the target before the seminar, reduced their haloperidol dose significantly more than psychiatrists working in specialised psychiatric hospitals settings who were also above the target before the seminar. University employed psychiatrists, who were above the minimum effective haloperidol target dose pre-seminar, probably also reduced the haloperidol dose compared with the reference-group.

Furthermore the number of patients seen by the psychiatrist made a difference. If the total number of patients was high and the psychiatrist recommended a dose above the target before the seminar, the dose was even higher after the seminar compared to a participant who had fewer patients. The dose decreased among participants who were above the target and had either a high number of first-episode schizophrenia patients or a high percentage of first-episode schizophrenia patients. These interaction-terms do not allow room for a direct effect from the dose before the seminar.

The analysis in this section indicated that changes in haloperidol dose were independent of years of experience. Instead, the following factors were of importance: country of origin in combination with the dose selected before the seminar, workplace in combination with dose selected before the seminar, and number and type of patients in combination with dose selected before the seminar. Chapter 7 analyses whether all these factors are simultaneously important.

6.5.2 Duration of treatment - what explains the changes?

No association was found between changes in duration of treatment and years of experience, country of origin, workplace and number of patients. This conclusion was independent of the type of patient being treated i.e. first- or multi-episode schizophrenia patients. Furthermore, the interactions between the pre-seminar duration of treatment questionnaire responses and the different variables did not have an effect on changes.

In other words, the characteristics of the participants did not explain the difference in changes in duration of treatment.

Instead, when the first-episode schizophrenia patient data were analysed, approximately 25% of the changes in duration of treatment could be understood with reference to the selected duration of treatment before the seminar. Respondents selecting a duration of treatment of less than 18 months pre-seminar increased their duration of treatment by 11 months on average compared with those selecting a duration of treatment above 18 months pre-seminar, who decreased their duration of treatment by approximately 7.8 months. So the net-increase in duration of treatment was approximately 3.3 months by participants who selected below the target before the seminar.

The same applied to the multi-episode schizophrenia patient data. Respondents who gave less than 60 months of treatment before the seminar increased their recommended duration of treatment substantially after the seminar. Therefore the seminars had an effect on the psychiatrists who were furthest out of line in terms of accepted knowledge concerning duration of haloperidol treatment.

To conclude, the selected duration of treatment before the seminar explained approximately 25% of the variation in the changes in the duration of treatment post-seminar; this is more than acceptable.

Chapter 7 Multivariate analysis of changes

Chapter 7 Multivariate analysis of changes

The above conclusions rest on several analyses investigating the relationship between the two dependent variables (duration of treatment and minimum effective haloperidol dose) and one independent variable (e.g. workplace, years of experience) controlled for by behaviour before the seminar (e.g. selected haloperidol dose before the seminar) and their interaction.

The changes in haloperidol dose may not be due to interaction between workplace and haloperidol dose before the seminar. Instead, it could be that the effect of workplace and haloperidol dose before the seminar, on change in haloperidol dose is cancelled out by the interaction between the number of patients and the haloperidol dose before the seminar. This may be the case if district hospitals had many first-episode schizophrenia patients; the reduction in haloperidol dose used at district hospitals is due to the large number of first-episode schizophrenia patients seen at these hospitals compared to the other hospitals. Put differently, working at a district hospital and prescribing a haloperidol dose above the target should result in a lower haloperidol dose after the seminar, independent of the number of first-episode schizophrenia patients. The multivariate analysis presented in this chapter tests exactly this; whether an effect of a variable is present independent of the influence of another variable.

In this chapter all the variables are entered into three distinct models. The first two models explain the changes in duration of treatment concerning first- and multi-episode schizophrenia patients, while the last model analyses the changes in minimum effective haloperidol dose. The interaction-variables are also included. However, the interaction between the different independent variables (e.g. years of experience and number of patients seen) was not included because of the low number of valid cases, and therefore the low statistical significance.

7.1 Multivariate analysis of changes in haloperidol dose

Table 48 below presents the significant model explaining the changes in minimum effective haloperidol dose. All insignificant variables have been omitted.

Table 48: Multivariate regression analysis of factors relating to changes in minimum effective haloperidol dose

	Regression coefficient	Beta-coefficient	Significance (T-test)
Constant	0.179		0.759
Interaction number of schizophrenia patients per year and above 3 mg/day before the seminar	-0.057	-0.264	0.024
Interaction percentage who have schizophrenia and dummy above 3 mg/day before the seminar	-0.103	-0.651	0.000
Interactions total number of patients, percentage of patients that have schizophrenia and dummy above 3 mg/day of haloperidol before the seminar	0.00057	0.406	0.001
Interaction dummy above 3 mg/day of haloperidol before the seminar and dummy group 1	2.640	0.198	0.082
Interaction dummy above 3 mg/day of haloperidol before the seminar and dummy group 2	3.952	0.325	0.002
Explained variation R^2 = 36.0%			**n=83**

As can be seen, this model is different from any of the other models in Chapter 5. The explanation of changes in haloperidol dose was different when all variables were introduced simultaneously.

The model in Table 48 explains 36.0% of the variation in changes in haloperidol dose. The best model in Chapter 6 explained 29.4% change (see Table 47, page 111). In this model the explanatory power is increased significantly.

The haloperidol dose ***decreased*** among those psychiatrists who were above the target of 3 mg/day before the seminar and were either seeing many schizophrenia patients numerically or had a high percentage of schizophrenia patients, compared with the participants who also were above the target but saw less schizophrenia patients in total or percentage-wise. The seminar had an effect on these participants in the intended direction.

Furthermore, the haloperidol dose ***increased*** among the respondents who were above the target of 3 mg/day before the seminar saw many patients in general, ***and*** had a high

percentage of schizophrenia patients compared to those participants who were also above the target but had fewer patients *and* a lower percentage of schizophrenia patients. In other words, particularly good learning took place among psychiatrists who were above the target before the seminar, who saw many schizophrenia patients percentage-wise, *but* this learning was reduced if the particular participant, in addition, saw many patients in total. Therefore, a high number of patients had a ***negative*** learning effect in general, but a *positive* learning effect if these were predominantly schizophrenia patients.

When the standardised beta-coefficients were compared, the variables concerning the type and number of patients explain most of the variation. However, country of origin was also of importance.

The respondents from Group 2 countries, who selected above the 3 mg/day target before the seminar, increased their haloperidol dose compared to respondents from group 3 countries, who also were above the target. The same tendency was present to a lesser extent among participants from group 1 countries. The difference between group 1 and 3 respondents, who were above the target before the seminar, was minimally significant ($p=0.08$). In other words, the greatest effect of the seminar was present among Group 3 psychiatrists. These respondents did not increase their haloperidol dose, when they were above the target before the seminar. These findings are not surprising, especially when it was considered that Group 3 countries - compared to groups 1 and 2 – had the greatest need to learn.

In summary, the *participants who learned the most* had the following characteristics:

They were above the 3 mg/day target before the seminar,
They saw many schizophrenia patients numerically or percentage-wise
They had a low patient number in total and
They were from a Group 3 country.

Finally, a note on the variables that were *not* significant in the multivariate model. From the model it can be concluded that the dose before the seminar did not *directly* affect the dose after the seminar. The seminar did not have a direct effect on those participants who were above the target-dose before the seminar. Instead, the seminar has an indirect effect on these participants through the interaction variables such as number of schizophrenia patients seen.

Furthermore, the interaction between workplace and haloperidol dose before the seminar did not significantly affect the changes in haloperidol dose, i.e. the association between workplace and haloperidol dose selected before the seminar was spurious. Therefore it may be that the district hospitals have many first-episode schizophrenia patients compared to other hospitals.

The significant variables explain 36% of the changes in the haloperidol dose, which is relatively impressive.

7.2 Multivariate analysis of changes in duration of treatment

Table 49 reports the multivariate analysis of changes in duration of treatment of first-episode schizophrenia patients. All the insignificant variables have been left out.

Table 49:Multivariate analysis of factors relating to changes in duration of treatment of first-episode schizophrenia patients

	Regression coefficient	Beta-coefficient	Significance (T-test)
Constant	-6.273		0.000
Dummy below 18 months of treatment before the seminar	11.209	0.492	0.000
Explained variation R^2 = 24.2%			**n=121**

Changes in selected duration of treatment were explained by the pre-seminar duration of treatment questionnaire response. Participants below the recommended target of 18 months for first episode patients increased their duration of treatment by 11.2 months on average compared with the respondents who were above the target. The net-increase in the duration of treatment of participants below the target-period before the seminar was the numerical difference between the constant and the dummy: 4.9 months[7]. In other words, those who were above the target period reduced their duration of treatment by 6.27 months on average.

Duration of treatment recommended before the seminar accounted for 24.2% of the changes in duration of treatment. It is quite unusual for a variable with only two categories to explain almost a quarter of all changes. Normally much more complex models are needed in order to explain so much of the variation. Also here the other

[7] It is only in the unique situation where the explanation of changes in duration of treatment is made up of one dummy-variable, that the constant equals the behaviour of the reference-group.

variables did not contribute to the explanation of the changes in duration of treatment; they were all insignificant.

The same held true when duration of treatment of multi-episode schizophrenia patients was analysed. The result of the multivariate analysis is shown in Table 50.

Table 50: Multivariate regression analysis of factors relating to changes in duration of treatment for multi-episode schizophrenia patients

	Regression coefficient	Beta-coefficient	Significance (T-test)
Constant	-2.348		0.289
Dummy below 60 months of treatment before the seminar	15.667	0.458	0.000
Explained variation R^2 = 21.0%			**n=117**

Table 50 shows that the respondents who selected below 60-months treatment before the seminar increased the duration of treatment by 15.67 months after the seminar compared with the respondents above 60-months before the seminar. The net-increase was 13.3 months.

In this case 21% of the changes in duration of treatment of multi-episode schizophrenia patients were explained by knowledge of the recommended duration of treatment before the seminar. Even taking the simplicity of this variable into consideration, the change was once again quite remarkable.

To summarise, those respondents who were below the recommended duration of treatment for multi-episode patients increased their duration of treatment significantly. In short those psychiatrists who most needed to learn more - those below the target - learned more.

Chapter 8 Discussion

Chapter 8 Discussion

The overall objective of this study was to assess the effect of an educational programme (i.e. an evidence-based schizophrenia seminar presented by the Lundbeck Institute in Denmark) in changing the knowledge, attitudes and treatment habits (behaviour) of psychiatrists attending the programme.

Changes directly attributable to the effect of the seminar were identified in respect of treatment decisions regarding the minimum effective dose of haloperidol in relapse prevention, and treatment durations for first- and multiple-episode schizophrenia patients.

Other treatment decisions that changed significantly, but could not be attributed solely to the effect of the seminar, were the optimal effective haloperidol dose in acute schizophrenia treatment and the drug-class used. Both of these changes were in the desired direction, namely a reduction in the optimal effective haloperidol dose and a change from conventional antipsychotics to the new generation antipsychotics. Background changes in psychiatrists' knowledge also contributed to this change in knowledge and treatment behaviour.

Additionally, it was shown that not all psychiatrists needed to update their knowledge or change their treatment practices; there were many who treated patients within the internationally recommended doses and for the optimal duration prior to attending the seminar. Although expected, it was reassuring that this study confirmed that the greatest effect in achieving change was seen in psychiatrists who were least knowledgeable about recent treatment recommendations and who were furthest from treating their patients in line with current treatment guidelines.

The multivariate analyses of changes in minimum effective haloperidol dose and treatment duration of schizophrenia patients also indicated that the seminars had an effect on the psychiatrists whose knowledge before the seminars was least up to date according to international treatment recommendations. The effect of education was, however, dependent upon a number of factors:

- A high estimated number of patients seen in total,
- A high estimated number of schizophrenia patients, percentage and numerically,
- The nationality of the psychiatrist.

The effective haloperidol dose *decreased* among those psychiatrists who were above the target before the seminar and were either seeing many schizophrenia patients numerically or had a high percentage of schizophrenia patients, compared with the participants who also were above the target but saw less schizophrenia patients in total or percentage-wise. However, the haloperidol dose *increased* among the psychiatrists who were above the target before the seminar, saw many patients in general, *and* had a high percentage of schizophrenia patients compared to those participants who were also above the target but had fewer patients *and* a lower percentage of schizophrenia patients. Effective learning was apparent among psychiatrists who selected a dose above the target dose before the seminar and saw a large proportion of schizophrenia patients, *but* this learning was reduced if the particular psychiatrist, in addition, saw many patients in total. Therefore, a high caseload was associated with a *negative* learning effect in general, but a *positive* learning effect if these were predominantly schizophrenia patients. This suggested that psychiatrists familiar with treating schizophrenia patients were more likely to alter their treatment behaviour, although if the total patient number was too great, this was not the case.

The results obtained from comparing the questionnaires completed 2-weeks and 6-months after the seminar indicated that many of the participants gradually lost newly acquired knowledge after attending these seminars. Although the lack of retention of the knowledge was expected (Andrade et al., 2003; RIA, 1990), it remains of concern, and indicated that strategies should be developed to address this problem in future. The Institute strongly encourages participants to go back to their home countries and use the evidence-based materials provided to present similar local workshops to their colleagues and other mental health care workers. Not only does this assist in disseminating evidence-based treatment guidelines, but it also facilitates the retention of new information. However, it appears that this alone is not sufficient and in future, consideration should be given to introducing specific post-seminar refresher courses (e.g. by e-mail). Another area of concern was that some (albeit few) delegates actually changed their opinions regarding the antipsychotic class and optimal duration of treatment in the wrong direction – i.e. from atypical to conventional antipsychotics, and to a shorter duration of maintenance treatment. The reasons for these changes are not immediately apparent, and should be the subject of future studies.

New research and information regarding the brain and its diseases make it essential that psychiatrists and other clinicians remain regularly updated. The goal of Continued

Medical Education is to use evidence-based medical education to keep doctors abreast of latest research and treatment recommendations.

The results presented here provide empirical evidence to suggest that the Lundbeck Institute's evidence-based seminars in the treatment of schizophrenia succeed in their overall goal of improving the care of patients with schizophrenia. Although some psychiatrists fail to adhere to international treatment recommendations fully after attending the seminar, the results confirm that the participants generally change their treatment practices in line with the internationally accepted recommendations.

8.1 Study limitations

There are several factors in the design of this study that limit its validity.

Selection-bias

Firstly, the selection of the participating countries and psychiatrists was neither random nor representative. While the dataset offered a unique opportunity to investigate the effects of the seminar on psychiatrists from around the world, not all regions of the world are represented in the study. Of particular note is the lack of participants from Latin America and Asia, and that 84% of participants originate from the extended Europe. The Institute had no control over which countries were invited, however, 29 countries are represented. A fairer distribution of countries may provide a different balance.

There were no standard recruitment procedures for the selection of participants. It was, however, recommended that psychiatrists attending the seminar should at least be able to understand and converse in basic English, and have an interest in education. This is clearly a substantial limitation of this study and limits the potential applicability of the results in various countries.

It is possible that the selection process favoured psychiatrists who were keener about the subject and more willing to learn. This would mean that they were more knowledgeable than others prior to the seminar, with less to learn. If that were the case then it would strengthen the results of this study. Showing changes in their knowledge and behaviour would be more difficult to achieve for such a group. However, this is purely speculative and no attempt has been made to test the veracity of this statement.

Another selection limitation of this study includes the fact that the effect of cultural background differences was not addressed in this study.

Lack of a control group

A second significant limitation is the lack of a control group in this study. A control group would enable quantification of the changes in background knowledge that may have explained much of the observed changes – as clearly demonstrated in some of the results presented.

To offset the lack of a control group in this study, the pre-seminar data of the participants in the "later" seminars were regarded as the control group for the "early" seminar participants (e.g. The pre-seminar data of the 1999 seminar participants acted as the control group for those who participated in 1998. Hence many pre-seminar datasets contained data from the first 18 pre-seminar questionnaires as the control for last seminar in this study.) In this way, background changes in treatment principles could be evaluated by comparing the pre-seminar data of the earlier participants with the pre-seminar data of later participants.

However, it should be noted that the clear change in many of these results within a two-week period after the seminar could not be explained as normal background changes in psychiatry.

Self-report questionnaires

The questionnaires used in this study were developed prior to the first seminar in 1997, with the intention of doing a study to track changes in knowledge, attitude and behaviour. The questionnaires were developed by the Lundbeck Institute and may not necessarily represent the optimal style of question-setting technique to measure such change.

The self-reporting nature of the seminar questionnaires also present limitations in that the data may not be a true reflection of the psychiatrists' actual treatment of schizophrenia patients, but rather a recollection of the discussions held at the seminar, or rather a reflection on treatment intentions.

This limitation is partly offset by the two case reports which participants were requested to complete, based on data from their patient files. This could be considered as a more reliable indication of their actual treatment habits. Here again the inclusion of a control group would have resulted in a more objective evaluation of change. Also, a file-review

(case audit) of a sample of the attending psychiatrists, using a similar sample of psychiatrists who did not attend as a control, could have provided an objective measure of the effectiveness of the seminar in achieving its goals. Another method may be to use hospital pharmacy data, which is available in certain countries, or verify treatment by receiving the actual prescriptions of the patients treated by the participants.

Lack of an audit of clinical files

This study should ideally have included a sample audit of patient files of the psychiatrists. This could have countered the self-reporting nature of the questionnaires. Patient files could have been used to compare the prescribing habits (actual behaviour) to the questionnaire responses (intended behaviour). It could have been useful to audit the patient files of a control group compared to the patient files of psychiatrists who attended the seminars.

The international nature of this study contributed to the complexity of using a control group. The participants were from many different countries and thus recorded their patient notes in many different languages. Acquiring access to patient records and actually retrieving data, (in foreign languages, in many different locations in each country that sent psychiatrists to the seminars) would present a daunting challenge. Moreover, had the psychiatrists concerned been randomly selected, one may have been required to travel vast distances to a particular hospital to retrieve data on one psychiatrist and the control. This was considered impractical. In an attempt to minimise this limitation, two case studies were included in the pre-seminar and 6-month post-seminar questionnaires, where doctors were asked to read the cases and find similar cases in their patient records and then answer the questions relating to the areas of treatment we were researching. In this way, data were collected, albeit in a self-reporting format and in relatively small numbers, relating to the actual treatment of patients. The treatment data could then be compared to the data of the psychiatrists' knowledge and their treatment intentions. This allowed for a comparison of knowledge and practise behaviour.

Inconsistent guidelines

There are major inconsistencies and large variations in the treatment recommendations put forward by various authorities in the field of psychiatry. For example, the recommended optimal dose of haloperidol in treatment guidelines varies from 5-14 mg/day (Baldessarini et al., 1988), 11-19 mg/day (Davis et al., 1989), and 5-20 mg/day (Marder, 1996; APA 1997; APA 2004), with newer evidence for ultra-low doses of 1-2 mg/day (Oosthuizen et al., 2001; McEvoy et al., 1991; McEvoy, personal

communication, 2006) while others have until recently studied doses as high as 60 mg/day (Rifkin et al., 1991) and even 200 mg/day (Chang et al., 1994). Challenges to the validity of the concept of minimum effective dose for haloperidol exist, resulting in similarly varying results for haloperidol doses in relapse prevention.

Similar inconsistencies in study results and treatment guidelines are found with regard to schizophrenia treatment duration recommendations, the management of agitated patients, and guidelines for suicide management.

These inconsistencies contribute significantly, understandably, to scepticism of psychiatrists towards evidence-based treatment guidelines, and clearly contribute to a lack of consensus.

The pharmaceutical industry association

The educational seminars studied are hosted and presented by The Lundbeck Institute. Also, the content of these seminars have been written and reviewed by international experts, and have also been evaluated for objectivity by educational and accreditation authorities, and found to be of high standard and lack any bias. However, it is possible that there may be individuals whose answers may be influenced by the association with the pharmaceutical company Lundbeck. Were this to influence the participant's answers in the questionnaire, one should foresee that this may influence the measurement of change.

The use of the English language

The use of the English language throughout this seminar is clearly a limitation to this study. English is spoken as a home language in only of the 29 countries represented in this study. All presentations, literature, discussion and questionnaires used in this study were in English.

Differing diagnostic classification systems

Most, but not all psychiatrists who attend the seminars follow the American Psychiatric Association (APA) DSM diagnostic classification system for psychiatry, with many countries predominantly following the ICD system of the WHO. Due to some subtle, but often important differences between these two systems, it is clear that these diagnostic differences are a confounder in the study, and should be mentioned as a limitation.

8.2 Problems identified and recommendations for future studies

From my reading of the literature, this study is the first of its kind, using trained psychiatrists and attempting to measure the effect of continued medical education. By reviewing the limitations and problems identified from this study, recommendations for future studies emerge.

Selection process

The selection of participants in this study is far from optimal. Although any similar international study would be expensive, it is suggested that participant selection is well thought through prior to study initiation. Selection of participants should attempt to define a universal process for the selection of countries participating and also of the individual psychiatrists. This may be rather difficult to achieve, but may be addressed through own-language education, education taking place in the home country and by doing a randomised selection process of participants. The selection of a randomised and representative sample of participants, and a control group, in future studies would significantly enhance the value of the results.

Language

Teaching in a native language is preferable. Although most international psychiatric journals are printed in English, and international congresses and symposia are conducted in English, it would be naïve to assume that all psychiatrists are willing, or even able, to follow training in English. After the seminars at the Institute, we ask the participants to evaluate the seminars. Data have been collected asking the participants to what degrees they experienced language problems during the seminar. Although these data have not been analysed, experience shows that most participants do not find language to have been a problem during the seminar, but there have been a few who have reported some or much difficulty. Future studies should take the matter of home-language teaching into account where possible.

Retention of knowledge

There is a clear trend of limited long-term retention of new information over time. Although ideal education has not been fully defined, it is clear that didactic lecturing is of little benefit. There should be an emphasis in education in measuring prior knowledge and then presenting the new knowledge in the context of existing knowledge of the participants. Integrating presentations with workgroups seems to enhance knowledge retention. Promoting discussion of the new knowledge, as well as strengthening the

process by encouraging sharing of the new knowledge with others in the field, can further enhance knowledge retention.

The Lundbeck Institute's model of education encourages psychiatrists to return to their home countries and hospitals and use the training they received to train other psychiatrists, registrars, students and mental health workers. It may be possible that the repetition this training creates may increase long-term knowledge retention. This could be studied in future studies, by comparing knowledge-retention of participants who teach their new knowledge, obtained through CME, to others, versus participants who do not teach the new knowledge.

Audit problems

Completing an audit of patient files in this study was considered but was deemed excessively expensive and possible completely impractical, taking patient consent and language issues in the different countries into account. In the future, obtaining hospital pharmacy data, or checking prescriptions could address the lack of an audit to verify participant treatment practises.

8.3 Conclusion

The successful integration of international treatment recommendations into daily psychiatric practise could enhance the quality of life of schizophrenia patients. The value of consensus-seeking, evidence-based medical education in the treatment of schizophrenia needs to be further encouraged. However, evidence-based medical principles alone do not achieve optimal treatment outcomes.

Clinical experience is a cornerstone for all forms of medicine. The practice of evidence-based medicine demands the synergy of experience and science (Sartorius, personal communication, April 2006).

There is, to my mind, no conflict between the science of medicine and the art of treating the individual patient. Good medicine is a fine art that aims to find the symbiosis of science in medical research, and the art of individualising treatment for each particular patient.

The true skill of psychiatry is an art that integrates the complexity of the brain and the human personality, with the ambiguity of diagnosis and the understanding our patient's non-verbal communication and the reality of stigma and suicide, and the subtlety of giving honest answers, yet always treating our patients with compassion and respect while tirelessly instilling hope.

Little wonder that ancient Egyptian medical scrolls were referenced as "Art" rather than "Science" in the old library at Alexandria.

To be doctors we should be
"scientists with our brains
and artists with our hearts"
(*Ancient Chinese proverb)*

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Appendices:

Appendix 1:

Lundbeck Institute

Pre-seminar Questionnaire Schizophrenia

Participant Name: _____ **Week:** _____
Country: _____ **Date: D**_____**M**_____**Y**_____

1. Educational background

Psychiatrist ☐
GP ☐ ***Choose One Only***
Psychologist ☐
Other ☐ _____

2. Where do you practise? (Please tick only the primary place)

University Hospital ☐
District or General Hospital ☐
Private Practice ☐ ***Choose One Only***
Specialised Psychiatric Hospital ☐
Other ☐

3. How many years of experience (including training) do you have in treating psychiatric patients? _____

4. Number of different patients you see on average per month: _____

5. Please indicate the type of patients you see regularly

(Please tick one or more boxes as appropriate)

Acute	☐	Forensic	☐	
Chronic	☐	Rehabilitated	☐	***Choose One or More***
Adolescents	☐	Mixed	☐	
Elderly	☐	Other	☐	

6. Primary responsibility? (Please tick one or more boxes as appropriate)

Out patients only ☐
In patients only ☐
Mixed group ☐ ***Choose One or More***
Rehabilitation ☐
Other ☐

7. Based on your current patient caseload, please indicate the approximate percentage of patients you treat for the following disorders ?

Schizophrenia	_____ %
Organic disorders	_____ %
Depression	_____ %
Mania	_____ %
Bipolar	_____ %
Personality disorders	_____ %
Other	_____ %

8. Approximate number of first-episode schizophrenia patients you see per year? _____

Diagnosis

9. When diagnosing patients with schizophrenia do you use

	Always	Mostly	Sometimes	Never
DSM IV	☐	☐	☐	☐
ICD 10	☐	☐	☐	☐

10. How useful do you find diagnostic tools when diagnosing patients with schizophrenia?

Very useful	☐
Useful	☐
Not very useful	☐
Not useful at all	☐

Treatment of acute episodes

The following questions are designed to learn more about your treatment habits. Although the treatment of each patient will naturally be adapted to his/her individual situation, every doctor has some standards, which he/she modifies according to the individual patients' needs. These questions, based on hypothetical cases, are not designed to test your textbook knowledge, but rather to learn more about your treatment habits of an average patient.

Case 1:
A 24 year old unmarried male student with a first-episode paranoid schizophrenia (ICD 9: 295.3; ICD 10: F20.0) is not tense, posing no danger to himself or others and has no insomnia.

A. If oral monotherapy with oral haloperidol appears to you to be indicated, what average daily dose of haloperidol do you think should be administered at the end of the first week of treatment if the patients exhibit no serious side effects?

_____ mg haloperidol daily ☐ Don't know

B. If oral monotherapy with olanzapine, sertindole or risperidone appears to you to be indicated, what average daily dose do you think should be administered after titrating the dose up?

Olanzapine	_____ mg/month	☐ Don't know
Sertindole	_____ mg/month	☐ Don't know
Risperidone	_____ mg/month	☐ Don't know

C. When would you change this patient's antipsychotic medication if the predominantly positive psychotic symptoms prove resistant to the first treatment with haloperidol?

After _____ weeks of full treatment ☐ Don't know

D. If you could choose the first antipsychotic for this patient, which drug would you use?

Clozapine	☐	_____ mg/day
Flupentixol	☐	_____ mg/day
Haloperidol	☐	_____ mg/day
Risperidone	☐	_____ mg/day
Olanzapine	☐	_____ mg/day
Sertindole	☐	_____ mg/day
Zuclopentixol	☐	_____ mg/day
Fluphenazine decanoate	☐	_____ mg/month
Flupentixol decanoate	☐	_____ mg/month
Haloperidol decanoate	☐	_____ mg/month
Perphenazine decanoate	☐	_____ mg/month
Zuclopentixol decanoate	☐	_____ mg/month
Other	☐	_____mg/day _____mg/month

☐ Don't know

Please note that all doses should be given in mg/month for depot antipsychotics

E. What would you give this patient as a second antipsychotic?

Clozapine	☐	_____ mg/day
Flupentixol	☐	_____ mg/day
Haloperidol	☐	_____ mg/day
Risperidone	☐	_____ mg/day
Olanzapine	☐	_____ mg/day
Sertindole	☐	_____ mg/day
Zuclopentixol	☐	_____ mg/day
Fluphenazine decanoate	☐	_____ mg/month
Flupentixol decanoate	☐	_____ mg/month
Haloperidol decanoate	☐	_____ mg/month
Perphenazine decanoate	☐	_____ mg/month
Zuclopentixol decanoate	☐	_____ mg/month
Other	☐	_____ mg/day_____mg/month

☐ Don't know

Please note that all doses should be given in mg/month for depot antipsychotics

F. When would you consider using clozapine in the patient described in case 1?

First line treatment ☐
Second antipsychotic ☐
Third antipsychotic ☐
I never use clozapine ☐
Don't know ☐

Relapse prevention

Minimum duration of antipsychotic relapse prevention for first-episode patients

Case 2:
A 24 year old unmarried male student suffered a first schizophrenia episode with paranoid and hallucinatory symptoms (ICD 9: 295.3; ICD 10: F20.0) two months ago. The patient was treated with an oral antipsychotic drug and his symptoms have now remitted.

A. If you had no further knowledge about the patient, what would you recommend for further treatment?

☐ Discontinuation of antipsychotics within 3 months

☐ Antipsychotic relapse prevention for _____ months with:

Flupentixol	☐	_____ mg/day
Haloperidol	☐	_____ mg/day
Perphenazine	☐	_____ mg/day
Risperidone	☐	_____ mg/day
Olanzapine	☐	_____ mg/day
Sertindole	☐	_____ mg/day
Zuclopentixol	☐	_____ mg/day
Fluphenazine decanoate	☐	_____ mg/month
Flupentixol decanoate	☐	_____ mg/month
Haloperidol decanoate	☐	_____ mg/month
Perphenazine decanoate	☐	_____ mg/month
Zuclopentixol decanoate	☐	_____ mg/month
Other	☐	_____ mg/day_____mg/month

☐ Don't know

Please note that all doses should be given in mg/month for depot antipsychotics

Minimum duration of antipsychotic relapse prevention for multi-episode patients

Case 3:
A 30 year old female married attorney suffered a first paranoid-hallucinatory schizophrenia episode a year ago, full remission was achieved with antipsychotic treatment (drug not specified), then discontinuation of the antipsychotic. Two months after the discontinuation the patient suffered a second schizophrenia episode (ICD 9: 295.3; ICD 10: F20.0) which has just remitted fully under antipsychotic treatment.

B. If you had no further knowledge about the patient, what would you recommend for further treatment?

☐ Discontinuation of antipsychotic within 3 months

☐ Antipsychotic relapse prevention for _____ months with:

Clozapine	☐	_____ mg/day
Flupentixol	☐	_____ mg/day
Haloperidol	☐	_____ mg/day
Perphenazine	☐	_____ mg/day
Risperidone	☐	_____ mg/day
Olanzapine	☐	_____ mg/day
Sertindole	☐	_____ mg/day
Zuclopentixol	☐	_____ mg/day
Fluphenazine decanoate	☐	_____ mg/month
Flupentixol decanoate	☐	_____ mg/month
Haloperidol decanoate	☐	_____ mg/month
Perphenazine decanoate	☐	_____ mg/month
Zuclopentixol decanoate	☐	_____ mg/month
Other	☐	_____ mg/day_____mg/month

☐ Don't know

Please note that all doses should be given in mg/month for depot antipsychotics

C. If you treated this patient for at least one year, down to which minimum dose could you reduce the prophylactic antipsychotic, according to the literature, without significantly increasing the relapse risk? Please answer according to your best knowledge of the literature for all the drugs below.

- **Oral antipsychotics**

Haloperidol	_____ mg/day	☐ Don't know
Risperidone	_____ mg/day	☐ Don't know
Olanzapine	_____ mg/day	☐ Don't know
Sertindole	_____ mg/day	☐ Don't know
Flupentixol	_____ mg/day	☐ Don't know
Zuclopentixol	_____ mg/day	☐ Don't know

- **Depot antipsychotics**

Haloperidol decanoate	_____ mg/month	☐ Don't know
Fluphenazine decanoate	_____ mg/month	☐ Don't know
Flupentixol decanoate	_____ mg/month	☐ Don't know
Zuclopentixol decanoate	_____ mg/month	☐ Don't know

The following questions are intended to determine on which data your treatment habits are based (own experience and/or results in the scientific literature).

11. How high do you estimate the relapse rate of the patient described in case 1 if no antipsychotic relapse prevention is administered? Please answer both the following questions:

According to my experience the relapse rate within the first year is approximately _____% ☐ Don't know

According to my knowledge of the scientific literature the relapse rate within the first year is approximately _____% ☐ Don't know

12. How high do you estimate the relapse rate after a first schizophrenia episode if continuous antipsychotic relapse prevention is administered? Please answer both the following questions:

According to my experience the relapse rate within the first year is approximately _____% ☐ Don't know

According to my knowledge of the scientific literature the relapse rate within the first year is approximately _____% ☐ Don't know

13. If antipsychotic medication is discontinued in a long term remitted (relapse free for 1 - 5 years on antipsychotic treatment) multiple-episode schizophrenia patient, how high would you estimate the average relapse rate to be?

According to my experience the relapse rate within the first year is approximately _____% ☐ Don't know

According to my knowledge of the scientific literature the relapse rate within the first year is approximately _____% ☐ Don't know

14. If average schizophrenia patients (20-40 years old, no structural brain pathology) are administered an antipsychotic relapse prevention therapy with conventional drugs for 5 years in a medium dosage range, what percentage can be expected to suffer from:

Mild, reversible tardive dyskinesia, approximately _____% ☐ Don't know
Severe, irreversible tardive dyskinesia, approx. _____% ☐ Don't know

Alternative treatment

7 A. From current literature, for which of the following diagnosis is ECT primarily indicated?

Depression	☐
Treatment-resistant depression	☐
Schizophrenia	☐
Severely psychotic, aggressive, acute schizophrenia	☐
Treatment-resistant schizophrenia	☐
Mania	☐
Don't know	☐

7 B. Does your hospital use any written guidelines for ECT treatment?

☐ no
☐ yes
☐ I don't know

7 C. Do you use ECT?

☐ no
☐ yes

If yes, what percentage of your patients with schizophrenia get ECT? _____%

Quality Management

8. Do you use quality management routinely in your hospital?

☐ yes (If yes, please bring the material with you to the seminar)
☐ no

If you answered yes to question 8, please answer questions A-C

A. Do you feed the results of quality management back to your team of health care providers in your hospital?

☐ yes ☐ no

B. Do you compare your results with other hospitals?

☐ yes ☐ no

C. Do you have regular quality meetings?

☐ yes ☐ no

9. Do you use written treatment guidelines which apply to the whole hospital?

☐ yes (If yes, please bring the material with you to the seminar)
☐ no

If yes, how often are they updated?

☐ On a regular basis
☐ They are updated whenever it is judged to be needed
☐ They have not been updated
☐ Don't know

10. Quality management is an unnecessary burden on everyday work?

☐ Agree strongly
☐ Agree slightly
☐ Neither agree nor disagree
☐ Disagree slightly
☐ Disagree strongly

11. Quality management is a management responsibility?

☐ Agree strongly
☐ Agree slightly
☐ Neither agree nor disagree
☐ Disagree slightly
☐ Disagree strongly

Psychoeducation

12. Have psychoeducational interventions (interventions combining information imparting and therapeutic strategies) for patients with schizophrenia or their relatives taken place in your hospital in the past 6 months?

☐ yes
- ☐ For patients only
- ☐ For patient relatives only
- ☐ Bifocal groups (patients and relatives)
- ☐ Single family interventions
- ☐ Multiple family interventions
- ☐ Other

☐ no
- ☐ No suitable patients
- ☐ No suitable group moderators
- ☐ No time
- ☐ Structural problems
- ☐ No interest
- ☐ Not yet but interventions are planned
- ☐ Other

If you answered yes to question 1, please answer questions A-C:

A. What percentage of your patients with schizophrenia and/or their relatives is offered psychoeducation?

Patients: _____%
Relatives: _____%

B. According to which strategy are these interventions performed?

•Focus on:-
- ☐ Psychotherapeutic strategies (behavioural)
- ☐ Psychoeducational strategies (supportive)

•Indication
- ☐ Schizophrenics only
- ☐ Mixed diagnoses

•Duration
- ☐ < 3 months
- ☐ 3 to 6 months
- ☐ > 6 months

•Setting ***(Tick more than one, if necessary)***
- ☐ in patient only
- ☐ out patient only
- ☐ day hospital
- ☐ mixed

C. In your opinion, how do patients / relatives / professionals in your opinion generally accept psychoeducation?

	Highest resistance				Highest acceptance
Patients	☐	☐	☐	☐	☐
Relatives	☐	☐	☐	☐	☐
Professionals	☐	☐	☐	☐	☐

Local Workshops

13. To what extent have you arranged local workshops where you practise?

☐ Formal agreement about a local workshop has been made

How many local workshops have you agreed to do? _____

Is a date set for the local workshop ☐yes ☐no

☐ Informal agreement about a local workshop has been made

☐ I intent to arrange local workshops, but I don't know when
Please indicate the number of local workshops you plan to do _____

☐ I have no current plans of arranging local workshops

Patient case studies

One of the objectives of the seminars at the Lundbeck Institute is to reach consensus on the treatment of schizophrenia. To encourage this we would like to present some data from the real life treatment of patients with schizophrenia. Thus we would like you to fill in a patient diary sheet for two patients as described below. If you don't have a patient in your ward that fits the description, please leave the form blank.

All patients should be between 18-60 years of age, with a diagnosis of paranoid schizophrenia, multiple episode with no other serious illness and not dangerous to themselves or others.

Patient 1
Acute patient:
The patient should have been admitted approximately 4 to 6 weeks ago.

Patient 2
Chronic patient:
The patient should have stayed in the hospital for 4 to 6 months.

Patient 1

Diagnosis (full text or coded) _____
Other important diagnosis _____

Did you use a diagnostic tool? 1 ☐ **ICD10** 2 ☐ **DSM IV** 3 ☐ **Other** 4 ☐ **No**

Number of previous episodes _____
Number of previous admissions _____
Date of this admission: day _____ month _____ Year _____
Today's date: day _____ month _____ Year _____

Psychopathological Findings

(Tick only one box in each line, please)

	None/not at all ill	Borderline	Mild	Moderate	Marked	Severe	Extremely Severe
Positive symptoms	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐
Negative symptoms	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐
Depression	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐
Other findings	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐
Current CGI	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐

CGI relative to admission

0 ☐ Very much improved
1 ☐ Much improved
2 ☐ Minimally improved
3 ☐ No change
4 ☐ Minimally worse
5 ☐ Much worse
6 ☐ Very much worse

Side Effects (SEs)

(Tick only one box in each line, please)

	None	*Mild* and not interfering with patient's performance	Interfering *moderately* with patient's performance	Interfering *markedly* with patient's performance
Tardive dyskinesia	0 ☐	1 ☐	2 ☐	3 ☐
Other EPS	0 ☐	1 ☐	2 ☐	3 ☐
Psychic side effects*	0 ☐	1 ☐	2 ☐	3 ☐
Other important SEs	0 ☐	1 ☐	2 ☐	3 ☐
Global side effect score	0 ☐	1 ☐	2 ☐	3 ☐

***** delirium, tiredness, insomnia, restlessness, depression or quantitative disturbance of consciousness

Current therapeutic consequences

0 ☐ No action
1 ☐ More frequent assessment
2 ☐ Reduction in dose of drug(s)
3 ☐ Discontinuation of drug(s)

Psychotropic Medication

All current antipsychotics

a) generic name _____if oral ___ mg/day / if depot ___ mg/month
b) generic name _____if oral ___ mg/day / if depot ___ mg/month
c) generic name _____if oral ___ mg/day / if depot ___ mg/month
d) generic name _____if oral ___ mg/day / if depot ___ mg/month

Co-medication:

Anti-parkinsonian
1 ☐ No
2 ☐ Yes - If yes, given as prophylactic Rx? 1 ☐ No 2 ☐ Yes

Benzodiazepines
1 ☐ No
2 ☐ Yes - If yes, given as prophylactic Rx ? 1 ☐ No 2 ☐ Yes

Antidepressants
1 ☐ No
2 ☐ Yes - If yes, given as prophylactic Rx? 1 ☐ No 2 ☐ Yes

Other important medication: _____

How many different neuroleptics has the patient received since admission?____

Psychoeducation (PE)

Does the patient take part in PE? 1 ☐ No
2 ☐ Yes - If yes 1 ☐ Group sessions 2 ☐ Others: _____

Do relatives take part in PE? 1 ☐ No
2 ☐ Yes - If yes 1 ☐ Group sessions 2 ☐ Others: _____

Patient 2

Diagnosis (full text or coded) _____
Other important diagnosis _____

Did you use a diagnostic tool? 1 ☐ **ICD10** 2 ☐ **DSM IV** 3 ☐ **Other** 4 ☐ **No**

Number of previous episodes _____
Number of previous admissions _____
Date of this admission: day _____ month _____ Year _____
Today's date: day _____ month _____ Year _____

Psychopathological Findings

(Tick only one box in each line, please)

	None/not at all ill	Borderline	Mild	Moderate	Marked	Severe	Extremely Severe
Positive symptoms	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐
Negative symptoms	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐
Depression	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐
Other findings	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐
Current CGI	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐

CGI relative to admission

0 ☐ Very much improved
1 ☐ Much improved
2 ☐ Minimally improved
3 ☐ No change
4 ☐ Minimally worse
5 ☐ Much worse
6 ☐ Very much worse

Side Effects (SEs)

(Tick only one box in each line, please)

	None	*Mild* and not interfering with patient's performance	Interfering *moderately* with patient's performance	Interfering *markedly* with patient's performance
Tardive dyskinesia	0 ☐	1 ☐	2 ☐	3 ☐
Other EPS	0 ☐	1 ☐	2 ☐	3 ☐
Psychic side effects*	0 ☐	1 ☐	2 ☐	3 ☐
Other important SEs	0 ☐	1 ☐	2 ☐	3 ☐
Global side effect score	0 ☐	1 ☐	2 ☐	3 ☐

***** delirium, tiredness, insomnia, restlessness, depression or quantitative disturbance of consciousness

Current therapeutic consequences

0 ☐ No action
1 ☐ More frequent assessment
2 ☐ Reduction in dose of drug(s)
3 ☐ Discontinuation of drug(s)

Psychotropic Medication

All current antipsychotics

a) generic name _____if oral ___ mg/day / if depot _____ mg/month
b) generic name _____if oral ___ mg/day / if depot _____ mg/month
c) generic name _____if oral ___ mg/day / if depot _____ mg/month
d) generic name _____if oral ___ mg/day / if depot _____ mg/month

Co-medication:

Anti-parkinsonian
1 ☐ No
2 ☐ Yes - If yes, given as prophylactic Rx? 1 ☐ No 2 ☐ Yes

Benzodiazepines
1 ☐ No
2 ☐ Yes - If yes, given as prophylactic Rx ? 1 ☐ No 2 ☐ Yes

Antidepressants
1 ☐ No
2 ☐ Yes - If yes, given as prophylactic Rx ? 1 ☐ No 2 ☐ Yes

Other important medication: _____

How many different neuroleptics has the patient received since admission? _____

Psychoeducation (PE)

Does the patient take part in PE? 1 ☐ No
2 ☐ Yes - If yes 1 ☐ Group sessions 2 ☐ Others: _____

Do relatives take part in PE? 1 ☐ No
2 ☐ Yes - If yes 1 ☐ Group sessions 2 ☐ Others: _____

Appendix 2:

Lundbeck Institute

2 Week follow-up Questionnaire of Schizophrenia seminar

Participant Name: _____ Week: _____
Country: _____ Date: D_____M_____Y_____

Diagnosis

1. How useful do you find diagnostic tools for patients with schizophrenia?

Very useful ☐
Useful ☐
Not very useful ☐
Not useful at all ☐

2. Do you think that diagnosing patients with schizophrenia using ICD 10 and DSM IV are:

Identical ☐
Almost identical ☐
Similar ☐
Totally different ☐
Don't know ☐

Treatment of acute episodes

The following questions are designed to learn more about your treatment habits. Although the treatment of each patient will naturally be adapted to his/her individual situation, every doctor has some standards, which he/she modifies according to the individual patients' needs. These questions, based on hypothetical cases, are not designed to test your textbook knowledge, but rather to learn more about your treatment habits of an average patient.

Case 1:
A 24 year old unmarried male student with a first-episode paranoid schizophrenia (ICD 9: 295.3; ICD 10: F20.0) is not tense, posing no danger to himself or others and has no insomnia.

A. If oral monotherapy with oral haloperidol appears to you to be indicated, what average daily dose of haloperidol do you think should be administered at the end of the first week of treatment if the patients exhibit no serious side effects?

_____ mg haloperidol daily ☐ Don't know

B. If oral monotherapy with olanzapine, sertindole or risperidone appears to you to be indicated, what average daily dose do you think should be administered after titrating the dose up?

Olanzapine	_____ mg/month	☐ Don't know
Sertindole	_____ mg/month	☐ Don't know
Risperidone	_____ mg/month	☐ Don't know

C. When would you change this patient's antipsychotic medication if the predominantly positive psychotic symptoms prove resistant to the first treatment with haloperidol?

After _____ weeks of full treatment ☐ Don't know

D. If you could choose the first antipsychotic for this patient, which drug would you use?

Clozapine	☐	_____ mg/day
Flupentixol	☐	_____ mg/day
Haloperidol	☐	_____ mg/day
Risperidone	☐	_____ mg/day
Olanzapine	☐	_____ mg/day
Sertindole	☐	_____ mg/day
Zuclopentixol	☐	_____ mg/day
Fluphenazine decanoate	☐	_____ mg/month
Flupentixol decanoate	☐	_____ mg/month
Haloperidol decanoate	☐	_____ mg/month
Perphenazine decanoate	☐	_____ mg/month
Zuclopentixol decanoate	☐	_____ mg/month
Other	☐	_____mg/day _____mg/month

☐ Don't know

Please note that all doses should be given in mg/month for depot antipsychotics

E. What would you give this patient as a second antipsychotic?

Clozapine	☐	_____ mg/day
Flupentixol	☐	_____ mg/day
Haloperidol	☐	_____ mg/day
Risperidone	☐	_____ mg/day
Olanzapine	☐	_____ mg/day
Sertindole	☐	_____ mg/day
Zuclopentixol	☐	_____ mg/day
Fluphenazine decanoate	☐	_____ mg/month
Flupentixol decanoate	☐	_____ mg/month
Haloperidol decanoate	☐	_____ mg/month
Perphenazine decanoate	☐	_____ mg/month
Zuclopentixol decanoate	☐	_____ mg/month
Other	☐	_____ mg/day_____mg/month

☐ Don't know

Please note that all doses should be given in mg/month for depot antipsychotics

F. When would you consider using clozapine in the patient described in case 1?

First line treatment ☐
Second antipsychotic ☐
Third antipsychotic ☐
I never use clozapine ☐
Don't know ☐

Relapse prevention

Minimum duration of antipsychotic relapse prevention for first-episode patients

Case 2:
A 24 year old unmarried male student suffered a first schizophrenia episode with paranoid and hallucinatory symptoms (ICD 9: 295.3; ICD 10: F20.0) two months ago. The patient was treated with an oral antipsychotic drug and his symptoms have now remitted.

D. If you had no further knowledge about the patient, what would you recommend for further treatment?

☐ Discontinuation of antipsychotics within 3 months

☐ Antipsychotic relapse prevention for _____ months with:

Flupentixol	☐	_____ mg/day
Haloperidol	☐	_____ mg/day
Perphenazine	☐	_____ mg/day
Risperidone	☐	_____ mg/day
Olanzapine	☐	_____ mg/day
Sertindole	☐	_____ mg/day
Zuclopentixol	☐	_____ mg/day
Fluphenazine decanoate	☐	_____ mg/month
Flupentixol decanoate	☐	_____ mg/month
Haloperidol decanoate	☐	_____ mg/month
Perphenazine decanoate	☐	_____ mg/month
Zuclopentixol decanoate	☐	_____ mg/month
Other	☐	_____ mg/day_____mg/month

☐ Don't know

Please note that all doses should be given in mg/month for depot antipsychotics

Minimum duration of antipsychotic relapse prevention for multi-episode patients

Case 3:
A 30 year old female married attorney suffered a first paranoid-hallucinatory schizophrenia episode a year ago, full remission was achieved with antipsychotic treatment (drug not specified), then discontinuation of the antipsychotic. Two months after the discontinuation the patient suffered a second schizophrenia episode (ICD 9: 295.3; ICD 10: F20.0) which has just remitted fully under antipsychotic treatment.

E. If you had no further knowledge about the patient, what would you recommend for further treatment?

☐ Discontinuation of antipsychotic within 3 months

☐ Antipsychotic relapse prevention for _____ months with:

Clozapine	☐	_____ mg/day
Flupentixol	☐	_____ mg/day
Haloperidol	☐	_____ mg/day
Perphenazine	☐	_____ mg/day
Risperidone	☐	_____ mg/day
Olanzapine	☐	_____ mg/day
Sertindole	☐	_____ mg/day
Zuclopentixol	☐	_____ mg/day
Fluphenazine decanoate	☐	_____ mg/month
Flupentixol decanoate	☐	_____ mg/month
Haloperidol decanoate	☐	_____ mg/month
Perphenazine decanoate	☐	_____ mg/month
Zuclopentixol decanoate	☐	_____ mg/month
Other	☐	_____ mg/day_____mg/month

☐ Don't know

Please note that all doses should be given in mg/month for depot antipsychotics

F. If you treated this patient for at least one year, down to which minimum dose could you reduce the prophylactic antipsychotic, according to the literature, without significantly increasing the relapse risk? Please answer according to your best knowledge of the literature for all the drugs below.

- **Oral antipsychotics**

Haloperidol	_____ mg/day	☐ Don't know
Risperidone	_____ mg/day	☐ Don't know
Olanzapine	_____ mg/day	☐ Don't know
Sertindole	_____ mg/day	☐ Don't know
Flupentixol	_____ mg/day	☐ Don't know
Zuclopentixol	_____ mg/day	☐ Don't know

- **Depot antipsychotics**

Haloperidol decanoate	_____ mg/month	☐ Don't know
Fluphenazine decanoate	_____ mg/month	☐ Don't know
Flupentixol decanoate	_____ mg/month	☐ Don't know
Zuclopentixol decanoate	_____ mg/month	☐ Don't know

The following questions are intended to determine on which data your treatment habits are based (own experience and/or results in the scientific literature).

4. **How high do you estimate the relapse rate of the patient described in case 1 if no antipsychotic relapse prevention is administered? Please answer both the following questions:**

According to my experience the relapse rate within the first year is approximately _____% ☐ Don't know

According to my knowledge of the scientific literature the relapse rate within the first year is approximately _____% ☐ Don't know

5. **How high do you estimate the relapse rate after a first schizophrenia episode if continuous antipsychotic relapse prevention is administered? Please answer both the following questions:**

According to my experience the relapse rate within the first year is approximately _____% ☐ Don't know

According to my knowledge of the scientific literature the relapse rate within the first year is approximately _____% ☐ Don't know

6. **If antipsychotic medication is discontinued in a long term remitted (relapse free for 1 - 5 years on antipsychotic treatment) multiple-episode schizophrenia patient, how high would you estimate the average relapse rate to be?**

According to my experience the relapse rate within the first year is approximately _____% ☐ Don't know

According to my knowledge of the scientific literature the relapse rate within the first year is approximately _____% ☐ Don't know

7. **If average schizophrenia patients (20-40 years old, no structural brain pathology) are administered an antipsychotic relapse prevention therapy with conventional drugs for 5 years in a medium dosage range, what percentage can be expected to suffer from:**

Mild, reversible tardive dyskinesia, approximately _____% ☐ Don't know
Severe, irreversible tardive dyskinesia, approx. _____% ☐ Don't know

Alternative treatment

8. From current literature, for which of the following diagnosis is ECT primarily indicated?

Depression	☐
Treatment-resistant depression	☐
Schizophrenia	☐
Severely psychotic, aggressive, acute schizophrenia	☐
Treatment-resistant schizophrenia	☐
Mania	☐
Don't know	☐

Quality Management

9. Quality management is an unnecessary burden on everyday work?

☐ Agree strongly
☐ Agree slightly
☐ Neither agree nor disagree
☐ Disagree slightly
☐ Disagree strongly

10. Quality management is a management responsibility?

☐ Agree strongly
☐ Agree slightly
☐ Neither agree nor disagree
☐ Disagree slightly
☐ Disagree strongly

Psychoeducation

11. In your opinion, how do patients / relatives / professionals in your opinion generally accept psychoeducation?

	Highest resistance				Highest acceptance
Patients	☐	☐	☐	☐	☐
Relatives	☐	☐	☐	☐	☐
Professionals	☐	☐	☐	☐	☐

Appendix 3:

Lundbeck Institute

6 Month follow-up Questionnaire of Schizophrenia seminar

Participant Name: _____ Week: _____
Country: _____ Date: D_____M_____Y_____

Diagnosis

1. How useful do you find diagnostic tools for patients with schizophrenia?

Very useful ☐
Useful ☐
Not very useful ☐
Not useful at all ☐

2. Do you think that diagnosing patients with schizophrenia using ICD 10 and DSM IV are:

Identical ☐
Almost identical ☐
Similar ☐
Totally different ☐
Don't know ☐

Treatment of acute episodes

Case 1:
A 24 year old unmarried male student with a first-episode paranoid schizophrenia (ICD 9: 295.3; ICD 10: F20.0) is not tense, posing no danger to himself or others and has no insomnia.

A. If oral monotherapy with oral haloperidol appears to you to be indicated, what average daily dose of haloperidol do you think should be administered at the end of the first week of treatment if the patients exhibit no serious side effects?

_____ mg haloperidol daily ☐ Don't know

B. If oral monotherapy with olanzapine, sertindole or risperidone appears to you to be indicated, what average daily dose do you think should be administered after titrating the dose up?

Olanzapine _____ mg/month ☐ Don't know
Sertindole _____ mg/month ☐ Don't know
Risperidone _____ mg/month ☐ Don't know

When would you change this patient's antipsychotic medication if the predominantly positive psychotic symptoms prove resistant to the first treatment with haloperidol?

After _____ weeks of full treatment ☐ Don't know

D. If you could choose the first antipsychotic for this patient, which drug would you use?

Clozapine	☐	_____ mg/day
Flupentixol	☐	_____ mg/day
Haloperidol	☐	_____ mg/day
Risperidone	☐	_____ mg/day
Olanzapine	☐	_____ mg/day
Sertindole	☐	_____ mg/day
Zuclopentixol	☐	_____ mg/day
Fluphenazine decanoate	☐	_____ mg/month
Flupentixol decanoate	☐	_____ mg/month
Haloperidol decanoate	☐	_____ mg/month
Perphenazine decanoate	☐	_____ mg/month
Zuclopentixol decanoate	☐	_____ mg/month
Other	☐	_____mg/day _____mg/month

☐ Don't know
Please note that doses should be given in mg/month for depot antipsychotics

E. What would you give this patient as a second antipsychotic?

Clozapine	☐	_____ mg/day
Flupentixol	☐	_____ mg/day
Haloperidol	☐	_____ mg/day
Risperidone	☐	_____ mg/day
Olanzapine	☐	_____ mg/day
Sertindole	☐	_____ mg/day

Zuclopentixol	☐	_____ mg/day
Fluphenazine decanoate	☐	_____ mg/month
Flupentixol decanoate	☐	_____ mg/month
Haloperidol decanoate	☐	_____ mg/month
Perphenazine decanoate	☐	_____ mg/month
Zuclopentixol decanoate	☐	_____ mg/month
Other	☐	_____ mg/day_____mg/month

☐ Don't know

Please note that all doses should be given in mg/month for depot antipsychotics

F. When would you consider using clozapine in the patient described in case 1?

First line treatment ☐
Second antipsychotic ☐
Third antipsychotic ☐
I never use clozapine ☐
Don't know ☐

Relapse prevention

Minimum duration of antipsychotic relapse prevention for first-episode patients

Case 2:
A 24 year old unmarried male student suffered a first schizophrenia episode with paranoid and hallucinatory symptoms (ICD 9: 295.3; ICD 10: F20.0) two months ago. The patient was treated with an oral antipsychotic drug and his symptoms have now remitted.

G. If you had no further knowledge about the patient, what would you recommend for further treatment?

☐ Discontinuation of antipsychotics within 3 months

☐ Antipsychotic relapse prevention for _____ months with:

Flupentixol	☐	_____ mg/day
Haloperidol	☐	_____ mg/day
Perphenazine	☐	_____ mg/day
Risperidone	☐	_____ mg/day
Olanzapine	☐	_____ mg/day
Sertindole	☐	_____ mg/day
Zuclopentixol	☐	_____ mg/day
Fluphenazine decanoate	☐	_____ mg/month
Flupentixol decanoate	☐	_____ mg/month
Haloperidol decanoate	☐	_____ mg/month
Perphenazine decanoate	☐	_____ mg/month
Zuclopentixol decanoate	☐	_____ mg/month
Other	☐	_____ mg/day_____mg/month

☐ Don't know

Please note that all doses should be given in mg/month for depot antipsychotics

Minimum duration of antipsychotic relapse prevention for multi-episode patients

Case 3:
A 30 year old female married attorney suffered a first paranoid-hallucinatory schizophrenia episode a year ago, full remission was achieved with antipsychotic treatment (drug not specified), then discontinuation of the antipsychotic. Two months after the discontinuation the patient suffered a second schizophrenia episode (ICD 9: 295.3; ICD 10: F20.0) which has just remitted fully under antipsychotic treatment.

H. If you had no further knowledge about the patient, what would you recommend for further treatment?

☐ Discontinuation of antipsychotic within 3 months

☐ Antipsychotic relapse prevention for _____ months with:

Clozapine	☐	_____ mg/day
Flupentixol	☐	_____ mg/day
Haloperidol	☐	_____ mg/day
Perphenazine	☐	_____ mg/day
Risperidone	☐	_____ mg/day
Olanzapine	☐	_____ mg/day
Sertindole	☐	_____ mg/day
Zuclopentixol	☐	_____ mg/day
Fluphenazine decanoate	☐	_____ mg/month
Flupentixol decanoate	☐	_____ mg/month
Haloperidol decanoate	☐	_____ mg/month
Perphenazine decanoate	☐	_____ mg/month
Zuclopentixol decanoate	☐	_____ mg/month
Other	☐	_____ mg/day_____mg/month

☐ Don't know

Please note that all doses should be given in mg/month for depot antipsychotics

I. If you treated this patient for at least one year, down to which minimum dose could you reduce the prophylactic antipsychotic, according to the literature, without significantly increasing the relapse risk? Please answer according to your best knowledge of the literature for all the drugs below.

- **Oral antipsychotics**

Haloperidol	_____ mg/day	☐ Don't know
Risperidone	_____ mg/day	☐ Don't know
Olanzapine	_____ mg/day	☐ Don't know
Sertindole	_____ mg/day	☐ Don't know
Flupentixol	_____ mg/day	☐ Don't know
Zuclopentixol	_____ mg/day	☐ Don't know

- **Depot antipsychotics**

Haloperidol decanoate	_____ mg/month	☐ Don't know
Fluphenazine decanoate	_____ mg/month	☐ Don't know
Flupentixol decanoate	_____ mg/month	☐ Don't know
Zuclopentixol decanoate	_____ mg/month	☐ Don't know

The following questions are intended to determine on which data your treatment habits are based (own experience and/or results in the scientific literature).

3. **How high do you estimate the relapse rate of the patient described in case 1 if no antipsychotic relapse prevention is administered? Please answer both the following questions:**

According to my experience the relapse rate within the first year is approximately _____% ☐ Don't know

According to my knowledge of the scientific literature the relapse rate within the first year is approximately _____% ☐ Don't know

4. **How high do you estimate the relapse rate after a first schizophrenia episode if continuous antipsychotic relapse prevention is administered? Please answer both the following questions:**

According to my experience the relapse rate within the first year is approximately _____% ☐ Don't know

According to my knowledge of the scientific literature the relapse rate within the first year is approximately _____% ☐ Don't know

5. **If antipsychotic medication is discontinued in a long term remitted (relapse free for 1 - 5 years on antipsychotic treatment) multiple-episode schizophrenia patient, how high would you estimate the average relapse rate to be?**

According to my experience the relapse rate within the first year is approximately _____% ☐ Don't know

According to my knowledge of the scientific literature the relapse rate within the first year is approximately _____% ☐ Don't know

6. **If average schizophrenia patients (20-40 years old, no structural brain pathology) are administered an antipsychotic relapse prevention therapy with conventional drugs for 5 years in a medium dosage range, what percentage can be expected to suffer from:**

Mild, reversible tardive dyskinesia, approximately _____% ☐ Don't know
Severe, irreversible tardive dyskinesia, approx. _____% ☐ Don't know

Alternative treatment

7. From current literature, for which of the following diagnosis is ECT primarily indicated?

Depression	☐
Treatment-resistant depression	☐
Schizophrenia	☐
Severely psychotic, aggressive, acute schizophrenia	☐
Treatment-resistant schizophrenia	☐
Mania	☐
Don't know	☐

Quality Management

8. Quality management is an unnecessary burden on everyday work?

☐ Agree strongly
☐ Agree slightly
☐ Neither agree nor disagree
☐ Disagree slightly
☐ Disagree strongly

9. Quality management is a management responsibility?

☐ Agree strongly
☐ Agree slightly
☐ Neither agree nor disagree
☐ Disagree slightly
☐ Disagree strongly

Local Workshops

10. To what extent have you arranged local workshops where you practise?

☐ Formal agreement about a local workshop has been made

How many local workshops have you agreed to do? _____

Is a date set for the local workshop ☐yes ☐no

☐ Informal agreement about a local workshop has been made

☐ I intent to arrange local workshops, but I don't know when
Please indicate the number of local workshops you plan to do _____

☐ I have no current plans of arranging local workshops

Patient case studies

One of the objectives of the seminars at the Lundbeck Institute is to reach consensus on the treatment of schizophrenia. To encourage this we would like to present some data from the real life treatment of patients with schizophrenia. Thus we would like you to fill in a patient diary sheet for two patients as described below. If you don't have a patient in your ward that fits the description, please leave the form blank.

All patients should be between 18-60 years of age, with a diagnosis of paranoid schizophrenia, multiple episode with no other serious illness and not dangerous to themselves or others.

Patient 1
Acute patient:
The patient should have been admitted approximately 4 to 6 weeks ago.

Patient 2
Chronic patient:
The patient should have stayed in the hospital for 4 to 6 months.

Patient 1

Diagnosis (full text or coded) _____
Other important diagnosis _____

Did you use a diagnostic tool? 1 ☐ **ICD10** 2 ☐ **DSM IV** 3 ☐ **Other** 4 ☐ **No**

Number of previous episodes _____
Number of previous admissions _____
Date of this admission: day _____ month _____ Year _____
Today's date: day _____ month _____ Year _____

Psychopathological Findings

(Tick only one box in each line, please)

	None/not at all ill	Borderline	Mild	Moderate	Marked	Severe	Extremely Severe
Positive symptoms	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐
Negative symptoms	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐
Depression	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐
Other findings	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐
Current CGI	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐

CGI relative to admission

0 ☐ Very much improved
1 ☐ Much improved
2 ☐ Minimally improved
3 ☐ No change
4 ☐ Minimally worse
5 ☐ Much worse
6 ☐ Very much worse

Side Effects (SEs)

(Tick only one box in each line, please)

	None	*Mild* and not interfering with patient's performance	Interfering *moderately* with patient's performance	Interfering *markedly* with patient's performance
Tardive dyskinesia	0 ☐	1 ☐	2 ☐	3 ☐
Other EPS	0 ☐	1 ☐	2 ☐	3 ☐
Psychic side effects*	0 ☐	1 ☐	2 ☐	3 ☐
Other important SEs	0 ☐	1 ☐	2 ☐	3 ☐
Global side effect score	0 ☐	1 ☐	2 ☐	3 ☐

***** delirium, tiredness, insomnia, restlessness, depression or quantitative disturbance of consciousness

Current therapeutic consequences

0 ☐ No action
1 ☐ More frequent assessment
2 ☐ Reduction in dose of drug(s)
3 ☐ Discontinuation of drug(s)

Psychotropic Medication

All current antipsychotics

a) generic name _____if oral ___ mg/day / if depot ___ mg/month
b) generic name _____if oral ___ mg/day / if depot ___ mg/month
c) generic name _____if oral ___ mg/day / if depot ___ mg/month
d) generic name _____if oral ___ mg/day / if depot ___ mg/month

Co-medication:

Anti-parkinsonian
1 ☐ No
2 ☐ Yes - If yes, given as prophylactic Rx? 1 ☐ No 2 ☐ Yes

Benzodiazepines
1 ☐ No
2 ☐ Yes - If yes, given as prophylactic Rx ? 1 ☐ No 2 ☐ Yes

Antidepressants
1 ☐ No
2 ☐ Yes - If yes, given as prophylactic Rx? 1 ☐ No 2 ☐ Yes

Other important medication: _____

How many different neuroleptics has the patient received since admission?___

Psychoeducation (PE)

Does the patient take part in PE? 1 ☐ No
2 ☐ Yes - If yes 1 ☐ Group sessions 2 ☐ Others: _____

Do relatives take part in PE? 1 ☐ No
2 ☐ Yes - If yes 1 ☐ Group sessions 2 ☐ Others: _____

Patient 2

Diagnosis (full text or coded) _____
Other important diagnosis _____

Did you use a diagnostic tool? 1 ☐ **ICD10** 2 ☐ **DSM IV** 3 ☐ **Other** 4 ☐ **No**

Number of previous episodes _____
Number of previous admissions _____
Date of this admission: day _____ month _____ Year _____
Today's date: day _____ month _____ Year _____

Psychopathological Findings

(Tick only one box in each line, please)

	None/not at all ill	Borderline	Mild	Moderate	Marked	Severe	Extremely Severe
Positive symptoms	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐
Negative symptoms	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐
Depression	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐
Other findings	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐
Current CGI	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐

CGI relative to admission

0 ☐ Very much improved
1 ☐ Much improved
2 ☐ Minimally improved
3 ☐ No change
4 ☐ Minimally worse
5 ☐ Much worse
6 ☐ Very much worse

Side Effects (SEs)

(Tick only one box in each line, please)

	None	*Mild* and not interfering with patient's performance	Interfering *moderately* with patient's performance	Interfering *markedly* with patient's performance
Tardive dyskinesia	0 ☐	1 ☐	2 ☐	3 ☐
Other EPS	0 ☐	1 ☐	2 ☐	3 ☐
Psychic side effects*	0 ☐	1 ☐	2 ☐	3 ☐
Other important SEs	0 ☐	1 ☐	2 ☐	3 ☐
Global side effect score	0 ☐	1 ☐	2 ☐	3 ☐

***** delirium, tiredness, insomnia, restlessness, depression or quantitative disturbance of consciousness

Current therapeutic consequences

0 ☐ No action
1 ☐ More frequent assessment
2 ☐ Reduction in dose of drug(s)
3 ☐ Discontinuation of drug(s)

Psychotropic Medication

All current antipsychotics

a) generic name _____if oral ___ mg/day / if depot _____ mg/month
b) generic name _____if oral ___ mg/day / if depot _____ mg/month
c) generic name _____if oral ___ mg/day / if depot _____ mg/month
d) generic name _____if oral ___ mg/day / if depot _____ mg/month

Co-medication:

Anti-parkinsonian
1 ☐ No
2 ☐ Yes - If yes, given as prophylactic Rx? 1 ☐ No 2 ☐ Yes

Benzodiazepines
1 ☐ No
2 ☐ Yes - If yes, given as prophylactic Rx ? 1 ☐ No 2 ☐ Yes

Antidepressants
1 ☐ No
2 ☐ Yes - If yes, given as prophylactic Rx ? 1 ☐ No 2 ☐ Yes

Other important medication: _____

How many different neuroleptics has the patient received since admission? ___

Psychoeducation (PE)

Does the patient take part in PE? 1 ☐ No
2 ☐ Yes - If yes 1 ☐ Group sessions 2 ☐ Others: _____

Do relatives take part in PE? 1 ☐ No
2 ☐ Yes - If yes 1 ☐ Group sessions 2 ☐ Others: _____

Appendix 4:

Extended Abstract

This study reports on the effect of education. It analyses changes in knowledge, attitude and behaviour among psychiatrists who attended evidence-based schizophrenia seminars presented by the Lundbeck Institute in Denmark.

The objectives of the study were two-fold. Firstly, it set out to determine whether changes occurred in knowledge, attitude and treatment habits (behaviour) two weeks and six months after the seminar; specifically, changes in choice of optimal haloperidol dose, duration of maintenance treatment and drug-class (conventional versus new generation antipsychotic) used and whether these changes could be ascribed to the schizophrenia seminars. Secondly, it attempted to identify factors that could predict the likelihood of participants learning new knowledge or changing their behaviour.

The **haloperidol dose prescribed** was analysed in two situations: acute treatment setting where the most *effective dose* is used, and in maintenance treatment of schizophrenia where the *minimum effective dose* is used to prevent a relapse. In the acute episode situation, respondents were asked what they thought the *most effective haloperidol dose* would be. In the case of relapse prevention in multi-episode patients, the respondents were asked what the *minimum effective haloperidol dose* would be for a 30-year-old female, without increasing the relapse risk. Changes in doses of haloperidol selected were measured using two case studies in the questionnaires (Cases 1 and 2 – see appendices 1 and 3).

The analysis of change in selected minimum effective haloperidol dose showed that the average recommended dose dropped significantly after the seminar, in comparison with the dose before the seminar. However, evidence of change was less apparent with regard to the most effective haloperidol dose.

Changes in the selected optimal **duration of treatment** were measured for both first-episode and multi-episode schizophrenia patients. The analyses showed that significant changes occurred in the selected duration of treatment of multi-episode schizophrenia patients when the duration of treatment before the seminar and 6-months after were compared. The change in the duration of treatment of first-episode schizophrenia patients was not significant. However, the comparison of mean scores took account of the fact that not all participants were expected to change their behaviour; some participants knew the correct optimal duration of treatment before the seminar. The

chapter analysing the changes in prescribing pattern showed that participants who were prescribing less than the recommended minimum duration of treatment increased the duration of their treatment after the seminar, compared to those who were prescribing a longer duration than the recommended duration of treatment. A significant change occurred in the behaviour of those participants who, according to accepted guidelines, should change their behaviour.

Changes in the antipsychotic **drug-class** selected were analysed for both first-episode and multi-episode schizophrenia patients. Furthermore, a differentiation was made between the intended behaviour and the actual behaviour. Explain how!

Concerning the intended behaviour, there was a significant shift towards new generation drugs from before the seminar to 6-months after the seminar. However - and quite interestingly - the actual drug-class used did not change significantly from what it was before the seminar to 6-months after the seminar, despite a significant change in the ?intended drug-class in question. This suggests that if the significant change in the intended drug-class selected was due to the seminar, the seminar had a greater effect on the *intended* behaviour than on the actual behaviour.

Overall, despite significant changes from before the seminar to 6-months after the seminar in all areas, these changes may not necessarily be attributable to the seminar. Knowledge develops over time, so a general increase in background knowledge i.e. ????? or e.g. could account for the changes. To take this factor into account, the development in knowledge was analysed by comparing certain key characteristics of the respondents in the pre-dataset and the 6-months-dataset.

The analysis of delegates' knowledge showed that the knowledge of the minimum effective haloperidol dose and optimal duration of treatment was stable over time. There was no significant difference between the knowledge of the participants who joined the seminar in the first two years they were held versus those who attended the seminar in the last two years with regard to the minimum effective haloperidol dose and optimal duration of treatment.

By contrast, the most effective haloperidol dose selected and the antipsychotic drug-class selected changed over time depending on when participants attended the seminar. There was a significant difference between the earlier participants at the seminars and later participants. In respect of the most effective haloperidol dose, more of the earlier participants were above the target dose of 5 mg/day than the later participants. Thus,

at best, changes in the effective haloperidol dose seem to be only partially attributable to the effects of seminar learning.

More of the later participants tended to use new generation drugs before the seminar than the earlier participants. Furthermore, the changes in drug-class selected two weeks after the seminar were insignificant among those who attended the later seminars. The latter indicates that the seminar primarily affected earlier participants only. Based on this, the study concluded that the change in drug-class selected from before the seminar to 6-months after the seminar was probably due to changes in background knowledge about new generation antipsychotic drugs.

Despite the knowledge of duration of treatment and haloperidol dose being stable across time, the respondents of the pre-questionnaire and the respondents of the 6-months-questionnaire might be different. It could have been that particularly good learners filled in the 6-months questionnaire, resulting in an overestimation of the effects of the seminar. In order to take this into account, a comparison was made between the pre-dataset and the 6-months-dataset on four key-characteristics; country of origin; years of practice; number of patients; and workplace. The comparisons showed no significant difference between the datasets.

In light of this, it seems the seminars have a significant effect on the duration of treatment and the minimum effective dose of haloperidol used, but a less than significant effect on the most effective haloperidol dose and selection of drug-class. The study therefore concentrated on explaining variation in changes in optimal duration of treatment and minimum effective haloperidol dose.

Chapter 6 explores why some psychiatrists changed their behaviour and others did not. Put differently: why did the seminar have an effect on some participants and not others? Which factors influenced a psychiatrist's ability to learn and practise new behaviour? Comprehension of variation in changes is understood with regard to duration of treatment and minimum effective haloperidol dose.

The study investigated four hypotheses concerning changes in behaviour. Changes in behaviour after the seminar could be linked to certain nationalities, number of patients seen in clinical practice, number of years of psychiatric experience and workplace.

In respect of changes in the selected optimal duration of treatment, the study found that the duration of treatment before the seminar explained between 20 and 25% of all the

changes in behaviour depending on whether the patients were first-episode or multi-episode schizophrenia patients. Therefore a participant, whose selected optimal duration of treatment before the seminar was below that recommended in the seminar, increased the duration of their treatment after the seminar. None of the other factors affected the changes in duration of treatment of either first-episode or multi-episode schizophrenia patients. In this sense the seminar had the intended effect; those participants who most needed to change behaviour did so independently of other characteristics such as number of patients seen in clinical practice and nationality.

The seminars did not seem to have any direct effect on participants who chose a dose above the target haloperidol dose before the seminar. In other words, changes in the dose after a seminar could not be ascribed solely to the dose used before a seminar. It seems that the seminars had an indirect effect on the participants whose recommendation was above the target haloperidol dose before the seminar. Changes in haloperidol dose seemed to occur among participants who prescribed more than the target before a seminar **and** either saw many schizophrenia patients or had a high percentage of schizophrenia patients in their caseloads. These psychiatrists reduced their selected optimal haloperidol dose more compared with psychiatrists who were above the target, but either saw fewer first-episode schizophrenia patients or had a lower percentage of schizophrenia patients. Therefore, the number of schizophrenia patients and the percentages of schizophrenia patients in relation to the overall caseload, in combination with the recommended optimal haloperidol dose before the seminar, all had a role in explaining the decreases in the haloperidol dose selected.

Of the psychiatrists who prescribed more than the target dose before the seminar, those who **increased** the haloperidol dose saw a high percentage of schizophrenia patients and had many patients in general in their clinical practices, compared to those with a high percentage of schizophrenia patients, but a lower overall caseload. Therefore, the number of patients had a negative effect in general, but had a positive learning effect if the patients were mainly schizophrenia patients.

The country of origin also exercised an influence on the changes in the minimum effective dose of haloperidol. In order to ascertain this, psychiatrists were divided into three groups of countries. Country Group 2 respondents, who were above the target dose before the seminar, increased their selected optimal haloperidol dose, compared with Group 3 respondents, who also prescribed above the target before the seminar. To a lesser extent, the same was probably true for Group 1 participants.

In view of this, it was concluded that the seminars had no direct effect on psychiatrists who were prescribing more than the target effective haloperidol dose before the seminar. Participants' preferred effective haloperidol dose or optimal treatment duration pre seminar could not alone account for the changes in prescribed dose post seminar. It seems that the effect of the seminars depended firstly on the number and type of patients the psychiatrist saw, and secondly on the country of origin of the psychiatrist, in combination with the recommended dose before the seminar. The other variables (workplace, years of experience) did not influence the changes in optimal haloperidol dose selected.

In summary, the changes in behaviour concerning duration of treatment and haloperidol dose could validly be ascribed to the seminar. The change in the drug-class used was probably due to changes in background knowledge. There were differences between the participants with regard to changes in duration of treatment and changes in optimal haloperidol dose. The changes in the haloperidol dose were also dependent upon the dose being prescribed before the seminar. However, other factors such as caseload size and participant nationality must be taken into account in conjunction with the prescribed dose before the seminar. Changes in duration of treatment can be explained by the answers of respondents before attending the seminar.