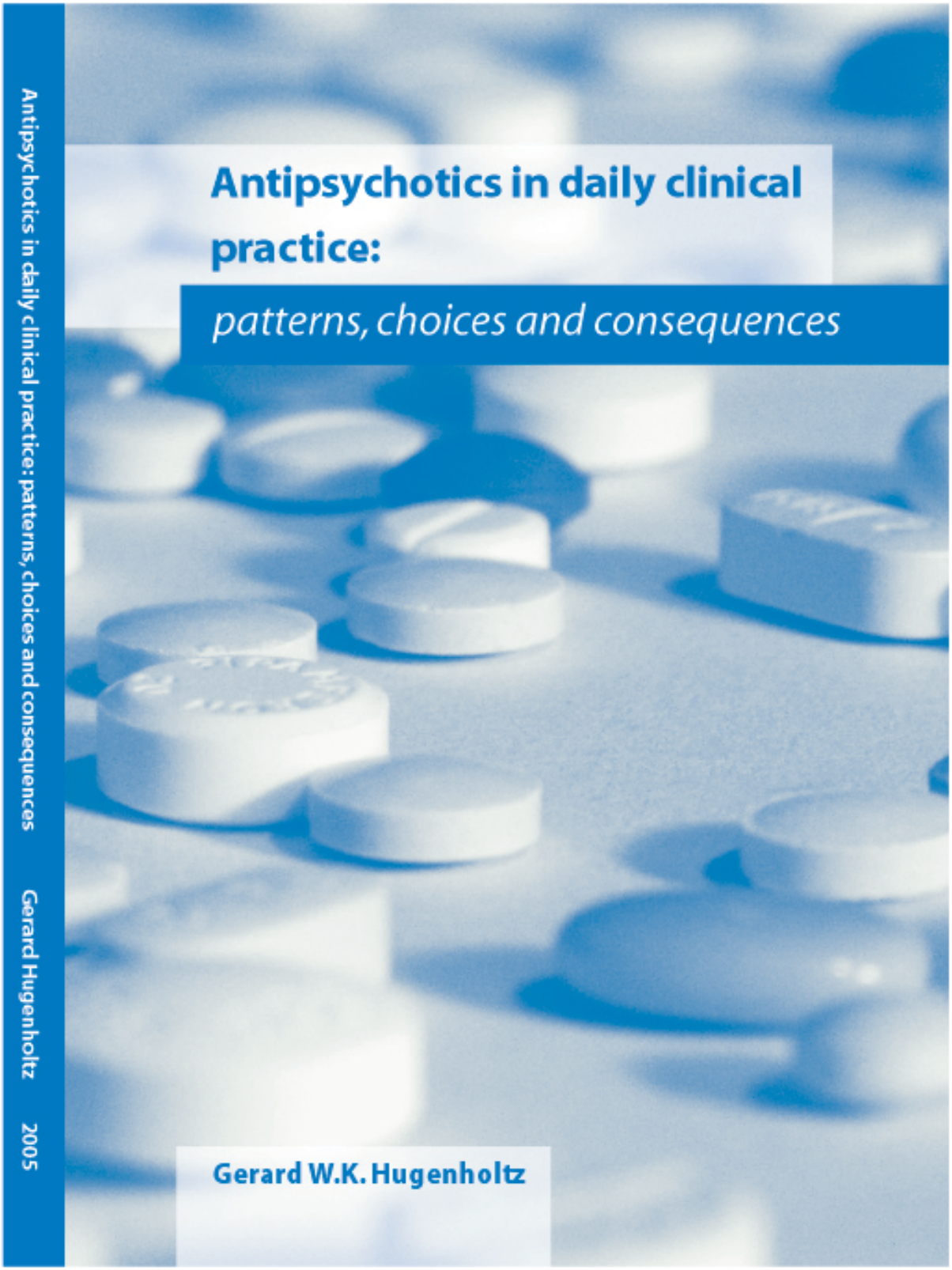

Antipsychotics in daily clinical practice: patterns, choices and consequences Gerard Hugenholtz 2005

Antipsychotics in daily clinical practice: patterns, choices and consequences

Gerard W.K. Hugenholtz

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Antipsychotics in daily clinical practice: patterns, choices and consequences

Antipsychotica in de dagelijkse klinische praktijk: patronen, keuzes en consequenties

(Met een samenvatting in het Nederlands)

Proefschrift ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de Rector Magnificus Prof. dr. W.H. Gispen ingevolge het besluit van het College voor Promoties in het openbaar te verdedigen op woensdag 7 december 2005 des middags om 12.45 uur

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Voor Monique, Alexander en Christiaan

CONTENTS

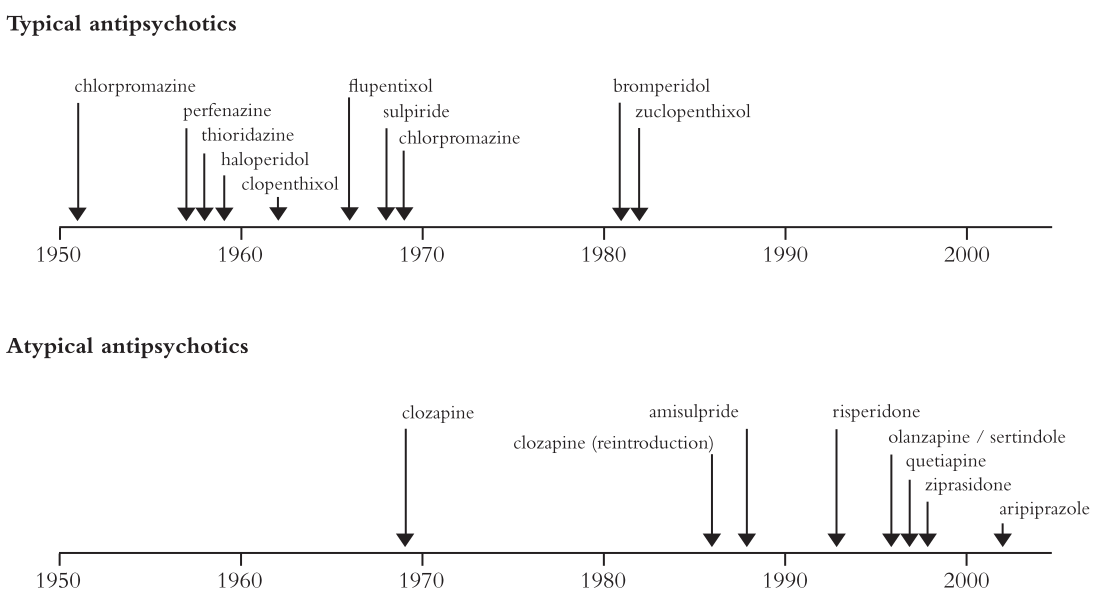
[1]

Introduction and objective

A SHORT HISTORY OF PHARMACOTHERAPY OF PSYCHOTIC DISORDERS

Psychopharmacological treatment of psychotic disorders dates back to the beginning of the 1950s with the introduction of chlorpromazine. Until then, this derivative of phenothiazine had been used as an antihistamine and an antiemetic. In 1951, the Frenchman Henri Laborit was the first to report on the effects of chlorpromazine on mental state, which he described as 'sedation without narcosis'.[1] Two other Frenchmen, Pierre Deniker and Jean Delay, were the first to evaluate chlorpromazine's effects in psychotic patients.[2] The effect of chlorpromazine clearly went beyond simple sedation as patients showed improvements in cognition and emotional behaviour. It appeared that the antipsychotic properties of chlorpromazine were unrelated to its sedative properties. In 1951 the drug was approved for the treatment of schizophrenia in several European countries and in 1954 the drug was approved for marketing in the USA. This was a major breakthrough in the treatment of patients with this mental disorder. Since then over 100 million people have been treated with chlorpromazine. It rapidly became clear that there was also a shadow side to these beneficial effects. Side-effects such as extrapyramidal symptoms, sedation and hepatic impairment reduced its popularity in the late 1960s.[3] It also triggered the development of other, pharmacologically cleaner, antipsychotics with the aim to maintain the beneficial effect but with fewer side-effects (Figure 1).

Figure 1 *Introduction of typical and atypical antipsychotics*



First, other phenothiazines such as fluphenazine, thioridazine, and perphenazine came to the market. Thereafter in 1959 haloperidol, the first antipsychotic with a different (butyrophenon) structure and with a more specific mode of action (dopamine receptor), was another landmark in the development of antipsychotics. Clinical experience and studies showed that haloperidol was a potent antipsychotic and since the 1970s it became one of the most prescribed antipsychotics in the world.[4] Today haloperidol is still considered as the standard to which new drugs are compared.[3]

CLOZAPINE: DISCOVERY OF AN ANTIPSYCHOTIC WITH A DIFFERENT PROFILE

Clozapine was introduced to the market in 1969 and its long-term treatment efficacy in schizophrenia and schizoaffective disorder was established during a 13-year study by Lindstrom from Sweden at the Psychiatric Research Centre in Uppsala.[5] He showed that many patients who had previously been extensively treated (mean duration almost nine years) with different antipsychotics and showed insufficient clinical effect and/or extrapyramidal side-effects, markedly improved after initiation of clozapine. Astonishingly, 85% of the patients could be discharged from the hospital within a year. Although clozapine was a very potent antipsychotic, and only few patients suffered from extrapyramidal side-effects, its use in clinical practice was hindered by the occurrence of other side-effects like sedation, hypersalivation, weight gain, constipation and seizures. Later on it appeared that approximately 1% of clozapine using patients develops potentially life threatening agranulocytosis. Thirteen reports of agranulocytosis in Finland of which eight were fatal, led to the withdrawal of clozapine from the market in 1975.[5] However, in 1987 clozapine was reintroduced because it had become clear that clozapine was, and still is the only effective antipsychotic for therapy resistant patients.[6] In 1989, it was approved in the USA, only after a large controlled clinical study by Kane et al. had confirmed the superiority of clozapine over other antipsychotics.[6] Therapy with clozapine requires regular haematological checks. A study in the USA has shown that these checks together with careful patient instruction has almost eliminated fatal toxicity of clozapine due to

agranulocytosis.[7] With these premises, the benefits of clozapine therapy outweigh the risks.[8]

THE NEW ATYPICAL ANTIPSYCHOTICS

Because of the clinical effects of clozapine it was declared to be a representative of a new class of antipsychotics: the 'atypical antipsychotics'. This term was introduced in 1976 for clozapine, thioridazine and sulpiride.[9] The definition of atypicality has not been uniform over the years. First it was used to indicate that the compound has a different efficacy. Clozapine was named atypical by Kane because of being effective in therapy refractory schizophrenia.[6] In addition, compared to typical antipsychotics, atypical antipsychotics claim to have a more pronounced effect on the negative symptoms associated with schizophrenia, such as lack of motivation, apathy and inability to express emotions.[10-12] Finally the term 'atypical' has also been used to indicate that atypical antipsychotics less frequently induce dopamine blockade related side-effects including extrapyramidal side-effects,[13-15] tardive dyskinesia[16] and hyperprolactinaemia.[17] However, this benefit is, at least partly, offset by other side-effects such as weight gain[13,17] and disturbance of glucose metabolism.[18,19]

After the awareness that clozapine was a unique antipsychotic in being effective in therapy resistant patients and with a much lower potential for extrapyramidal side-effects, the search began for a successor of clozapine without the dangerous side-effects. In 1983, risperidone was introduced as a new antipsychotic, also claiming to belong to the class of atypical antipsychotics. In 1996 olanzapine and sertindole have been introduced, quetiapine in 1997, ziprasidone in 1998 and aripiprazole in 2004.

The principal target for all antipsychotic drugs is the dopamine D2 receptor in the brain. One theory is that atypical antipsychotics transiently occupy D2 receptors and then rapidly dissociate to allow normal dopamine neurotransmission. This keeps prolactin levels normal, spares cognition, and obviates extrapyramidal side-effects. Another theory is that the atypical antipsychotics block 5HT2a receptors at the same time as they block dopamine receptors and that, somehow, this serotonin-dopamine balance confers

atypicality.[20] Aripiprazole has a novel mechanism of action: it is a dopamine D2 receptor partial agonist.[21]

THE KNOWLEDGE AND EVIDENCE GAP BETWEEN CLINICAL TRIALS AND CLINICAL PRACTICE

In general, most available evidence for the efficacy and safety of antipsychotics originates from randomised controlled trials (RCTs). However, a gap exists between the results of RCTs on schizophrenic patients and what is seen in daily practice.[22] The demographics of people included in trials are not representative of the patients in daily psychiatric patient care: men are more often included than women, children and elderly subjects are rarely investigated and participants often have a low socio-economic status. Furthermore, strict criteria for diagnosis are used and the duration of most trials is short while the compliance to dosing schedules is high. Comorbidity and co-medication are most often more frequent and more severe in practice than in the conditions of a clinical trial, making the patients participating in trials virtually incomparable with the patients eventually taking the drugs in daily practice.[23] Hofer studied the possible reasons for selective sampling of patients with schizophrenia for a clinical trial of an investigational antipsychotic and found that suicidal or violent patients and those with a history of compliance difficulties are underrepresented in clinical trials.[24] Storosum et al. found that strict application of the inclusion and exclusion criteria in trials on acute mania would result in including only 16% of patients in a typical clinical ward.[25] So, especially the more severely ill patients are not expected to be included in the study. We postulate that the percentage of admitted patients suffering from psychotic disorders, who would be eligible for inclusion in trials, is around 15%. The gap between trials and clinical practice seems to be larger in psychiatry than in other medical areas. So, there is a clear need to extend clinical trial knowledge, i.e. after drug approval. Pharmacoepidemiological research can provide the essential 'learning' component in the cycle that drives drug development, where clinical trials supply the 'confirming' part.[26] Through this, we can extend our knowledge as several other psychopharmacoepidemiologic studies have shown.[27-29]

OBJECTIVE OF THE THESIS

The main objective of this thesis is to detect and elucidate patterns, choices and consequences of the use of antipsychotics in daily clinical psychiatric practice in order to extend the knowledge about a drug beyond what we know from the laboratory conditions of clinical trials. Patterns of antipsychotic use are an important first step in revealing what happens in daily practice. Which treatment patterns do we observe and can we explain these patterns and relate them to clinical outcomes? What is the impact of choices that have been made in daily practice, and what are the consequences of treatment with antipsychotics.

OUTLINE OF THE THESIS

Chapter 2 reviews the doses of haloperidol used in RCTs with atypical antipsychotics in patients with schizophrenia and compares these doses with the officially recommended doses for haloperidol.

In Chapter 3 the patterns and dynamics of the prescribing of typical and atypical antipsychotics during 1994-2003 are described by investigating incidence and prevalence of their use in non-institutionalised patients.

Chapter 4 focuses on the determinants for the choice of either a typical or an atypical antipsychotic and what the implications are for the follow-up treatment.

Chapter 5 focuses on the choice for olanzapine oro-dispersible tablets and whether these are being used as a replacement for short-acting parenteral antipsychotics or for conventional olanzapine tablets. The impact of oro-dispersible olanzapine on follow-up antipsychotic therapy is also studied.

In Chapter 6 the extent and time of switching to another oral antipsychotic in newly admitted in-patients is investigated.

In Chapter 7 the reasons for switching antipsychotics after initiating oral treatment with either typical or atypical antipsychotics are investigated.

Chapter 8 investigates whether use of antipsychotics is associated with the risk on hip/femur fractures and whether pharmacological differences between antipsychotics are associated with the occurrence of fractures.

In Chapter 9 the prevalence of antidiabetic use in an inpatient and an outpatient population of users of antipsychotics were compared.

Finally, in Chapter 10 the results of the individual studies are put in a broader perspective.

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[2]

Haloperidol dose when used as active comparator in randomised controlled trials with atypical antipsychotics in schizophrenia: comparison with officially recommended doses

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Submitted for publication

SUMMARY

Background Atypical antipsychotics are claimed to be better tolerated than haloperidol. However, in many randomised controlled trials (RCTs) high doses of haloperidol were used.

Objective To determine the dose of haloperidol as a comparator drug in RCTs with atypical antipsychotics in patients with schizophrenia and to compare these doses with the officially recommended doses for haloperidol in the USA and the UK.

Methods We searched for RCTs in which atypical antipsychotics were compared to haloperidol for the treatment of schizophrenia. The required dose and mean dose of haloperidol were compared with officially recommended doses of haloperidol in USA and UK guidelines.

Results In all of the included studies (N=51), the midpoints of the required doses were above the midpoint of the official recommended doses in the USA and UK for moderately ill patients. In 88% (USA) and 80% (UK) they were above the upper border of the recommendations dose. Compared to recommended doses for severely ill patients in both the UK and USA (range: 6-15 mg daily), in 17 studies (35%) the mean actual used dose was above the upper dose border for severe ill patients (15 mg daily).

Conclusions Nearly all randomised clinical trials used haloperidol in doses which were higher than the official recommended doses for moderately or even very severely ill patients. Therefore, it is probable that the results of the RCTs were affected by the high dose of haloperidol, hampering the interpretation of the effects of atypical antipsychotics in their comparison with haloperidol.

INTRODUCTION

Since the 1970s, haloperidol is one of the most frequently prescribed antipsychotics worldwide. Since then haloperidol has often been used as a comparator in randomised controlled trials (RCTs), including those investigating the atypical antipsychotics. In these RCTs atypical antipsychotics were found to be equally effective against positive symptoms (hallucinations and delusions) but also to have a more pronounced effect on the negative symptoms associated with schizophrenia and to have a lower incidence of extrapyramidal side-effects than haloperidol.[1,2] However, many of these studies were criticised for the fact that haloperidol was used in doses that were higher than necessary to obtain an optimal effect, thus accounting for more side-effects.[3]

The objective of our study is to determine the required dose ranges and the actual used doses of haloperidol as a comparator drug in RCTs set up to evaluate the efficacy of atypical antipsychotics in schizophrenia and to compare these doses with the officially recommended doses for haloperidol in the USA and the UK.

METHODS

Data sources

First, we searched the Cochrane Library for published Cochrane reviews and included their reviews in which atypical antipsychotics were evaluated for the treatment of patients with schizophrenia, schizophreniform psychosis or other primary psychosis with one of the following atypical antipsychotics: amisulpride[4], aripiprazole[5], olanzapine[6], quetiapine[7], risperidone[8], sertindole[9] and ziprasidon.[10] Studies on clozapine were not included, since this antipsychotic is specifically indicated for treatment of refractory patients.

Second, for the gap between the end point of inclusion of the studies in the Cochrane reviews and January 2005, we electronically searched the Cochrane Collaboration Controlled Trial Register for any further RCTs in which atypical antipsychotics were compared with haloperidol for the same indication. The Cochrane Collaboration Controlled Trial Register incorporates results of group searches of Medline (1966 onwards), Embase

(1980 onwards), CINAHL (1982 onwards), PsycINFO (1974 onwards), PSYNDEX (1977 onwards), and LILACS (1982-99). We included studies containing 'haloperidol' AND 'schizophren*' and also all studies containing 'haloperidol' AND 'psychotic*' and also the names of the selected atypical antipsychotics for the years that were not covered by the Cochrane reviews. So, we searched for studies with amisulpride from 2000 onwards, aripiprazole from 2003 onwards, olanzapine from 1999 onwards, quetiapine from 2003 onwards, risperidone from 2001 onwards, sertindole from 1999 onwards and ziprasidone from 1999 onwards.

Study selection

Studies were eligible for inclusion in this review when they met the following inclusion criteria. The following atypical antipsychotics: amisulpride, aripiprazole, olanzapine, quetiapine, risperidone, sertindole and ziprasidone were evaluated. Oral formulations of haloperidol where used as comparator drug. Dosing information on the required dose (or dose range) of haloperidol according to the study protocol and/or the mean dose that was used in the RCT were published.

The study population consisted of adult (age between 18-65 years) psychiatric patients, treated for schizophrenia, schizophreniform psychosis or other primary psychosis; random treatment allocation was mentioned in the study; studies were English language, published in peer-reviewed journal and published as full report before January 2005.

In our review we used the results of the quality assessment used to select RCTs for the Cochrane reviews. The methodological quality of the additional RCTs included in this review was assessed by the first and second author (GH, EH) using the criteria described by Jadad.[11] This test gives evidence of the strength of the relationship between allocation concealment and direction of effect. Studies with a score of three and higher were rated as studies with good internal validity.

We manually examined potential papers to see if they met the inclusion criteria. All potentially relevant studies were individually assessed by both the first and second author (GH, EH) and in case of discrepancies consensus was

obtained after discussion. If multiple papers were published from the same RCT, the first full report was selected.

Patients

Patients were classified as inpatients or outpatients, according to the moment of inclusion into the RCT. We also collected information on the number of patients who were included in the haloperidol arm of the RCTs.

Outcomes

The first outcome was the required dose or dose range of haloperidol according to the RCT protocol. In case of a dose range, the midpoint required dose was calculated. The second outcome was the actually used dose, defined as the mean dose that was used in the RCT, if available accompanied by the standard deviation and dose range. If the mean used dose was not available, the median used dose was collected. Finally, the midpoint required dose and mean actual used dose were weighted for the number of patients included in the haloperidol arm of the studies.

Official dose recommendations

As recommended doses in de USA, we used the registered USA dose ranges of haloperidol for adults as retrieved from official FDA labelling (latest version: 1998): for moderate symptomatology 0.5 mg to 2.0 mg twice a day or three times a day (=1-6 mg daily; midpoint=3.5 mg); for severe symptomatology and for chronic or resistant patients and 'to achieve prompt control, higher doses may be required in some cases' 3.0 mg to 5.0 mg twice a day or three times a day (=6-15 mg daily; midpoint=10.5 mg).[12] As recommended doses for schizophrenia and other psychoses in the United Kingdom, we used dose ranges provided by the British National Formulary (BNF) 2005 edition[13]: for initial treatment 1.5–3 mg 2–3 times (=3-9 mg; midpoint=6 mg) daily; for severely affected or resistant patients 3–5 mg 2–3 times (=6-15 mg; midpoint=10.5 mg) daily; and 'for resistant schizophrenia up to 30 mg daily,[…] adjusted according to response to lowest effective maintenance dose'.

Dose recommendations for the USA were collected back until 1971 and for the UK back until 1970. No change of dose recommendation was found in the USA and UK since the introduction of the atypical antipsychotics.

RESULTS

From the Cochrane reviews we identified 89 RCTs in which atypical antipsychotics were studied for the treatment of patients with of schizophrenia, schizophreniform psychosis or other primary psychosis. We excluded studies in which haloperidol was not the comparator drug (N=40), that were not published in a peer-reviewed journal as a full report (N=8), for which no dosing information was available (N=2) or in which no oral formulation of haloperidol was used (N=2). Eventually, we included 37 RCTs from the Cochrane reviews (Table 1).

Table 1 *Randomised controlled trials included in the review*

Atypical antipsychotic under investigation	RCTs from Cochrane Reviews		RCTs from Cochrane Controlled Trial Register		Total	
	Identified	Included	Identified	Included	Identified	Included
Amisulpride	19	8	11	0	30	8
Aripiprazole	10	2	7	1	17	3
Olanzapine	16	4	110	5	129	9
Quetiapine	12	5	8	0	20	5
Risperidone	20	13	66	5	71	18
Sertindole	2	1	4	1	7	2
Ziprasidone	7	2	21	0	33	2
Both olanzapine and risperidone	3	2	32	2	35	4
Total	89	37	255	14	353	51

With our additional literature search, we identified 255 publications. Subsequently, we excluded studies that were not published in a peer-reviewed journal as full report (N=103), in which no oral formulation of haloperidol was used (N=11), were no RCT (N=76), had been published previously (N=37), included patients that were not treated for schizophrenia or other psychotic

disorders (N=9), investigated children or the elderly (N=2), were not published in English (N=1), or had a Jadad score lower than three (N=2). Eventually we included 14 additional RCTs, leading to a total of 51 RCTs in this review (Table 1).

Table 2 *Dose and dose range of haloperidol as a comparator drug with atypical antipsychotics*

RCT	In/out patient	Year	Patients on haloperidol N=4,259	Required daily dose of haloperidol in the RCT protocol	Mean actual used dose of haloperidol in the RCT
Amisulpride					
Pichot[26]	unknown	1988	20	20-30 mg	21.5 mg
Costa-e-Silva[27]	in	1990	20	20-30 mg	28 mg
Delcker[28]	In	1990	20	5-40 mg	22.5 mg
Möller[29]	in	1997	96	20 mg	20 mg
Speller[16]	in	1997	31	3-20 mg	unknown
Puech[30]	unknown	1998	64	16 mg	16 mg
Carriere[31]	in	2000	105	10-30 mg	17.5 mg
Colonna[32]	in/out	2000	118	5-20 mg	14.6 mg SD=6.8 mg
			Sum=474	**Weighted average 17.6 mg**	**Weighted average 17.9 mg**
Risperidone					
Borison[33]	unknown	1992	53	2-20 mg	18.0 mg SD=1.44 mg
Claus[34]	in	1992	21	2-20 mg	10.3 mg SD=1.4 mg
Ceskova[35]	in	1993	31	2-20 mg	9.9 mg SD=4.2 mg
Chouinard[36]	in	1993	21	20 mg	20 mg
Min[37]	in	1993	19	5-10 mg	8.9 mg
Marder[13]	in	1994	66	20mg	20 mg
Peuskens[38]	unknown	1995	226	10 mg	10 mg
Blin[39]	in	1996	20	4-12 mg	9.2 mg
Emsley[40]	unknown	1999	84	1-16 mg	5.6 mg
See[17]	in	1999	10	15-30 mg	unknown
Wirshing[41]	in/out	1999	33	5-30 mg	19.4 mg SD=5.6
Heck[42]	in	2000	37	9-24 mg	9.9 mg, range 3-18
Cavallaro[43]	in	2001	14	5-10 mg	6.5 mg
Zhang[44]	n	2001	37	20 mg	20 mg
Csernansky[45]	out	2002	188	5-20 mg	11.7 mg SD=5.0 mg
Green[46]	out	2002	30	2-16 mg	5.0 mg SD=1.5 mg
De Sena[14]	out	2003	13	Unknown	10.0 mg (median)
Marder[47]	out	2003	30	2-16 mg	11.7 mg SD=5.0 mg
			Sum=933	**Weighted average 12.3 mg**	**Weighted average 11.9 mg**

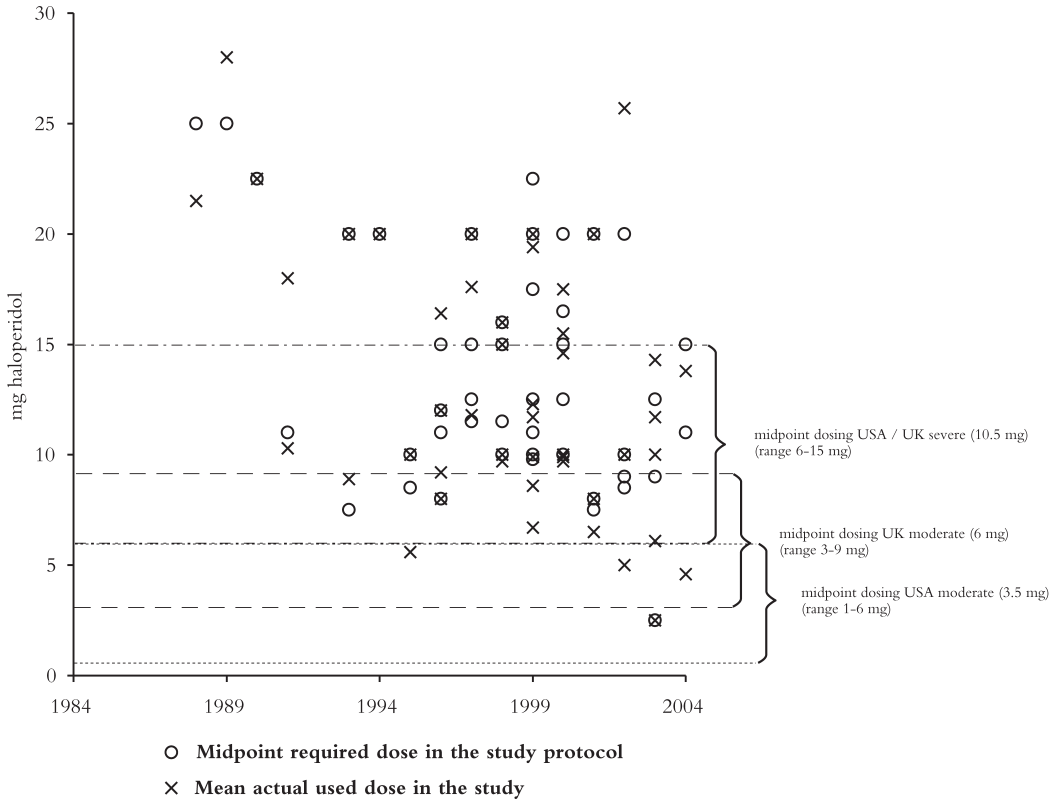
(continue)

Table 2 (continued)

RCT	In/out patient	Year	Patients on haloperidol N=4,259	Required daily dose of haloperidol in the RCT protocol	Mean actual used dose of haloperidol in the RCT
Olanzapine					
Beasley[48]	in	1996	69	10-20 mg	16.4 mg SD=4.0
Beasley[49]	in	1997	81	10-20 mg	17.6 mg
Tollefson[50]	unknown	1997	660	5-20 mg	11.8 mg SD=5.8
Ishigooka[51]	unknown	2001	84	4-12 mg	8.0 mg SD=3.0 mg
Altamura[52]	unknown	2002	11	5-20 mg	12.3 SD=3.3 mg
De Haan[53]	in	2003	12	2.5 mg	2.5 mg
Rosenheck[54]	in	2003	150	5-20 mg	14.3 mg SD=4.6 mg
Keefe[55]	in	2004	78	2-20 mg	4.6 mg
Kinon[56]	in	2004	48	10-20 mg	13.8 mg
			Sum=1193	**Weighted average 12.4 mg**	**Weighted average 12.0 mg**
Quetiapine					
Arvanitis[57]	in	1997	52	12 mg	12 mg
Copolev[58]	in	2000	227	6-16 mg	8 mg
Emsley[59]	in	2000	145	20 mg	20 mg
Inada[60]	unknown	2001	97	1.5-18 mg	6.7 mg
Purdon[61]	in	2001	12	10-20 mg	15.5 mg SD=3.3
			Sum=533	**Weighted average 13.4 mg**	**Weighted average 11.6 mg**
Sertindole					
Daniel[62]	out	1998	141	10 mg	10 mg
Hale[63]	in	2000	123	10 mg	10 mg
			Sum=264	**Weighted average 10.0 mg**	**Weighted average 10.0 mg**
Ziprasidone					
Goff[64]	in/out	1998	17	15 mg	15 mg
Hirsch[65]	out	2002	153	5-15 mg	8.6 mg
			Sum=170	**Weighted average 10.5 mg**	**Weighted average 9.2 mg**
Aripiprazol					
Daniel[66]	in	2000	63	10 mg	10 mg
Kane[67]	in	2002	104	10 mg	10 mg
Kujawa[68]	unknown	2003	433	7-10 mg	10 mg
			Sum=600	**Weighted average 8.9 mg**	**Weighted average 10.0 mg**
Both					
Jones[69]	in	1998	23	5-20 mg	9.7 mg SD=4.2 mg
Purdon[70]	out	2000	23	5-20 mg	9.7 mg SD=4.2 mg
Volovka[71]	in	2002	37	10-30 mg	25.7 mg SD=5.7
Purdon[15]	out	2003	9	Unknown	6.1 mg
			Sum=92	**Weighted average 15.6 mg**	**Weighted average 15.8 mg**

Of these RCTs, 47 provided data on both the required dose and the actual used dose of haloperidol in the RCT. Two studies did not provide information on the required daily dose;[14,15] two other studies did not provide information on mean actual used dose.[16,17] So, 49 studies provided data on required dose and 49 studies on actual used dose (Table 2).

Figure 1 *Midpoint required dose and mean actual used dose of haloperidol as a comparator drug compared to atypical antipsychotics*



Weighted averages of the required daily dose and mean actual dose of haloperidol were calculated for amisulpride (17.6 and 17.9 mg), aripiprazole (8.9 and 10.0 mg), olanzapine (12.4 and 12.0 mg), quetiapine (13.4 and 11.6 mg), sertindole (10.0 and 10.0 mg), ziprasidone (10.5 and 9.2 mg) and studies on both risperidone and olanzapine (15.6 and 15.8 mg).

Compared to the officially recommended doses in the USA, in 49 studies (100%) the midpoint required doses in the RCT protocol and in 46 studies

(94%) mean actual used doses were above the advised upper dose for moderate symptomatology (range: 1-6 mg daily) (Figure 1). Compared to recommended doses in the UK, in 49 studies (100%) the required doses in the RCT protocol and in 39 studies (80%) mean actual used doses were above the upper dose border for initial dosing (range: 3-9 mg daily). Compared to recommended doses for severely ill patients in both the UK and USA (range: 6-15 mg daily), in 36 studies (73%) midpoint required dose ranges and in 26 studies (53%) mean actual used doses were above the mean recommended doses (10.5 mg daily). Furthermore in 17 studies (35%) the mean actual used dose was above the upper dose border for severe ill patients (15 mg daily). During 1988-1994, weighted average required dose and weighted average actual used doses were 17.3 and 18.8 mg, during 1995-1999 12.6 and 11.9 mg and during 2000-2004 11.4 and 11.5 mg.

Discussion

In this review, we found that in more than 90% of all RCTs in which atypical antipsychotics were compared with haloperidol in patients with schizophrenia and other primary psychotic disorders, haloperidol was used in doses above the upper limit for the officially recommended dose range of haloperidol for moderately ill patients (USA recommendation) or for the initial treatment (UK recommendations). Even when we compare the doses in these RCTs with dose recommendations for psychotic patients with 'severely affected' (UK) or 'severe symptomatology' (USA), we found that in more than 70% of the RCTs the midpoint required doses and in 53% of the RCTs the mean actual used doses were above the mean recommended dose, and in 35% of studies even above the upper border of the recommended dose of 15 mg daily.

In a meta-analysis of 52 RCTs in which was controlled for the higher than recommended dose of comparator drugs, only a modest advantage in favour of atypical antipsychotics in terms of extrapyramidal side-effects remained.[18] However, differences in efficacy and overall tolerability between typical and atypical antipsychotics disappeared, suggesting that many of the perceived benefits of atypical antipsychotics are due to excessive doses of the comparator drug used in the RCTs. In our study we found that most studies were performed with doses of haloperidol, which must be considered to be too

high, and hampering the interpretation of the claimed benefit of atypical antipsychotics.

The study protocol dictates the instructions on how a drug has to be dosed. Not following these instructions is a violation of the protocol, and will often lead to exclusion of the patient from the study. Eventually, the actual used dose is a reflection of the required dose of haloperidol in the study.

High doses of haloperidol are known for being not more effective (or even less effective) than low doses.[3,18] A meta-analysis found no evidence that high doses affected the efficacy of haloperidol.[19] Furthermore, the dose response curve of haloperidol is beginning to flatten out after 3.3 mg. High doses of haloperidol are associated with more side-effects, particularly extrapyramidal side-effects[19] and may also induce negative symptomatology, explained by an excess of secondary negative symptoms associated with extrapyramidal side-effects.[20,21] In an RCT by Schooler[22], first episode psychosis patients were randomised towards haloperidol (mean modal dose 2.9 mg) or risperidone (mean modal dose=3.3 mg). No differences between the groups were found regarding the rating on the positive and negative syndrome scale scores and clinical global impression.

In the official dose recommendations from the USA and the UK, the possibility of using (very) high doses of haloperidol is mentioned for severely ill or resistant patients. However, such high doses should be used only occasionally. One could argue that (very) high doses of haloperidol in the studies were justified for at least some, if not many patients with severe pathology. However, severely ill patients were probably infrequently included in the RCTs, because of strict inclusion criteria (e.g. no suicidal patients) and patients had to be able to give informed consent. In various psychiatric disorders (depression, mania) it was found that only around 15% of patients actually treated in clinical practice would comply with the strict inclusion criteria as applied in recent RCTs in these indications.[23-25]

We selected RCTs that met very strict criteria on methodological quality. However, we do not expect very different results when all trials that were performed with atypical antipsychotics would have been included.

In conclusion, we found that nearly all randomised controlled trials which were set up to evaluate the efficacy and side-effects of atypical antipsychotics used haloperidol in off-label doses which were higher than the officially recommended doses for moderately or even very severely ill patients. Therefore, it is probable that the results of the RCTs were affected, hampering the interpretation of the effects of atypical antipsychotics in their comparison with haloperidol. RCTs in which atypical antipsychotics are compared with haloperidol in lower doses, corresponding with the official dose recommendations, are urgently needed.

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[3]

Incidence and prevalence of antipsychotic use in non-institutionalised patients in the Netherlands during 1994-2003

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SUMMARY

Background Over 20 drugs with varying pharmacological properties are currently available for the treatment of patients with psychotic disorders. Over the years, there has been a shift in favour of the use of atypical antipsychotics compared to typical antipsychotics.

Objective To describe the dynamics of the prescription of typical and atypical antipsychotics during 1994-2003 by investigating incidence and prevalence of antipsychotic use in non-institutionalised patients.

Methods The prevalence and incidence of antipsychotic use over time was calculated. Patients were stratified towards gender and age.

Results The prevalence of antipsychotic use increased 43% from 1994 until 2003. The overall incidence of antipsychotic use did not change. In 2003, the prevalence of atypical antipsychotics as a fraction of total antipsychotic use was 46% for all patients; 59% for age group 20-39 years old and 27% for 60 year and older.

Conclusions The increase in prevalence and decrease in incidence of use of antipsychotics indicate that the duration of use has increased over the years. Atypical agents were more frequently used in the younger than in the elderly, while the latter are more at risk for extrapyramidal side-effects.

INTRODUCTION

Over 20 drugs with varying pharmacological properties are currently available for the treatment of patients with psychotic disorders. Typical antipsychotics including haloperidol, pimozide, fluphenazine and zuclopenthixol are widely used in acute as well as in chronic forms of these illnesses.[1] The introduction of atypical antipsychotics (clozapine in 1988, risperidone in 1994, olanzapine and sertindole in 1996, quetiapine in 1998 and aripiprazole in 2004) has broadened treatment options.

Over the years, there has been a shift in favour of the use of atypical antipsychotics compared to typical antipsychotics.[2-7] The major claimed benefit of atypical antipsychotics is the lower incidence of extrapyramidal side-effects.[8,9] As drug-induced parkinsonism and tardive dyskinesia occur more frequently in older patients than in younger patients, difference in prescription rates between age groups can be expected.[10] In addition, compared to typical antipsychotics, atypical antipsychotics appear to have the advantage of a more pronounced effect on negative symptoms associated with schizophrenia, such as lack of motivation, apathy and inability to express emotions.[11-13] However, compared to typical antipsychotics, atypical antipsychotics also have disadvantages regarding adverse effects such as weight gain[8,14] and disturbance of glucose metabolism.[15,16]

The objective of the study was to obtain a better understanding of the dynamics of drug prescription of typical and atypical antipsychotics over the years by investigating incidence and prevalence of use in non-institutionalised patients over the years 1994-2003, and to evaluate these patterns between different gender and age groups.

METHODS

Setting and study population

The setting of the study was the PHARMO record linkage system. PHARMO includes pharmacy dispensing records from community pharmacies of all 950,000 community-dwelling residents of 25 population-defined areas in the Netherlands.[17] Since virtually all patients in the Netherlands are registered with a single community pharmacy, independent of prescriber, pharmacy records

are virtually complete with regard to prescription drugs. The computerised drug dispensing histories contain information concerning the dispensed drug, dispensing date, the prescriber, amount dispensed, prescribed dosage regimen, and the estimated duration of use. The duration of use of each dispensed drug is estimated by dividing the number of dispensed units by the prescribed number of units to be used per day. Patients were eligible for inclusion when they had at least 365 days of valid history.

Typical and atypical antipsychotics

All medication was classified according to the ATC-classification system.[18] Antipsychotics were defined as those drugs starting with the four digit ATC-code N05A. Lithium is not an antipsychotic, and was therefore excluded. Clozapine, olanzapine, quetiapine, risperidone and sertindole were classified as atypical antipsychotics; other drugs with four digits ATC-code N05A were classified as typical antipsychotics. Patients who received both a typical and an atypical antipsychotic on the day of measuring prevalence were measured both as a typical and as an atypical antipsychotic user.

Data analysis

Prevalence of antipsychotic use was ascertained by dividing the number of users of these drugs in the population studied on the second Wednesday in September of each year between 1994 and 2003 (nominator) through the number of people living in the investigated area (denominator) and expressed as users per 1,000 persons (1,000P) living in the defined catchment area.

Incidence of antipsychotic use was defined as the number of new users of typical and atypical antipsychotics (nominator) divided through the number of people living in the investigated area (denominator) and expressed as 1,000 persons per year (1,000PY). A new user was defined as having no use of any antipsychotic during the 365 days before inclusion. Data were collected back until 1993, in order to calculate the 1994 incidence.

In addition, prevalence and incidence estimates were calculated for males and females separately, as well as for different age groups: 20-39 years old, 40-59 years old and ≥60 years old. For the different age groups, the relative

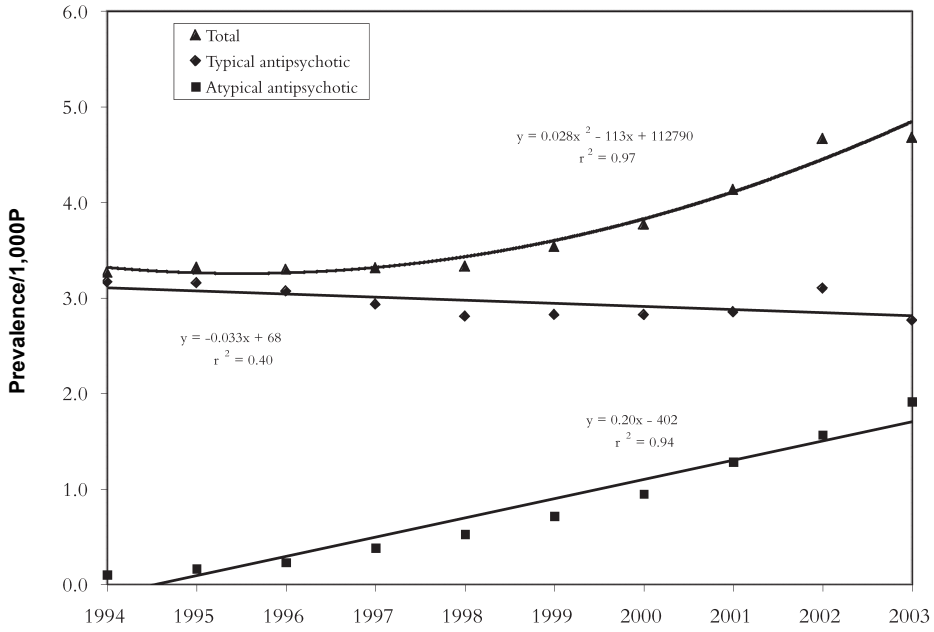
prevalence of atypical antipsychotic use in 2003 was ascertained by dividing the prevalence of atypical antipsychotics in 2003 compared to the prevalence of all antipsychotics in 2003. The relative incidence of atypical antipsychotic use in 2003 was ascertained by dividing the incidence of atypical antipsychotics in 2003 compared to the incidence of all antipsychotics use in 2003.

Linear regression analysis was performed on the incidence and prevalence of typical and atypical antipsychotic use from 1994 until 2003. The equation of the trend line and corresponding r^2 values were calculated.

RESULTS

During the study period (between 1994 and 2003) the overall prevalence of antipsychotic use increased with 43% from 3.3 to 4.7/1,000P (r^2=0.97), the prevalence of typical antipsychotic use decreased from 3.2 to 2.8/1,000P (r^2=0.40), and the prevalence of atypical antipsychotic use increased from 0.1 to 1.9/1,000P (r^2=0.94) (Figure 1).

Figure 1 *Prevalence of antipsychotic use per 1,000 patients (1,000P) during 1994-2003*



In contrast to the prevalence, the incidence of antipsychotic use (Figure 2) decreased during 1994-2003 from 2.0 to 1.7 /1,000PY (r^2=0.36). Among incident users typical antipsychotic use decreased from 2.0 to 1.2/1,000PY (r^2=0.90) and atypical antipsychotic use increased from 0.0 to 0.5/1,000PY (r^2=0.96).

Overall, the prevalence of antipsychotic use was higher for females than for males. The prevalence in females increased from to 3.9-4.8/1,000P and in males from to 2.6-4.3/1,000P. The incidence of antipsychotic use decreased in females from to 2.2-1.7/1,000P and in males the incidence remained the same: 1.8/1,000PY (1994) and 1.7/1,000PY (2003). We found no differences in the relative incidence and relative prevalence of typical and atypical antipsychotic use from 1994 until 2003 between men and women.

In 2003 the prevalence of atypical antipsychotics as a fraction of total antipsychotic use was 59% for age group 20-39 years old, 41% for 40-59 years old and 27% for 60 year and older. Prevalence of antipsychotic use among patients of 60 years and older increased gradually. A similar pattern was found in the incidence of atypical antipsychotics as a fraction of total antipsychotic use in 2003. This was 50% for age group 20-39 years old, 38% for 40-59 years old and 18% for 60 year and older (Figure 3).

Figure 2 *Incidence of antipsychotic use per 1,000 patient years (1,000PY) during 1994-2003*

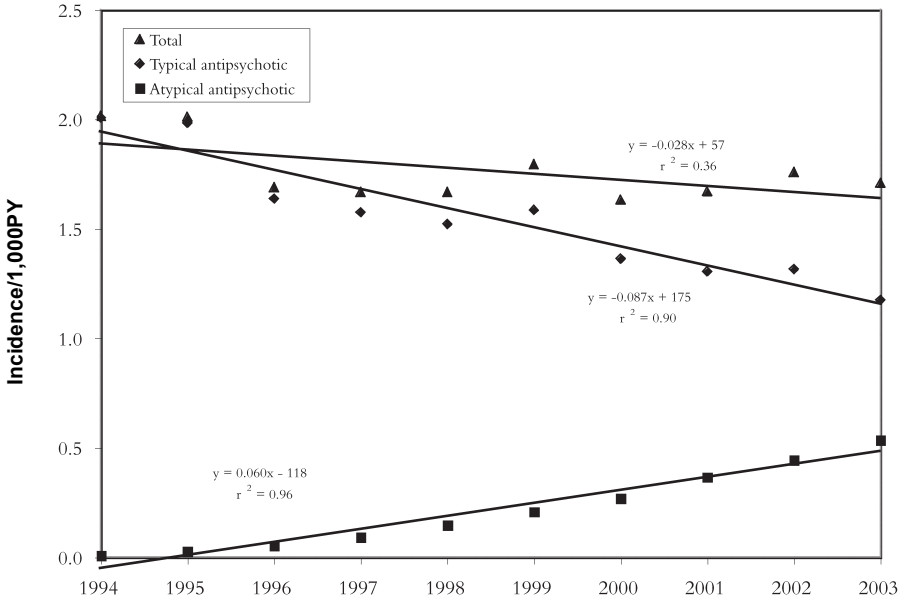
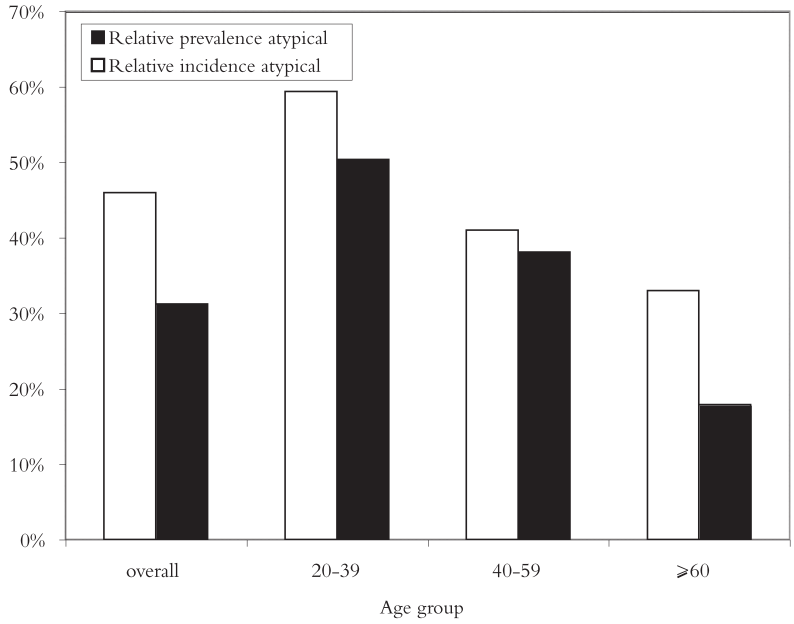


Figure 3 *Relative incidence and relative prevalence of atypical antipsychotics compared to the total amount of antipsychotics in 2003*



DISCUSSION

The results of the present study indicate that the overall use of antipsychotics increased over the years 1994 until 2003. There has been an increase of 59% in prevalent use, while the incident use remained the same. In other words: the increase of the use of antipsychotics cannot be explained by more patients being prescribed antipsychotics, but by longer use of antipsychotics once started. The increased long-term use of atypical antipsychotics suggests a better compliance to these drugs. Although antipsychotic therapy is often meant to be chronic, compliance towards medication is often problematic. The atypical antipsychotics are considered to be better tolerated than the typical antipsychotics, possibly leading to a higher compliance.[19]

The increased use of antipsychotics can be largely attributed to an increased prevalent as well as incident use of atypical antipsychotics. In 2003 atypical antipsychotics accounted for 41% of the prevalence of use of antipsychotics and for 31% of incident use. The finding that the increased prevalent use (i.e. long-term use) must be attributed to the increasing prevalent use of the newly introduced atypical antipsychotics is in line with studies in other countries.[4-7, 20] Similar trends were found for antidepressants by Meijer et.

al. over the 1990s, an overall increase in antidepressant use, and a greater increase of prevalent than of incident use, also indicating more long-term use.[21] Moreover the overall increase in the antidepressant use could be largely attributed to the new class of the selective serotonin reuptake inhibitors (SSRIs).

An intriguing finding is that older patients have a relative lower prevalent and also a relative lower incident use of atypical antipsychotics than younger patients. The atypical antipsychotics were being predominantly prescribed to patients younger than 60 years. Older patients are more at risk for developing extrapyramidal side-effects.[10] Since atypical antipsychotics are claimed to be superior with regard to the risk of extrapyramidal side-effects, we had expected higher use of atypical antipsychotics especially among the elderly.[8,9] In this respect it has to be noted that the relative low use of atypical antipsychotics in the elderly cannot be explained by recent warnings issued for the use of some atypical antipsychotics in the elderly, since these warnings were issued in 2003.[22]

The relative low use of atypical antipsychotics in the elderly is in line with another study where patients of 65 years and older, compared to younger patients, were less likely to be treated with atypical antipsychotics.[5] And again they are in line with findings regarding SSRIs versus the older tricyclic antidepressants.[23,24] Apparently, elderly who at least theoretically could have benefited most from new developments, do not.

Our finding that women have higher prevalent and incident use of antipsychotics than men, is in concordance with other studies.[3,6,25] Probably it is explained by the fact that many mental disorders are more common in females.[26]

A limitation of our study is that we measured only the use of antipsychotics in non-institutionalised patients, as the PHARMO record linkage system does not imply pharmacies of psychiatric or hospital pharmacies. In addition, we do not know whether the antipsychotic use of our patients was initiated while they were outpatients or during an admission. In a previous study among inpatients we found that patients who initiated atypical antipsychotic therapy switched less often, and continued their antipsychotic therapy longer compared to patients who initiated typical antipsychotic therapy.[19] Consequently, part of the increased incident use of atypical antipsychotics among our outpatients is

explained by a higher percentage of previous inpatients discharged from hospital with atypical antipsychotics compared to typical antipsychotics. Another limitation of our study is that our inclusion criteria of an antipsychotic free period of at least a year may have lead to a bias of selecting more 'real' new starters and fewer restarters (after a lapse of at least a year) in the later part of the study. Finally, we do not know the diagnoses of the patients who were prescribed antipsychotics. Thus, an increased use of antipsychotics for other diagnoses (e.g. psychotic depression, bipolar disorder, eating disorders) may have affected our findings. However, long-term use is also advocated for these indications.

In conclusion, we found an increase of use of antipsychotics during 1994-2003, which can be attributed to an increased prevalent as well as incident use of atypical antipsychotics, indicating an increased long-term use. In addition, we found that antipsychotics are more frequently used in women than in men, and that atypical antipsychotics are less frequently used among elderly patients who could have benefited the most.

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[4]

Short-acting parenteral antipsychotics drive choice for typical versus atypical agents

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SUMMARY

Background There is not enough insight into prescribing patterns of antipsychotics in daily practice and into factors that affect the choice between typical and atypical antipsychotics.

Objective The objective of this study was to investigate which antipsychotics (typical versus atypical) are prescribed in a psychiatric hospital, and which determinants affect the choice for one of these two classes of antipsychotics in newly admitted patients.

Methods In a retrospective cohort design, 522 newly admitted patients were followed from date of admission until discharge from the hospital. In the cohort of newly admitted patients treated with an oral antipsychotic a nested case-control study was conducted considering recipients of an atypical agent as cases. Controls were all other cohort members. The association of patient characteristics and the choice between typical versus atypical antipsychotics was studied using logistic regression analysis. The same analysis was performed with adjustment for possible confounding factors (age group, gender, DSM-IV diagnoses, use of short-acting parenteral antipsychotic, GAF-score, involuntary admissions and involuntary measures).

Results Patients treated with typical oral antipsychotics were more often previously treated with short-acting parenteral antipsychotics than patients treated with atypical antipsychotics (40.8% vs. 15.2%) (adjusted OR=0.20 CI=0.09-0.44). No statistical significant difference was found between patients with different severities of disease.

Conclusions Availability of injectable forms seems to drive the choice for oral antipsychotic agents. Future introductions of short-acting parenteral atypical antipsychotics may have a large impact on first-choice oral antipsychotic treatment.

INTRODUCTION

Antipsychotics are essential in the treatment of patients suffering from psychotic disorders, in clinical as well as in community settings.[1] Typical antipsychotic drugs such as haloperidol, pimozide, and others are widely used as first choice treatment for acute and chronic psychotic disorders.[2] However, these substances have a relatively limited effect on negative symptoms associated with schizophrenia, i.e. poverty of speech, lack of motivation, apathy and inability to express emotions.[3] Moreover, their use is associated with disabling adverse effects, including extrapyramidal side-effects.[4,5]

The introduction of atypical antipsychotics (clozapine, olanzapine, quetiapine, risperidone and ziprasidone) has changed treatment options for psychotic disorders. There has been a large shift in favour of the use of these atypical antipsychotics[6], although the precise therapeutic value of these agents remains controversial.[7-13] The effect on negative symptoms is not fully elucidated yet. All the newer agents seem to be superior with regard to risk on extrapyramidal side-effects but they have been associated with other side-effects, such as weight gain.[14] Official therapeutic guidelines, including the one on the pharmacotherapy of psychotic disorders in the Netherlands, had not decided yet between typical or atypical antipsychotics as first choice treatment.[15] For insight into prescribing patterns of antipsychotics in daily practice and into factors that affect the choice between typical and atypical antipsychotics, an observational study within a well defined group is needed.

The objective of this study was to investigate which groups of antipsychotics (typical versus atypical) are prescribed to newly admitted patients in a psychiatric hospital, and which determinants affect the choice for one or the other class of antipsychotics.

METHODS

Setting and study population

Data were retrospectively collected from the acute psychiatric admission wards of three psychiatric hospitals, serving a catchment area of about 720,000 inhabitants in the centre of the Netherlands, during 1997-1999. Patients, aged between 18 and 60 years old, who were admitted for a new hospitalisation of at

least three days were included in the cohort. 'Newly hospitalised' was defined as having no previous admission to the psychiatric centre for any indication in the two years before the inclusion date. We collected data back until 1995 for the 1997 admissions.

Design

In a retrospective cohort design, patients were followed from date of admission until discharge from the hospital. In the cohort of newly admitted patients treated with an oral antipsychotic a nested case-control study was conducted considering recipients of an atypical agent as cases. Controls were all other cohort members.

The drug use database and the clinical database were linked anonymously through record linkage methodology based on date of birth, gender and day of admission.[16] At admission, diagnoses were coded according to criteria based on the 'Diagnostic and Statistical Manual', (DSM)-IV by the treating psychiatrists.[17] Patients were rated on the Global Assessment of Functioning score (GAF). A low GAF-score is a measure for more severe illness. The admissions were classified as 'voluntary' or 'involuntary'. Involuntary measures at admission were also classified. Involuntary admissions and involuntary measures are reserved for more severely ill patients.

Antipsychotics were classified as typical or atypical. Clozapine, olanzapine, quetiapine, risperidone and sertindole were classified as atypical antipsychotics. Other drugs with four digits ATC-code N05A were classified as typical antipsychotics.[18] Lithium and levomepromazine also have a four digits ATC-code N05A but were excluded because they are not registered for psychotic disorders in the Netherlands. Drugs were stratified according to their route of administration: oral or parenteral. We differentiated between parenteral short-acting (e.g. haloperidol and zuclopenthixol-acetate) and long-acting (=depot) antipsychotics. We excluded 31 patients who received both an oral typical and an oral atypical antipsychotic on the day of admission. Patients receiving depot antipsychotics were excluded because atypical antipsychotic medication was not available, so a choice between typical and atypical was not possible.

The scientific committee and the board of the centre for mental health approved the study protocol with respect to privacy aspects.

Data analysis

The association of patient characteristics and the choice between typical versus atypical antipsychotics was studied using logistic regression analysis. Associations were estimated as odds ratios with corresponding 95 percent confidence interval (95% CI). The same analysis was performed with adjustment for possible confounding factors (age group, gender, DSM-IV diagnoses, use of short-acting parenteral antipsychotic, GAF-score, involuntary admissions and involuntary measures). Data were analysed using EGRET statistical software (version 2.0.31) by Cytel Software Corporation.

RESULTS

The characteristics of the cohort members are presented in Table 1. A total of 522 patients met the inclusion criteria. Most patients (60.9%) were younger than 40 years old, with a median age of 36 years.

Table 1 *Characteristics of the newly admitted patients*

Characteristics	**N (%)**
Age (years)	
<40	318 (60.9%)
≥40	204 (39.1%)
Female gender	249 (47.7%)
Any diagnosis (DSM-IV)*	
Schizophrenia and psychotic disorders	262 (50.2%)
Bipolar disorders	85 (16.3%)
Depressive disorders	66 (12.6%)
Other diagnosis	23 (4.4%)
Unknown diagnosis	65 (12.5%)

* Totals exceed 100% because of multiple diagnoses

Table 2 *Initial oral antipsychotic use of newly admitted patients*

	Atypical antipsychotics (cases, N=145)	Typical antipsychotic s(controls, N=377)	Odds Ratio (95% CI**)	Adjusted Odds Ratio (95% CI**)
Age 40-60	49 (33.8%)	155 (41.1%)	0.73 (0.49-1.09)	0.72 (0.41-1.28)
Female gender	64 (44.1%)	185 (49.1%)	0.82 (0.56-1.21)	0.72 (0.41-1.28)
Any DSM-IV diagnosis *				
Psychotic disorders	78 (53.8%)	184 (48.8%)	1.22 (0.83-1.79)	1.29 (0.64-2.63)
Bipolar disorders	9 (6.2%)	76 (20.2%)	0.26 (0.13-0.54)	0.36 (0.13-0.95)
Depressive disorders	18 (12.4%)	48 (12.7%)	0.97 (0.54-1.73)	0.64 (0.25-1.64)
Personality disorders	21 (14.5%)	66 (17.5%)	0.80 (0.47-1.36)	0.47 (0.21-1.04)
Anxiety disorders	7 (4.8%)	19 (5.0%)	0.96 (0.39-2.32)	0.54 (0.16-1.83)
Other disorders	8 (5.5%)	15 (4.0%)	-	-
Unknown disorders	25 (17.2%)	40 (10.6%)	-	-
Initial short-acting parenteral antipsychotics	22 (15.2%)	154 (40.8%)	0.26 (0.16-0.43)	0.20 (0.09-0.44)
Markers of severity				
Global Assessment of Functioning score				
<35	33 (22.8%)	99 (26.3%)	reference	reference
35-50	43 (29.7%)	127 (33.7%)	1.02 (0.60-1.72)	0.94 (0.52-1.70)
≥55	15 (10.3%)	25 (6.6%)	1.80 (0.85-3.82)	1.75 (0.75-4.09)
Missing GAF	54 (37.2%)	126 (33.4%)	-	-
Involuntary admission	29 (20.0%)	154 (40.8%)	0.32 (0.18-0.54)	0.49 (0.22-1.09)
Involuntary measures	18 (12.4%)	117 (31.0%)	0.36 (0.23-0.57)	0.63 (0.32-1.23)

* Totals exceed 100% because of multiple diagnoses
** 95% Confidence Interval

Psychotic disorders accounted for 50.2% of the diagnoses of the patients admitted. Other diagnoses included bipolar disorders (16.3%), depressive disorders (12.6%), and personality disorders (16.7%). The most frequently prescribed oral antipsychotic drugs were zuclopenthixol (33.7%), pimozide (13.4%) and haloperidol (12.6%). The proportion of atypical agents was 27.8%, consisting of clozapine (1.9%), olanzapine (14.8%) and risperidone (11.1%).

In Table 2, possible determinants of type of first oral antipsychotic used, are listed. We found 154 (40.8%) out of 377 patients treated with typical oral antipsychotics, which were initially treated with short-acting parenteral

antipsychotics. This was 15.2% in the group treated with an oral atypical antipsychotic (adjusted OR=0.20; 95% CI=0.09-0.44). The use of atypical antipsychotics was significantly lower in patients with bipolar disorders (adjusted OR=0.36; 95% CI=0.13-0.95).

No statistical significant difference was found between patients with different severities of disease at the time of admission, indicated by GAF-score, involuntary admission and involuntary measures. GAF-scores were missing in 180 (34.4%) of the patients. Analysis of these missing GAF-scores revealed that most missing GAF-scores were from the 1997 admissions, where 113 (64.6%) GAF-scores out of 175 admissions were missing: 26 (13.6%) out of 191 in 1998 and 41 (26.3%) out of 156.

Discussion

This study showed that availability of injectable forms seems to drive the choice for oral antipsychotic agents in patients newly admitted to a psychiatric hospital. Five times as many patients treated with oral typical antipsychotics compared to oral atypical antipsychotics were initially treated with short-acting parenteral agents.

Patients with psychotic illnesses may have delusions or hallucinations that may lead them to be aggressive or violent to themselves or others. Medication that is used in this context requires the properties of rapid onset of effect (tranquillisation or at least initial sedation in order to control aggressive or disorganised behaviour.[19] Antipsychotic effect is also needed, but can not be expected within one or two weeks.[20] In this context it's an unexpected finding that the markers of severity (GAF-scores, involuntary admissions and involuntary measures) of the patients receiving oral atypical antipsychotics did not differ from patients treated with oral typical antipsychotics. Although no statistical significances were found, it may be the case that severity of the disease is a determinant of the choice between patients in both groups.

In additional analyses, we included more variables (e.g. marital status, living situation before and after admission, etcetera) but found no association with choice of antipsychotic. In the final analysis we included only those

variables for which an association could be expected, based on prior publication.

After admission to a ward for acute psychiatric disorders, many patients with psychotic disorders were initially treated with a parenteral antipsychotic. The choice for one of the available injectable forms with immediate action, frequently done in a situation when rapid response to a psychotic crisis is needed, also affects follow-up treatment scenarios, assuming the administration of an antipsychotic results in a positive effect (e.g. control of aggression) on the acute status of the patient. As a result, the physician will often choose to continue the same type of medication in an oral formulation. The choice of oral medication seems to express the satisfaction about the effect of the short-acting parenteral antipsychotic on the non-psychotic symptoms. Moreover, in patients who have received a short-acting parenteral typical antipsychotic without troublesome adverse effects are more likely to continue their typical antipsychotic therapy.

At the time of the study, the official Dutch guidelines for prescribing antipsychotics in schizophrenic psychosis had not decided yet between typical or atypical antipsychotics as first choice treatment.[15] In the three hospitals, no financial or administrative barriers were made to prevent physicians from prescribing new and expensive atypical antipsychotics.

The large difference between initial use of typical and atypical antipsychotics is in line with the official Dutch guidelines for pharmacotherapy in bipolar disorders.[21] When antipsychotics are needed, the guidelines suggest typical antipsychotics or clozapine for these disorders.

There are some limitations to our study. One can argue that only data on admitted patients were available. However, we were interested in the more severely ill patients, who were admitted to a psychiatric hospital. Another limitation is the possibility that our selection of newly admitted patients may contain some patients previously admitted in another region, before moving to the catchment area of our hospital. Since patients in the Netherlands are preferably transferred to their home-region, this will consist of a minority of the included patients. Although we collected data from only three hospitals, the catchment area these hospitals serve is a rather large area, where admission in most cases will lead to admission to one of the investigated hospitals.

However, it is a limited geographical area, and therefore it can be argued that the results are not representative for other regions in the Netherlands or elsewhere.

Unfortunately, more than 30% of GAF-scores were missing. Most missing GAF-scores however were connected to the 1997 admissions. In this period it was not yet common practice to fill in GAF-scores into the hospital database. In 1998 and 1999 more attention was given to this subject. Moreover, patients with available GAF-scores did not differ in gender, age and only slightly in diagnostic categories when compared to patients with missing GAF-scores. It is therefore likely that our data are representative for the total population of patients.

If clinicians prescribe parenteral antipsychotics, there is no other choice than to prescribe typical antipsychotics at this time. So far since atypical antipsychotics are not yet available in parenteral formulations. Our study reveals that initial use of short-acting parenteral antipsychotics is—also after adjusting for possible confounding factors—a major determinant for the first-choice oral antipsychotic treatment. Therefore, we anticipate that upcoming introductions of short-acting parenteral atypical antipsychotics may have a large impact on first-choice oral antipsychotic treatment. Because of much higher pricing of atypical antipsychotics, a further shift in favour of the atypical antipsychotics will have a large impact on hospital budget. Re-investigating determinants of choice for oral antipsychotics is warranted after introduction of a short-acting parenteral formulation of atypical antipsychotics.

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[5]

Characteristics and follow-up treatment in initial users of oro-dispersible olanzapine tablets versus typical antipsychotic formulations

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SUMMARY

Background In a previous study, we have shown that initial, short-acting treatment with typical antipsychotics determines the type of subsequent long-term treatment.

Objective To investigate whether olanzapine oro-dispersible tablets are used as a replacement for short-acting parenteral typical antipsychotics or for conventional olanzapine tablets, and also the impact of oro-dispersible olanzapine on follow-up antipsychotic therapy.

Methods In a retrospective follow-up study, 198 patients were included in the cohort of starters of oro-dispersible olanzapine, 424 in the cohort of starters of short-acting parenteral typical antipsychotics and 691 patients in the cohort of starters of conventional olanzapine tablets. Markers for severity of disease were compared. The associations with follow-up antipsychotic therapy were studied using logistic regression analysis.

Results Of the 198 patients included in the oro-dispersible cohort 80% had atypical antipsychotics as follow-up therapy, compared to 45% (adj. RR=1.72; 95% CI=1.39-2.13) in the short-acting parenteral typical antipsychotic cohort.

Conclusions Our study reveals that oro-dispersible olanzapine is used as an alternative for short-acting parenteral typical antipsychotics and its use is a major driving factor towards the follow-up therapy with atypical antipsychotic treatment.

INTRODUCTION

Antipsychotics are essential in the treatment of patients suffering from psychotic disorders.[1] Administration of oral medication to patients who suffer from an acute psychotic exacerbation can be difficult. Patients may 'cheek' the administered medication and subsequently spit it out, or may have difficulties swallowing traditional oral tablets. In order to assure the systemic availability of medication in these patients, typical antipsychotics are often applied in short-acting parenteral forms.[2] Since 2002, also oro-dispersible atypical antipsychotic tablets are available and used for this purpose.[3,4] When these tablets are ingested, the freeze dried structure of these tablets disintegrates instantaneously, after which the saliva containing the drug is swallowed. Thus the drug is absorbed in the normal way.[5] Clinical research showed that such a formulation is well-tolerated by patients with schizophrenia.[6] However, to our knowledge, no studies into the actual use of these tablets in daily clinical practice have been published.

In a previous study, we have shown that initial, short-acting treatment with typical antipsychotics in hospitalised patients determines the type of subsequent long-term treatment: patients who received initially a parenteral typical antipsychotic were more likely to continue treatment with oral typical antipsychotics compared to patients not initially treated with a parenteral typical antipsychotic.[7]

The objective of our study is to investigate whether olanzapine oro-dispersible tablets are used as a replacement for short-acting parenteral typical antipsychotics or for conventional olanzapine tablets. Furthermore, we investigate the impact of the use of oro-dispersible olanzapine on follow-up antipsychotic therapy, and hypothesise that it will drive the choice towards the use of atypical antipsychotics.

METHODS

Setting and study population

Data were retrospectively collected at three psychiatric hospitals being part of Altrecht Institute for Mental Health Care, serving a catchment area of about 720,000 inhabitants in the centre of the Netherlands, from January 2002 until

August 2004, matching the period in which oro-dispersible tablets became available. All patients who were hospitalised for at least three days were eligible for inclusion in the cohorts.

Study design

We defined three cohorts: a cohort of patients starting treatment with olanzapine oro-dispersible tablets, a cohort of patients starting with short-acting parenteral typical antipsychotics and a cohort of patients starting with conventional olanzapine tablets. Starting was defined as the first prescription during the study period with at least a six-month history of no use of the drugs under investigation. Inclusion date was set on the date that patients had their first prescription of olanzapine oro-dispersible tablets, short-acting parenteral typical antipsychotics or conventional olanzapine tablets during admission. Patients could be included in more than one cohort.

Data collection

All medication use was collected from the hospital pharmacy drug use database and linked to the clinical database. Antipsychotics were classified as typical or atypical. Clozapine, olanzapine, risperidone and quetiapine were classified as atypical antipsychotics. Other drugs with four digits ATC-code N05A were classified as typical antipsychotics.[8] Lithium also has a four digits ATC-code N05A but was excluded because it is not an antipsychotic.

At admission, the diagnosis was established by the treating psychiatrist and coded according to DSM-IV criteria.[9] Diagnoses were classified as psychotic disorder, bipolar disorder, depressive disorder, dementia, other diagnosis or unknown diagnosis. To describe the severity of the disorder of the patients, some 'markers of severity' were defined and collected. The admissions were classified as 'voluntary' or 'involuntary'. Patients were also rated on the 'Global Assessment of Functioning' (GAF) scale. A low GAF-score is a measure for more severe illness. Also, the number of days patients were admitted in the three years before the inclusion date were collected. Previous use of olanzapine oro-dispersible tablets, short-acting parenteral typical antipsychotics or conventional olanzapine tablets was collected for the six months before the index date. Use

of concurrent medication (anticholinergics, antidepressants, benzodiazepines and lithium) was collected on the index date.

Follow-up antipsychotic treatment was collected at three months after admission, or at hospital discharge, whichever came first. Route of administration and formulation was collected for all antipsychotics (conventional oral tablet, oro-dispersible tablet, parenteral typical depot, short-acting parenteral typical). There is no oro-dispersible typical antipsychotic available. The scientific committee of the three hospitals approved the protocol and the board of Altrecht Institute for Mental Health Care approved the study protocol with respect to privacy aspects.

Data analysis

We performed two analyses. First we compared patient characteristics at admissions between the three cohorts, using χ^2-tests and t-tests. Second, we established antipsychotic use in the three cohorts at the end of hospital admission or at three months, whichever event occurs first. The strength of the associations with follow-up antipsychotic therapy was studied using logistic regression analysis. Reference group were patients in the cohort of short-acting parenteral typical antipsychotics. Associations were estimated as Relative Risk (RR) with corresponding 95 percent confidence interval (95% CI). The same analysis was performed with adjustment for possible confounding factors (age group, gender, DSM-IV diagnoses, and involuntary admission). SPSS for Windows (release 10.0.7 standard version); multivariate analysis was performed using EGRET statistical software (version 2.0.31) by Cytel Software Corporation.

RESULTS

We included 198 patients in the cohort of starters of oro-dispersible olanzapine and 424 in the cohort of starters of short-acting parenteral typical antipsychotics and 691 starters of conventional olanzapine tablets. The characteristics of the cohorts are shown in Table 1.

Table 1 *Characteristics of the patients*

	Oro-dispersible olanzapine (N=198)	Short-acting parenteral typical antipsychotics (N=424)	Conventional olanzapine tablets (N=691)
Age (years)			
16-24	36 (18%)	62 (15%)	111 (16%)
25-39	78 (39%) ##	157 (37%)	203 (29%)
40-59	64 (32%)	144 (34%)	217 (31%)
≥60	20 (10%) ##	61 (14%)	160 (23%)
Male gender	110 (56%) ##	266 (63%)	315 (46%)
Any diagnosis (DSM-IV)*			
Schizophrenia and psychotic disorders	117 (59%) ##	214 (50%)	235 (34%)
Bipolar disorders	15 (8%)	43 (10%)	75 (11%)
Depressive disorders	16 (8%) ##	23 (5%)	111 (16%)
Dementia	2 (1%)	10 (2%)	15 (2%)
Other diagnosis	27 (14%) #,##	115 (27%)	198 (29%)
Extended diagnosis	16 (8%) #	16 (4%)	2 (0%)
Unknown diagnosis	31 (16%)	68 (16%)	103 (15%)
Markers of severity			
Involuntary admission	85 (43%) ##	190 (45%)	141 (20%)
Mean GAF-score **	40.8 ##	39.8	44.6
Cumulative admitted days			
0-6 days	1 (1%) #,##	26 (6%)	32 (5%)
7 days – 4 weeks	31 (16%)	82 (19%)	113 (16%)
4 weeks - 6 months	101 (51%)	216 (51%)	341 (49%)
>6 months	65 (33%) #	100 (24%)	205 (30%)
Current co-medication			
Anticholinergics	47 (24%) #,##	30 (7%)	43 (6%)
Antidepressants	22 (11%) #	23 (5%)	98 (14%)
Benzodiazepines	132 (67%)	130 (31%)	192 (28%)
Lithium	9 (5%)	9 (2%)	34 (5%)
Previous use of:			
Olanzapine oro-dispersible tablet	0 (0%)	29 (7%)	29 (4%)
Short-acting parenteral typical	53 (27%)	0 (0%)	67 (10%)
Olanzapine tablets	75 (38%)	54 (13%)	0 (0%)

* Totals exceed 100% because of multiple diagnoses

** GAF-scores were missing in 71 (36%) in the cohort of starters of oro-dispersible olanzapine, 119 (28%) in the cohort of starters of short-acting parenteral typical antipsychotics and 219 (32%) in the cohort of starters of conventional olanzapine tablets.

# $p<0.05$, compared to short-acting parenteral typical antipsychotics

$p<0.05$, compared to conventional olanzapine tablets

Table 2 *Antipsychotic use at end of hospital admission or after three months*

Start medication / **Follow-up antipsychotic***	Oro-dispersible olanzapine (N=198)	short-acting parenteral typical antipsychotics (N=424)	RR** oro-disp versus short-acting parenteral typical antipsychotics (95% CI)	Adjusted# RR oro-disp versus short-acting parenteral typical antipsychotics (95% CI)##
No antipsychotic	11 (6%)	20 (5%)	1.18 (0.56-2.46)	1.38 (0.65-2.91)
Typical antipsychotic	92 (46%)	365 (86%)	0.54 (0.43-0.68)	0.55 (0.43-0.69)
Conventional oral tablet	23 (12%)	142 (33%)	0.35 (0.22-0.54)	0.37 (0.24-0.57)
Depot	31 (16%)	68 (16%)	0.98 (0.64-1.49)	0.94 (0.61-1.45)
Short-acting parenteral	61 (31%)	313 (74%)	0.42 (0.32-0.55)	0.42 (0.32-0.55)
Atypical antipsychotic	158 (80%)	191 (45%)	1.77 (1.43-2.19)	1.72 (1.39-2.13)
Conventional oral tablet	55 (28%)	153 (36%)	0.77 (0.57-1.05)	0.75 (0.55-1.03)
Oro-dispersible tablet	105 (53%)	33 (8%)	6.81 (4.61-10.08)	6.46 (4.35-9.58)
Depot	2 (1%)	8 (2%)	0.54 (0.11-2.52)	-
Short-acting parenteral	5 (3%)	4 (1%)	2.68 (0.72-9.97)	-

* Totals exceed 100% because of multiple antipsychotics
** Relative Risk of outcome in patients versus the with cohort on oro-dispersible olanzapine as a reference group
\# Adjusted for covariates as mentioned in methods section
95% Confidence Interval

Psychotic disorders accounted for 43% (566 out of 1,313) of the diagnoses of the included patients. Other diagnoses included bipolar disorders (10%; 133 out of 1,313), and depressive disorders (11%; 150 out of 1,313).

Focussing on involuntary admissions, starters of conventional olanzapine tablets differed from starters of oro-dispersible olanzapine ($p<0.05$), and starters of short-acting parenteral typical antipsychotics ($p<0.05$). Focussing on average GAF-scores, starters of conventional olanzapine tablets differed from starters of oro-dispersible olanzapine ($p<0.05$), and starters of short-acting parenteral typical antipsychotics ($p<0.05$).

Table 2 shows the follow-up antipsychotic therapy. At three months after inclusion in the cohort of oro-dispersible olanzapine, 85 out of 198 patients (43%) were still admitted, compared to 168 out of 424 (40%) in the short-acting parenteral typical antipsychotic cohort. Of the 198 patients included in the oro-dispersible cohort, 158 (80%) had atypical antipsychotics as

follow-up therapy, compared to 191 out of 424 (45%) (adj. RR=1.72; 95% CI=1.39-2.13) in the short-acting parenteral typical antipsychotic cohort. Of the included 198 patients in the oro-dispersible cohort, 105 (53%) were on oro-dispersible antipsychotics as follow-up therapy, compared to 33 (8%) in the short-acting parenteral typical antipsychotic cohort (RR=6.81; 95% CI=4.61-10.08). Use of typical short-acting parenteral typical antipsychotics was widely spread as follow-up antipsychotic therapy. However, only 49 out of 1,313 (4%) were only treated with this formulation as follow-up therapy, without any other antipsychotic formulation.

Discussion

In this study we found indications that olanzapine oro-dispersible tablets are used in patients comparable to the situations in which short-acting parenteral typical antipsychotics are used. This suggests that these oro-dispersible tablets are used as a replacement for the parenteral typical antipsychotics. Moreover, the oro-dispersible olanzapine tablet seems to drive the choice towards the use of atypical antipsychotics.

Patients with psychotic illnesses may have delusions or hallucinations that may lead them to be aggressive or violent to themselves or others.[10] Medication used in this context requires the properties of rapid onset of effect (tranquillization or at least initial sedation in order to control aggressive or disorganised behaviour).[11] Antipsychotic effect is also needed, but can be expected only after one to two weeks.[12] In such situations where acute administration of medication is needed, it can be difficult to put patients on conventional oral medication.[13] Parenteral formulations are sometimes needed to ensure the administration. When patients refuse parenteral formulations, oro-dispersible tablets can be used as an alternative. Comparing patient characteristics, we see that patients included in the cohort of patients on olanzapine oro-dispersible tablets match the cohort of patients in the cohort of short-acting parenteral typical antipsychotics. We found comparable rates of involuntary admission and GAF-score at admission, which are characteristics for severe illness, for patients in the cohort of olanzapine oro-dispersible tablets and short-acting parenteral typical antipsychotics. Thus, our findings indicate

that oro-dispersible olanzapine tablets are indeed used as an alternative for parenteral formulations.

The initial choice also affects follow-up treatment scenarios. Twice as many patients treated in the oro-dispersible cohort were eventually treated with atypical antipsychotics compared to patients in the short-acting parenteral typical antipsychotic cohort. This concurs with findings in our previous study, in which we found that short-acting parenteral typical antipsychotics drive the choice toward the oral typical antipsychotic therapy.[7] A comparable amount of patients on oro-dispersible tablets or short-acting parenteral typical antipsychotics are subsequently switched to depot-antipsychotic therapy, or are discharged with depot antipsychotics. These depot preparations, active for weeks at a time, are frequently used for those who find taking oral medication on a regular basis difficult or unacceptable.[11]

There are some limitations to our study. First, only data of admitted patients were available. However, we were interested in the more severely ill patients, who were admitted to a psychiatric hospital. Also, the amount of patients having follow-up antipsychotic therapy with short-acting parenteral typical antipsychotics is probably a large overestimation, since these prescriptions are prescribed PRN (pro re nata; 'as needed'), and are not expected to be executed at three months, and certainly not at discharge.

In conclusion, our study reveals that oro-dispersible olanzapine is used as an alternative for short-acting parenteral typical antipsychotics and its use is a major driving factor towards the follow-up therapy with atypical antipsychotic treatment.

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Less medication switching after initial start with atypical antipsychotics

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SUMMARY

Background Switching from one to another antipsychotic may be seen as an overall expression of unsatisfactory response to treatment, including both treatment failure and unacceptable adverse effects.

Objective To investigate the extent and time of switching to another oral antipsychotic in newly admitted in-patients that started oral typical or atypical antipsychotic therapy.

Methods In a retrospective follow-up study of 522 newly admitted patients who started with an oral antipsychotic, we applied a case-control analysis considering patients switching to another oral antipsychotics as cases. Association between patient characteristics and switching antipsychotic medication was evaluated using logistic regression analysis. A Kaplan-Meier analysis was performed to analyse time to switch.

Results Patients initially treated with an oral typical antipsychotic showed a twofold increased risk to switch to another antipsychotic compared to patients initially treated with an oral atypical antipsychotic (adjusted OR=1.79; 95% CI=1.15-2.78). The Kaplan-Meier survival analysis revealed that patients who started with a typical antipsychotic switched sooner (median is 24 days) compared to patients on atypical antipsychotics (median is 170 days).

Conclusions Atypical antipsychotics are less frequently associated with switching in comparison with typical antipsychotics suggesting overall better treatment satisfaction.

INTRODUCTION

Antipsychotics are indicated in the treatment of patients suffering from psychotic disorders in order to manage symptoms and prevent relapse.[1] During many years, typical antipsychotic drugs such as haloperidol have been widely used as first choice treatment for acute as well as chronic psychotic disorders.[2] The introduction of atypical antipsychotics (clozapine, olanzapine, quetiapine, risperidone, sertindole) has broadened treatment options for psychotic disorders. There has been a shift in favour of the use of atypical antipsychotics[3], although the precise therapeutic value of atypical antipsychotics remains controversial.[4-10] The use of typical antipsychotics is associated with adverse effects including extrapyramidal side-effects, tardive dyskinesia and hyperprolactinaemia.[11-13] Atypical antipsychotics seem to have different adverse effects such as weight gain and disturbance of glucose metabolism.[4,13-15] In addition, compared to typical antipsychotics, atypical antipsychotics appear to have a more pronounced effect on negative symptoms associated with schizophrenia, such as lack of motivation, apathy and inability to express emotions.[16-18]

In daily practice, switching from one to another antipsychotic may be seen as an overall expression of unsatisfactory response to treatment, including both treatment failure and unacceptable adverse effects.[19]

The objective of our study is to investigate the extent and time of switching to another antipsychotic between typical and atypical antipsychotics in newly hospitalised patients after initiating oral antipsychotic therapy.

METHODS

Setting and study population

Included in the cohort were all patients, aged between 18 and 60 years, who were admitted for a new hospitalisation of at least three days during 1997-1999 to one of the acute psychiatric admission wards of three psychiatric hospitals and who started treatment with an oral antipsychotic. The hospitals have recently merged to a large centre for mental health care, serving a catchment area of about 720,000 inhabitants in the centre of the Netherlands. 'Newly hospitalised' was defined as having no previous admission to any of these hospitals in the two years before the inclusion date.

Study design

In this retrospective follow-up study we applied a case-control analysis considering all patients that have switched to another oral antipsychotic as cases. We defined a switch as any switch from one oral antipsychotic to another oral antipsychotic, i.e. including switches within the classes of typical and atypical antipsychotics. Only the first switch to another oral antipsychotic was taken into account. Controls were patients who did not switch their initial oral antipsychotic during admission. Patients receiving both an oral typical and an oral atypical antipsychotic on the day of admission were excluded.

Medication and patient records were retrospectively collected over the period of January 1st, 1997 until December 31st 1999. The drug use database and the clinical database were linked anonymously through record linkage methodology based on date of birth, gender and day of admission.[20]

At admission, the diagnosis was established by the treating psychiatrist and coded according to DSM-IV.[21] Diagnoses were classified as psychotic disorder, bipolar disorder, depressive disorder, personality disorder, anxiety disorder, other or unknown diagnosis.

To describe the severity of the disorder of the patients, some 'markers of severity' were defined and collected. The admissions were classified as 'voluntary' or 'involuntary'. The use of restrictive measures such as separation and the involuntary application of medication were also noted. Involuntary admissions and restrictive measures are reserved for more severely ill patients. Another marker of the severity of the disease was the initial use of short-acting parenteral antipsychotics.[22]

Antipsychotics were classified as typical or atypical. Clozapine, olanzapine, quetiapine, risperidone and sertindole were classified as atypical antipsychotics. Other drugs starting with the four digits ATC-code N05A were classified as typical antipsychotics.[23] Lithium and levomepromazine also having a four digits ATC-code N05A were excluded because they are not registered for psychotic disorders in the Netherlands. Drugs were stratified according to their route of administration: oral or short-acting parenteral.

The scientific committee and the board of the centre for mental health care approved the study protocol with respect to privacy aspects.

Data analysis

The association of patient characteristics and the switch to another oral antipsychotic after initial treatment with a typical versus an atypical oral antipsychotic, was studied using logistic regression analysis. The strength of the associations was expressed as odds ratios with corresponding 95 percent confidence interval (95% CI). The same analysis was performed with adjustment for possible confounding factors (age group, gender, DSM-IV diagnoses, initial use of short-acting parenteral antipsychotic, involuntary admissions and/or restrictive measures). Additionally, a Kaplan-Meier plot was constructed to analyse time to switch in the subgroup of patients starting with oral typical or oral atypical antipsychotics. Data were analysed using EGRET statistical software (version 2.0.31) by Cytel Software Corporation.

RESULTS

The characteristics of the cohort are presented in Table 1. A total of 522 patients met the inclusion criteria. Most patients (60.9%) were younger than 40 years old, with a median age of 36 years. Schizophrenia and other psychotic disorders accounted for 50.2% of the diagnoses of the patients admitted. Other diagnoses included bipolar disorders (16.3%), depressive disorders (12.6%) and personality disorders (16.7%). The most frequently prescribed oral antipsychotic drugs were zuclopenthixol (30.1%), pimozide (13.8%) and haloperidol (13.0%). The proportion of atypical agents was 27.8%, mostly consisting of olanzapine (15.9%) and risperidone (11.5%).

Table 1 *Patient characteristics*

	N=522	%
Age ≥40	204	39.1%
Female gender	249	47.7%
DSM-IV diagnosis*		
Psychotic disorder	262	50.2%
Bipolar disorder	85	16.3%
Depressive disorder	66	12.6%
Personality disorder	87	16.7%
Anxiety disorder	26	5.0%
Other	23	4.4%
Unknown	65	12.5%
First oral antipsychotic		
Typical antipsychotics		
Zuclopenthixol	157	30.1%
Pimozide	72	13.8%
Haloperidol	68	13.0%
Bromperidol	24	4.6%
Penfluridol	14	2.7%
Perphenazine	9	1.7%
other typical antipsychotics	21	4.0%
Atypical antipsychotics		
Olanzapine	83	15.9%
Risperidone	60	11.5%
Clozapine	13	2.5%
Sertindole	1	0.2%

* Totals exceed 100% because of multiple diagnoses

Table 2 *Switching behaviour after initial start with typical or atypical antipsychotics*

	Switch to atypical antipsychotic	Switch to typical antipsychotic	No switch
All patients (N=522)	65 (12.5%)	188 (36.0%)	269 (51.5%)
Starting with atypical antipsychotic (N=157)	19 (12.1%)	35 (22.3%)	103 (65.6%)
Starting with typical antipsychotic (N=365)	46 (12.6%)	153 (41.9%)	166 (45.5%)

In Table 2 switching behaviour after initial start with typical or atypical antipsychotics is listed. Of all patients, 48.5% switched from the first oral antipsychotic to another oral antipsychotic. Patients starting with an oral atypical antipsychotic switched less quickly to another antipsychotic (Figure 1). The median time to switch was 24 days for typical antipsychotics and 170 days for atypical antipsychotics.

In Table 3, possible determinants for switching to another oral antipsychotic treatment are listed. Compared to atypical oral antipsychotics, patients starting with a typical oral antipsychotic have a higher risk to switch to another antipsychotic (adjusted OR=1.79; 95% CI=1.15-2.78). Out of 253 patients who switched to another antipsychotic, 120 (47.4%) patients were initially treated with short-acting parenteral antipsychotics. This was 20.8% in the group treated with an oral atypical antipsychotic (adjusted OR=2.19; 95% CI=1.41-3.40). Out of 253 patients who switched to another antipsychotic, 88 (34.8%) had an involuntary admission and/or restrictive measures. This was 17.5% in the group treated with an oral atypical antipsychotic (adjusted OR=1.97; 95% CI=1.31-2.96).

Table 3 *Determinant for switching from one to another oral antipsychotic*

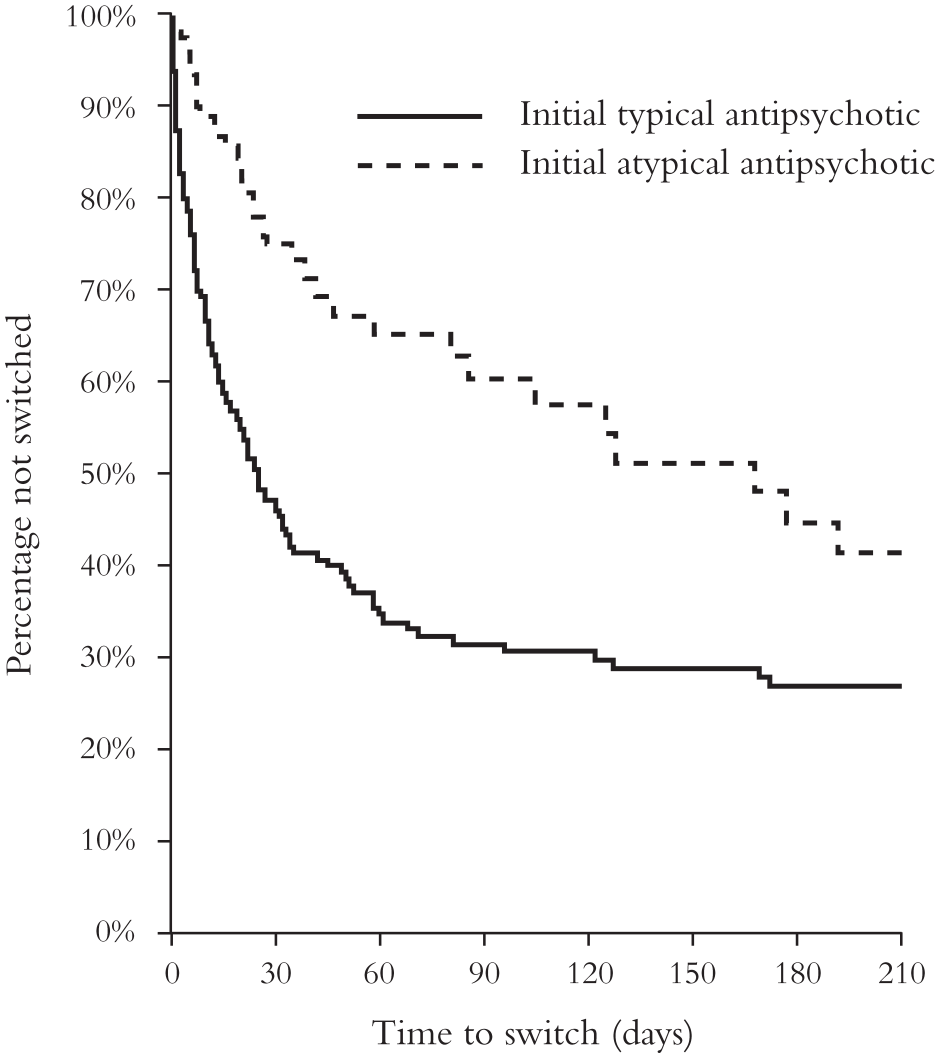
	Cases switch to another antipsychotic (N=253)	Controls no switch (N=269)	Crude OR (95% CI)	Adjusted** OR (95% CI)
Age ≥40	94 (37.2%)	110 (40.9%)	0.85 (0.60-1.22)	0.78 (0.53-1.15)
Female gender	115 (45.5%)	134 (49.8%)	0.84 (0.60-1.18)	1.05 (0.71-1.55)
First oral antipsychotic is typical	54 (21.3%)	103 (38.3%)	**2.27 (1.56-3.33)**	**1.79 (1.15-2.78)**
DSM-IV diagnosis*				
Psychotic disorder	136 (53.8%)	126 (46.8%)	1.32 (0.94-1.86)	1.12 (0.71-1.77)
Bipolar disorder	51 (20.2%)	34 (12.6%)	**1.75 (1.09-2.80)**	1.37 (0.77-2.45)
Depressive disorder	26 (10.3%)	40 (14.9%)	0.66 (0.39-1.11)	1.09 (0.59-2.01)
Personality disorder	37 (14.6%)	50 (18.6%)	0.75 (0.47-1.19)	0.93 (0.55-1.57)
Anxiety disorder	8 (3.2%)	18 (6.7%)	0.46 (0.19-1.07)	0.74 (0.30-1.81)
Other	11 (4.3%)	12 (4.5%)	-	-
Unknown	24 (9.5%)	41 (15.2%)	-	-
Indices for severity of the disease				
Involuntary admission and/or restrictive measures	88 (34.8%)	47 (17.5%)	**3.11 (2.16-4.45)**	**1.97 (1.31-2.96)**
Initial short-acting parenteral antipsychotic	120 (47.4%)	56 (20.8%)	**3.43 (2.34-5.04)**	**2.19 (1.41-3.40)**

* Totals exceed 100% because of multiple diagnoses

** Adjusted for age group, gender, diagnosis, initial short-acting parenteral antipsychotics and involuntary admission and or restrictive measures

Significant associations are printed in bold

Figure 1 *Time to switch for patients on typical or atypical antipsychotics*



Discussion

In this observational study we found that patients initially treated with a typical oral antipsychotic have a twofold increased risk to switch to another antipsychotic compared to patients treated with an atypical oral antipsychotic. The indices for severity of the disease (initial use of short-acting antipsychotics and the involuntary admission and/or restrictive measures) were identified as important determinants for switching. In addition, patients starting with a typical antipsychotic switched sooner than patients on atypical antipsychotics.

Efficacy and incidence of adverse effects of atypical versus typical antipsychotics have been established in randomised controlled trials (RCT). Bias

in the selection of the patients in RCTs will affect the validity of the results, so it does not necessarily imply validity outside this group. Although observational data have a lower internal validity than those obtained from RCTs, they can provide important information about the use and effects in daily clinical practice. Unacceptable adverse effects or insufficient effectiveness will often result in switching to other therapeutic options. Switching to another oral antipsychotic is therefore an overall measure for dissatisfaction of the initial choice by all parties (patient, physician, family, nurses, etcetera) involved in the treatment.

There are some limitations to our study. Although we aimed to study newly hospitalised patients, our cohort may contain some patients previously admitted on a psychiatric ward of general hospitals in our region or hospitalised in another region than the catchment area of our hospital. Since patients in the Netherlands are preferably transferred to their home-region, the latter will consist of a very small minority of the included patients. Another limitation of our study is that we have no information available on antipsychotic treatment before admission. We don't know if and how patients were treated with antipsychotics before treatment. Negative experiences with antipsychotic treatment before admission may have influenced the choice for an antipsychotic after admission. In our clinical setting medication of preferent use is included in a local formulary. With exception of clozapine, this formulary did not contain atypical antipsychotics until 1999. However, their use was not restricted in any way. Asking psychiatrists towards their opinion of the use of atypical antipsychotics, many of them had the impression that the newer antipsychotics were less potent in treating psychotic disorders in the acute clinical setting. Although we don't know why a specific antipsychotic was chosen in this study, this impression could have affected the primary and secondary choice for an antipsychotic. In our study, the majority of both patients starting with an oral typical or atypical antipsychotic switched to typical antipsychotics. Negative experience with both typical or atypical antipsychotics is no reason to switch to atypical antipsychotic agents.

In our study among hospitalised patients, 48.5% switched their treatment with an oral antipsychotic during the first admission. This is higher than was found in a retrospective cohort study of an outpatient population with

schizophrenia, where approximately 25% of all patients switched from one antipsychotic to a different antipsychotic during twelve months of therapy.[24] Also in a cohort of 21,873 patients with schizophrenia and stable 3-month prescription of any antipsychotic medication, 25% had their medication switched during the next year.[25] A plausible explanation of these findings in comparison to our findings, is the more severely ill cohort of patients in our clinical setting.

In conclusion, atypical antipsychotics are in comparison with typical antipsychotics less frequently associated with switching, suggesting overall better treatment satisfaction.

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[7]

Reasons for switching between antipsychotics in daily clinical practice

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SUMMARY

Background Previous research that atypical antipsychotics were switched less often than typical antipsychotics, suggesting overall better treatment satisfaction with atypical antipsychotics.

Objective The objective of this study was to investigate the reasons for switching antipsychotics after initiating oral treatment with either typical or atypical antipsychotics in a clinical setting.

Methods A total of 123 patients that switched antipsychotic therapy were recruited from 17 psychiatric hospitals, of which 46% of patients switched because of lack of effect and 45% because of adverse effects.

Results No significant differences were found between users of atypical versus typical antipsychotics in reasons for switching, either because of overall adverse events, or lack of effectiveness. In users of atypical antipsychotics extrapyramidal effects were reported less often as reason for switching (adjusted OR=0.18; 95% CI=0.07-0.51). Patients on atypical antipsychotics switched more often because of weight gain (adjusted OR=12.8; 95% CI=1.50-109).

Conclusions In case of switching, no difference was found between typical and atypical antipsychotics in the frequency of tolerability or reported lack of effectiveness. However, the type of side- effect as a reason for switching differed between atypical and typical antipsychotics.

INTRODUCTION

Antipsychotics are frequently used to manage acute symptoms and to prevent relapse in the treatment of patients with psychotic disorders.[1] The introduction of atypical antipsychotics has broadened the treatment options. Switching from one to another antipsychotic may be seen as an overall expression of an unsatisfactory response to the initial treatment, including both treatment failure and the experience of adverse effects.[2,3]

In a previous retrospective follow-up study, of 522 newly admitted patients who started with an oral antipsychotic, we found that compared to atypical oral antipsychotics, patients starting with a typical oral antipsychotic had a higher risk to switch to another antipsychotic (adjusted OR=1.79; 95% CI=1.15-2.78).[4] Moreover, the median time to switch was 24 days for patients on typical antipsychotics and 170 days for atypical antipsychotics. However, since this was a retrospective database study, we were unable to distinguish between switching due to a lack of effect, due to the occurrence of adverse effects, or because of other reasons.

The objective of the study presented here was to investigate the reasons for switching between antipsychotics—after initiating oral treatment with either typical or atypical antipsychotics—in a clinical setting, and to study whether typical and atypical antipsychotics differ in that respect.

METHODS

Setting and study population

We designed a prospective observational study to assess reasons for switching from one antipsychotic to another in normal clinical practice. Hospital pharmacists in 17 psychiatric hospitals in the Netherlands agreed to each select up to ten consecutive hospitalised patients, aged between 18 and 60 years, in whom antipsychotic treatment had been altered by their physicians. Patients were included from June 2002 until February 2003. The prescribing physicians were asked to fill in a short questionnaire concerning reasons for switching as well as clinical details of the patient.

Data collection

We defined a switch as any change in therapy from one oral antipsychotic to another oral antipsychotic. Clozapine, olanzapine, quetiapine, risperidone and sertindole were classified as atypical antipsychotics. All other antipsychotics were classified as typical antipsychotics. Relevant clinical information was provided by the physician, including indication for prescribing an antipsychotic and psychiatric comorbidity. Possible reasons for the switch were categorised into: adverse effects, lack of effect, wish of the patient, or other reason. Furthermore, information on the duration of the initial antipsychotic treatment was gathered.

Data analysis

We compared the frequency of types of switch in patients that were switched from atypical versus patients switched from typical antipsychotics and adjusted for possible confounding factors including age, gender and indication, using unconditional logistic regression. The strength of the associations was expressed as odds ratios with 95 percent confidence intervals (95% CI).

RESULTS

A total of 123 patients who switched oral antipsychotic treatment were recruited. Most patients (57.7%) were younger than 40 years of age. Psychotic disorders accounted for 75.6% of the diagnoses of the patients. Other diagnoses included bipolar disorders (7.3%), depressive disorders (6.5%) and personality disorders (13.0%). The initial (i.e. before switch) proportion of typical agents was 43.9%, mostly consisting of zuclopenthixol (18.7%; median dose=28 mg). The initial proportion of atypical antipsychotics was 56.1%, mostly consisting of olanzapine (26.0%; median dose=15 mg), risperidone (18.7%; median dose=4 mg) and quetiapine (9.8%; median dose=600 mg).

In Table 1 reasons for switching are listed. Most important findings are that in users of atypical antipsychotics, extrapyramidal effects were reported less often as reason for switching (adjusted OR=0.18; 95% CI=0.07-0.51). Patients on atypical antipsychotics switched more often because of weight gain (adjusted OR=12.8; 95% CI=1.50-109).

Table 1 *Reported reasons for switching antipsychotic treatment*

	Atypical		Typical		Crude	Adjusted**
	to typical N=26	to atypical N=43	To typical N=10	to atypical N=44	Odds Ratio*** (95% CI)	Odds Ratio*** (95% CI)
Adverse effects						
Any	7 (26.9%)	23 (53.5%)	1 (10.0%)	24 (54.5%)	0.89 (0.44-1.83)	0.60 (0.23-1.62)
EPS	0 (0.0%)	11 (25.6%)	0 (0.0%)	20 (45.5%)	0.32 (0.14-0.75)	0.18 (0.07-0.51)
Sexual	0 (0.0%)	1 (2.3%)	0 (0.0%)	0 (0.0%)	-	-
Weight gain	5 (19.2%)	6 (14.0%)	1 (10.0%)	0 (0.0%)	10.1 (1.25-80.5)	12.8 (1.50-109)
Other	2 (7.7%)	6 (14.0%)	0 (0.0%)	6 (13.6%)	1.05 (0.34-3.23)	0.95 (0.27-3.38)
No effect	12 (46.2%)	21 (48.8%)	6 (60.0%)	18 (40.9%)	1.15 (0.56-2.34)	0.94 (0.35-2.51)
Patient wish	10 (38.5%)	6 (14.0%)	3 (30.0%)	11 (25.0%)	0.86 (0.38-1.97)	0.71 (0.28-1.84)
Compliance	6 (23.1%)	0 (0.0%)	2 (20.0%)	3 (6.8%)	0.93 (0.27-3.24)	0.78 (0.19-3.11)
Other	0 (0.0%)	4 (9.3%)	1 (10.0%)	3 (6.8%)	0.77 (0.18-3.23)	0.38 (0.07-2.14)

* Totals exceed 100% because of multiple reported reasons for switching
** Adjusted for age, gender and indication for prescribing an antipsychotic
*** For the switch from atypical versus switch from typical

Patients switching because of weight gain, were initially treated with olanzapine (12 patients) or haloperidol (1 patient). No difference in reasons for switching was seen between diagnoses.

In an analysis on reasons for switching antipsychotic treatment in relation to time we found that patients who were switched within a week, did so mostly because of adverse effects or other reasons, while only two patients (15.4%) switched because of lack of effect. Patients who were switched after at least two weeks do so mostly because of lack of effect.

DISCUSSION

We found no differences in the frequency of tolerability or reported lack of effectiveness as reasons for switching from atypical versus typical antipsychotics. Focusing on specific adverse effects, however, we found that patients on atypical antipsychotics switched less often because of extrapyramidal side-effects and more often because of weight gain.

In our previous retrospective follow-up study we found that patients initially treated with an atypical antipsychotic showed a better overall treatment satisfaction.[4] However, in that study we had no information on reasons for switching. Combining the data found in both studies we conclude, that these patients switched sooner, because of adverse events. The majority of patients switched to atypical antipsychotics, both from a typical and an atypical antipsychotic.

Nearly all patients on atypical antipsychotics who switched because of extrapyramidal side-effects, consisted of patients on risperidone. The patients starting with risperidone and switching because of extrapyramidal side-effects, were on a median dose of 3.5 mg, ruling out high dosing as a plausible reason for the occurrence of extrapyramidal side-effects. Nearly all patients who switched because of weight gain, were patients who used olanzapine. Since we only included patients who switched their medication, one must be aware, that substances that were used more often, have a higher chance to be switched and included in our cohort.

In conclusion, in patients switching antipsychotic treatment, no difference was found in the frequency of tolerability or reported lack of effectiveness. However, the type of side-effect as a reason for switching differed between atypical and typical antipsychotics. We found that early switching of antipsychotic treatment was related to the occurrence of adverse effects, while switching after at least a few weeks was related to lack of effect.

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[8]

Risk of hip/femur fractures in patients using antipsychotics

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Bone (in press)

SUMMARY

Background A hip/femur fracture is a devastating event, especially for the elderly: the majority will never regain their pre-fracture levels of physical and social activities. Antipsychotics are probably associated with the occurrence of fractures, but have not been investigated systematically in these.

Objective To investigate whether use of antipsychotics is associated with hip/femur fractures and whether pharmacological differences between antipsychotics are related to the occurrence of fractures.

Methods A case-control study was conducted, in which cases were defined as patients with a hip/femur fracture. Each patient was matched to one control patient. The association between use of antipsychotics and the occurrence of hip/femur fractures was evaluated using conditional logistic regression.

The study included 44,500 patients from 683 general practices from different geographical areas in the UK, registered within the General Practice Research Database (GPRD). Exposure to antipsychotics was categorised as 'no use', 'current use' and 'prior use'.

Results Both current and prior use of antipsychotics were associated with an approximately two-fold increased risk of fractures. After adjustment for possible confounders, a small significant effect remained for current users (OR=1.3; 95% CI: 1.1-1.5) and prior users (OR=1.3; 95% CI: 1.2-1.5). We did not find an association between dose of antipsychotics, or between the degree of blockade of the alpha-1 adrenoceptor or histamine-1 receptor and risk of fractures. The total number of days of antipsychotic use was significantly associated with an increased risk of hip/femur fractures.

Conclusions There is a small increased risk of hip/femur fractures associated with the use of antipsychotics. This risk increases with long-term use.

INTRODUCTION

A hip/femur fracture is a devastating event, especially for the elderly. The one-year mortality after hip/femur fracture is about 20%, and 20% of those living in the community at the time of their hip/femur fracture have to be admitted to a nursing home.[1] Of those returning to living in the community, the majority will never regain their pre-fracture levels of physical and social activities.[1]

The possible association between the use of several psychotropics, especially benzodiazepines and antidepressants, and hip/femur fractures has received much interest during recent years. In contrast, antipsychotics have not been investigated systematically. Some studies, although not directly focused on antipsychotics, have reported an association between the use of antipsychotics and fractures.[2,3] It has been postulated that the use of these drugs may lead to an increased tendency to fall as result of orthostatic hypotension or sedation.[3-8] Furthermore, long-term use of some antipsychotics has been associated with decreased bone mineralisation leading to weaker bones [9-14], and a higher probability that a fall will result in a fracture.

The objective of our study was to investigate whether short and long-term uses of antipsychotics are associated with hip/femur fractures and whether pharmacological differences between antipsychotics are related to the occurrence of fractures.

METHODS

Setting

Data were collected from 683 general practices in different geographical areas in the UK, registered within the General Practice Research Database (GPRD) which is owned by the Department of Health in the UK.[15] General practitioners (GPs) play a key role in the health care system in the UK, as they are responsible for primary health care and specialist referrals. Patients are semi-permanently affiliated to a practice, which centralises the medical information from the GPs, specialist referrals and hospitalisations. The data recorded in the GPRD include demographic information, prescription data, clinical events, preventive care provided, specialist referrals, hospital admissions and their major outcomes.[15] Clinical data are stored and retrieved by means of the

Oxford Medical Information Systems (OXMIS) and Read codes for diseases that are cross-referenced to the International Classification of Diseases (ICD-9). Each entry in the GPRD is internally validated by cross-checking within the practice and by comparisons with external statistics.[15] Only data from practices that pass this quality control are compiled and are part of the GPRD. Several independent validation studies have confirmed the high level of completeness and validity of the GPRD, specifically with regard to recording of fractures.[15-17] Nazareth et al. found that 74% of all consultations of patients with psychotic disorder were recorded, as were 95% of prescriptions.[18]

Study design

A case-control study was conducted using GPRD data collected from 1987 to 1999. We selected patients with a hip fracture (ICD-9=820) or with other femur fractures (ICD-9=821). A hip fracture is a fracture to the proximal end of the femur, not to the pelvis. The fracture can occur to the femoral head, femoral neck, or at the proximal end of the femur, just below the neck of the bone. In this study, our definition of hip/femur fracture included both types of fractures. We defined cases as permanently registered patients (those residing in the practice neighbourhood) with a first record of a hospital admission for a hip/femur fracture recorded in their medical records between the enrolment date of their practice in the GPRD and the end of data collection (July 1999). The date of the occurrence of the hip/femur fracture was termed the index date. Each case was matched to one control patient by year of birth (within a one-year margin), sex and medical practice. If no eligible control was available, the age criterion was expanded consecutively at one-yearly intervals to a maximum of ten years. If no eligible control patient could be found, then an age- and sex-matched control patient from another practice was selected. Patients who already had a prescription for any antipsychotic at the start of the collection of the GPRD (1987) were excluded, preventing the inclusion of patients who were receiving regular treatment with antipsychotics before 1987. The selected control patient was assigned the same index date as that of their matched case patient. For the small number of control patients who had been transferred to another practice or died prior to this date, an index date was randomly selected between registration and dates of transfer or death.

Exposure assessment

All psychotropic drugs were classified according the ATC-system of the WHO.[19] Drugs starting with the four digit ATC-code N05A were classified as antipsychotics, with the exception of lithium, which is not an antipsychotic. Antipsychotic drugs were stratified according to their alpha-1 adrenoceptor and histamine-1 receptor blocking capacity and on the extent of this effect (low, intermediate or high).[20] The information recorded by the GPs included the name, dose, frequency and number of dosages prescribed. For this study, we assumed that a subject was exposed for the duration of the prescription supply. If the prescription length was unknown, a 30-day period was presumed (average prescription length was 34 days). We analysed medication use from five years before the index date.

Exposure to antipsychotics was categorised as 'no use' when there was no recorded use of antipsychotic medication in the five-year period before the index date, 'current use' when the supply of the most recent prescription lasted at least until the index date or ended no more than six days before the index date, and 'prior use' when the most recent prescription ended seven or more days before the index date. Current users were subdivided into recent and non-recent starters (recent starters were patients who had their first prescription of antipsychotic medication 30 days or less before the index date).

The dose of the antipsychotic was based on the last prescription with a record on the dosage regimen and it was standardised to the number of Defined Daily Doses (DDD), a technical unit of measurement defined as the average dose per day for a drug used for its main indication in adults.[21] Daily dosages were categorised as low (<0.5 DDD), normal (0.5-1.5 DDD), or high (≥1.5 DDD). The duration of antipsychotic use was determined by cumulating the number of days of antipsychotic medication that was prescribed before the index date. Treatment episodes were defined as series of subsequent prescription refills for an antipsychotic agent independent of switching to another antipsychotic or changes in dose regimen. Duration of use was subdivided into no-use, 0-30 days, 30-90 days, 90-180 days, 180 days-1 year, 1-2 years, 2-3 years, >3 years.

Assessment of potential confounders

Potential confounders in this study were clinical variables based on diagnosis and/or medication use that have previously been associated with risk of fractures.[22] The diagnosis of neurologic/psychiatric condition in the year before the index date included cerebrovascular disease, dementia, depression, psychotic disorder and seizures. The diagnosis of somatic condition in the year before the index date included anaemia, back pain, heart failure, chronic obstructive pulmonary disease (COPD), diabetes, falls, osteoporosis, rheumatoid arthritis, and thyrotoxicosis. Medication use in the 6-month period before the index date included antidepressants[23], anticonvulsants, antiparkinson drugs, benzodiazepines[24,25] as well as somatic drugs: cardiovascular drugs, inhaled corticosteroids and/or bronchial drugs, NSAIDs, systemic corticosteroids, biphosphonates, calcitonin, vitamin D, thiazides and disease-modifying antirheumatic drugs (DMARDs). Furthermore, the most recent data on smoking status (history of smoking, or no/ unknown history of smoking) and the last known body mass index (BMI; <20, 20-24, 25-29, ≥30 kg/m^2, or unknown) were gathered at the index date.

Data analysis

The strength of the association between use of antipsychotics and the occurrence of hip/femur fractures was estimated using conditional logistic regression and expressed as crude and adjusted odds ratios (OR) with 95% confidence intervals (95% CI). Covariates were included in the regression model if they were either independently significantly associated with the outcome ($p<0.05$), or induced a 10% change or more in the crude matched OR for use of antipsychotics. We evaluated potential confounding by indication by estimating the association between antipsychotic use and hip/femur fractures in patients with a recorded indication for schizophrenia or any other psychotic disorder. Data were analysed using SPSS for Windows (release 10.0.7 standard version). A trend analysis was performed for the association between cumulative duration of use of antipsychotics and risk of fractures.

RESULTS

The study population consisted of 22,250 patients with a hip/femur fracture and an equal number of matched controls. The characteristics of the study population are shown in Table 1. The majority of subjects were older than 60 years (89.4%) and female (75.8%). Compared to controls, cases had a higher prevalence of medical conditions and used more medication. The most prevalent medical conditions among cases and controls were COPD, heart failure, and cerebrovascular disease. Compared to 3.7% of the controls, 15.5% of cases had a history of falls. The most frequently prescribed drugs among cases and controls in the 6-month time window before the index date were hypnotics/anxiolytics.

Table 2 shows the association between use of antipsychotics and risk of hip/femur fracture. Both current use and prior use were associated with an approximately two-fold increased risk of fractures. After adjustment for possible confounders, a small effect remained for current users (OR=1.3; 95% CI: 1.1-1.5) and prior users (OR=1.3; 95% CI: 1.2-1.5). We found 2,797 patients with a diagnosis of psychotic disorder (1,905 cases and 892 controls). No statistical differences in risk on hip/femur fractures associated with antipsychotic use were seen in patients with and without a diagnosis of psychotic disorders.

Table 3 shows the association between the effect of dosing, individual antipsychotics and receptor effects of current users and the risk of hip/femur fractures. We found a two-fold increase in the overall crude risk among users of antipsychotics, but no association with dosing regimes, individual antipsychotics or the differential effects on the alpha-1 adrenoceptor or the histamine-1 receptor. After adjustment for possible confounders, no significant associations were found (except for promazine).

Figure 1 shows the association between days of use of antipsychotics and the risk of fractures. We found a small increased risk on fractures immediately after the initiation of antipsychotic therapy. With longer use of antipsychotics, the risk of fracture further increased. Although the confidence intervals overlaid, the linear trend analysis showed a significant slope.

Table 1 *Characteristics of cases and control patients*

Characteristic	Cases (N=22,250) No. (%)	Controls (N=22,250) No. (%)
Age (years)		
18-59	2,344 (10.5)	2,339 (10.5)
60-79	7,616 (34.2)	7,920 (35.6)
≥80	12,290 (55.2)	11,991 (53.9)
Mean age	76.9	76.7
Female gender	16,872 (75.8)	16,872 (75.8)
Body Mass Index		
<20	1,595 (7.2) *	935 (4.2)
20-24	4,121 (18.5)	4,080 (18.3)
25-29	2,330 (10.5) *	3,298 (14.8)
≥30	765 (3.4) *	1,253 (5.6)
Unknown	13,439 (60.4)	12,684 (57.0)
Smoking status		
Yes	2,705 (12.2) *	2,534 (11.4)
No / Unknown	19,545 (87.8)	19,716 (88.6)
Neurological/psychiatric condition		
Cerebrovascular disease	3,299 (14.8) *	2,136 (9.6)
Dementia	2,062 (9.3) *	953 (4.3)
Depression	1,313 (5.9) *	719 (3.2)
Psychotic disorder	1,905 (8.6) *	892 (4.0)
Seizures	686 (3.1) *	292 (1.3)
Somatic condition		
Anaemia	1,139 (5.1) *	670 (3.0)
Back pain	1,911 (8.6) *	1,238 (5.6)
Heart failure	3,119 (14.0) *	2,490 (11.2)
COPD	4,508 (20.3) *	3,564 (16.0)
Diabetes	1,363 (6.1) *	1,085 (4.9)
Falls	3,444 (15.5) *	817 (3.7)
Osteoporosis	1,260 (5.7) *	505 (2.3)
Rheumatoid arthritis	717 (3.2) *	336 (1.5)
Thyrotoxicosis	390 (1.8) *	262 (1.2)

(continue)

Table 1 (continued)

Characteristic	Cases (N=22,250) No. (%)	Controls (N=22,250) No. (%)
Psychotropic drug use in 6-month period before the index date		
Anticonvulsants	915 (4.1) *	360 (1.6)
Antidepressants	2,895 (13.0) *	1,607 (7.2)
Antiparkinson drugs	1,022 (4.6) *	394 (1.8)
Hypnotics/anxiolytics	4,848 (21.8) *	3,421 (15.4)
Somatic drug use in 6-month period before the index date		
Cardiovascular drugs	130 (0.6) *	255 (1.1)
Inhalation corticosteroids / bronchial drugs	2,243 (10.1) *	1,806 (8.1)
NSAIDs	4,134 (18.6) *	3,212 (14.4)
Systemic corticosteroids	1,600 (7.2) *	985 (4.4)
Biphosphonates	202 (0.9) *	72 (0.3)
Calcitonin	5 (0.0)	1 (0.0)
Vitamin D	175 (0.8) *	102 (0.5)
Thiazides	2,642 (11.9) *	2,872 (12.9)
DMARDs	256 (1.2) *	120 (0.5)

* $p<0.05$

Table 2 *Association between use of antipsychotics and risk of fractures*

Antipsychotic use	Cases No. (%)	Controls No. (%)	Crude OR	Adjusted OR
No use	19,251 (86.5)	20,702 (93.0)	reference	reference
Current user	1,495 (6.7)	751 (3.4)	**2.2 (2.0-2.4)**	**1.3 (1.1-1.5)**
Recent starter	215 (1.0)	135 (0.6)	**1.8 (1.4-2.2)**	1.2 (0.9-1.6)
Non-recent starter	1,280 (5.8)	616 (2.8)	**2.3 (2.1-2.5)**	**1.3 (1.1-1.5)**
Prior user	1,504 (6.8)	797 (3.6)	**2.1 (1.9-2.3)**	**1.3 (1.2-1.5)**

* Adjusted for medical condition (cerebrovascular disease, dementia, depression, psychotic disorder, seizures, anaemia, backpain, heartfailure, COPD, diabetes, falls, osteoporosis, rheumatoid arthritis, thyrotoxicosis) and medication (antidepressants, anticonvulsants, antiparkinson drugs, hypnotic/anxiolytics, cardiovascular drugs, inhalation corticosteroids and/or bronchial drugs, NSAIDs, systemic corticosteroids, biphosphonates, vitamin D, thiazides). Also for BMI and smoking status.

Significant associations are printed in bold

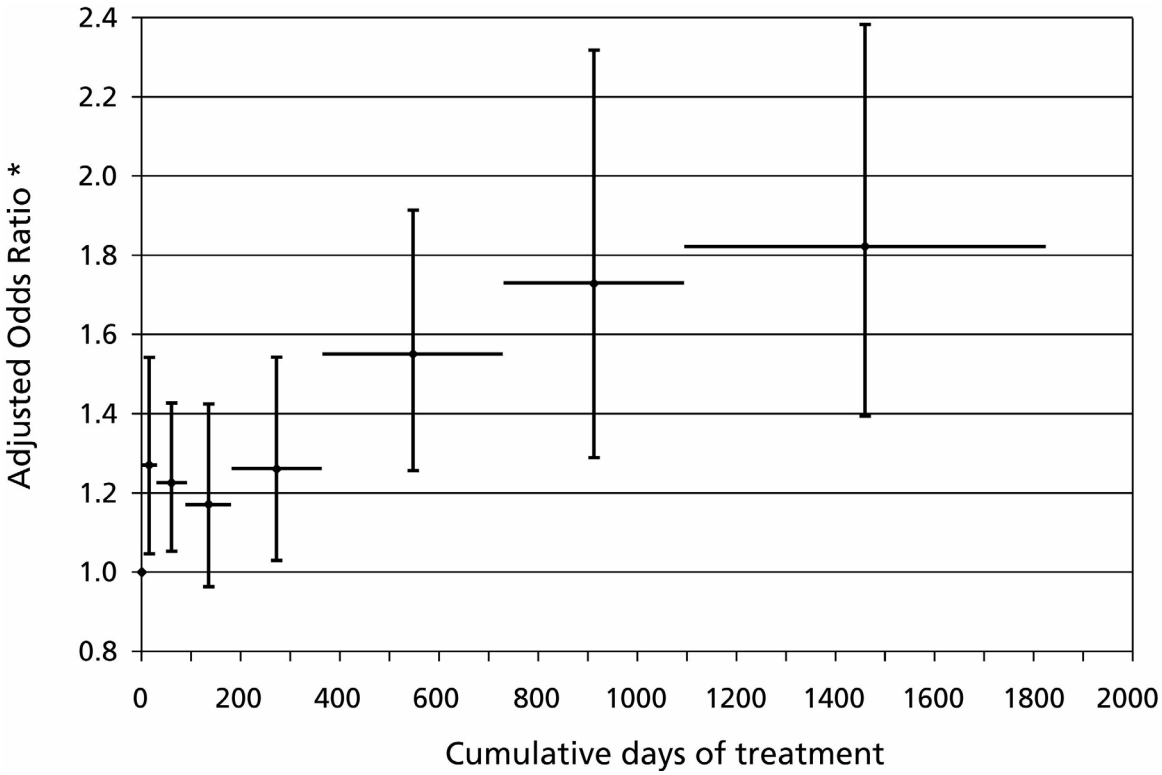
Table 3 *Effect of dose and substance receptor effect on the risk of fracture in current users of antipsychotics*

Antipsychotic use	Cases No. (%)	Controls No. (%)	Crude OR	Adjusted OR
Dosing				
No use	19,251 (92.8)	20,702 (96.5)	reference	reference
<0.5 DDD	1,038 (5.0)	532 (2.5)	**2.2 (2.0-2.5)**	1.1 (0.8-1.4)
0.5-1.5 DDD	113 (0.5)	60 (0.3)	**2.1 (1.5-2.9)**	0.7 (0.5-1.1)
≥1.5 DDD	23 (0.1)	9 (0.0)	**2.7 (1.2-6.1)**	1.4 (0.5-3.6)
Unknown DDD	321 (1.5)	150 (0.7)	-	-
Last prescribed antipsychotics				
No use	19,251 (92.8)	20,702 (96.5)	reference	reference
Thioridazine	741 (3.6)	382 (1.8)	**2.2 (2.0-2.6)**	1.2 (0.9-1.6)
Trifluoperazine	162 (0.8)	83 (0.4)	**2.1 (1.6-2.8)**	1.1 (0.7-1.6)
Chlorpromazine	140 (0.7)	59 (0.3)	**2.7 (1.9-3.7)**	1.5 (0.9-2.3)
Haloperidol	134 (0.6)	70 (0.3)	**2.1 (1.6-2.9)**	1.0 (0.6-1.5)
Promazine	126 (0.6)	41 (0.2)	**3.3 (2.3-4.8)**	**1.7 (1.0-2.7)**
Other antipsychotics	192 (0.9)	116 (0.5)	-	-
Receptor effect[20]				
Strength alpha-1 blocking effect				
No use	19,251 (92.8)	20,702 (96.5)	reference	reference
Low	25 (0.1)	8 (0.0)	**3.7 (1.6-8.5)**	1.4 (0.5-3.5)
Intermediate	198 (1.0)	104 (0.5)	**2.1 (1.6-2.7)**	0.9 (0.7-1.3)
High	1,206 (5.8)	594 (2.8)	**2.3 (2.1-2.6)**	1.2 (0.9-1.6)
Unknown	66 (0.3)	45 (0.2)	-	-
Strength histamine-1 blocking effect				
No use	19,251 (92.8)	20,702 (96.5)	reference	reference
Low	1,074 (5.2)	547 (2.5)	**2.2 (2.0-2.5)**	1.1 (0.8-1.5)
Intermediate	185 (0.9)	88 (0.4)	**2.5 (1.9-3.3)**	1.1 (0.8-1.7)
High	170 (0.8)	71 (0.3)	**2.5 (1.9-3.4)**	1.3 (0.9-1.8)
Unknown	66 (0.3)	45 (0.2)	**-**	-

* Adjusted for medical condition: cerebrovascular disease, dementia, depression, psychotic disorder, seizures, anaemia, backpain, heartfailure, COPD, diabetes, falls, osteoporosis, rheumatoid arthritis, and thyrotoxicosis. Medication: antidepressants, anticonvulsants, antiparkinson drugs, hypnotic/anxiolytics, cardiovascular drugs, inhalation corticosteroids and/or bronchial drugs, NSAIDs, systemic corticosteroids, biphosphonates, vitamin D and thiazides. Also for BMI and smoking status.

Significant associations are printed in bold

Figure 1 *Association between cumulative days of use of antipsychotics and risk of fractures*



* Adjusted for: medical condition (cerebrovascular disease, dementia, depression, psychotic disorder, seizures, anaemia, backpain, heart failure, COPD, diabetes, falls, osteoporosis, rheumatoid arthritis, Thyrotoxicosis), Medication (antidepressants, anticonvulsants, antiparkinson drugs, hypnotic/anxiolytics, cardiovascular drugs, inhalation corticosteroids and/or bronchial drugs, NSAIDs, systemic corticosteroids, biphosphonates, vitamin D, thiazides). Also for BMI and smoking status.

Discussion

In this study, we found evidence for an increased risk of hip/femur fractures among patients with current or prior use of antipsychotics. We did not find major differences between individual antipsychotics, dosing effects, nor an association with affinity for the alpha-1 adrenoceptor and the histamine-1 receptor. Finally, the cumulative dose (total number of days of antipsychotic use) was significantly associated with an increased risk on hip/femur fractures.

It has been estimated that 90% of hip/femur fractures are associated with falls.[26] Risk factors for fractures can be classified into those that pertain to the risk of falling and those that relate to the propensity of fracturing following a fall.[1] Risk factors involved in falling are physical impairments (e.g. dizziness, vision problems), and use of medication (e.g. benzodiazepines).[27] In our analyses, we adjusted for a range of medical conditions and medications that are associated with falling, as described in the methods section.

Patients who are vulnerable for orthostatic hypotension or sedative effects of antipsychotics are likely to be at risk for fracture shortly after initiating treatment. Antipsychotics like clozapine and risperidone are associated with blocking of the alpha-1 adrenoceptor. It has been advised that the hemodynamical effects of such drugs are monitored in elderly patients, as they are more vulnerable to the vasodilatory side-effects of alpha-1 blocking agents. Adverse events that have been reported in clinical trials of alpha-1 blocking agents include dizziness, weakness, postural hypotension and syncope.[4,28] Antipsychotics like clozapine and the phenothiazines cause histamine-1 receptor blocking in the central nervous system, which can cause sedation. Sedation is also a well known cause of fractures.[6,8,24,29]

Remarkably, we did not find an association between different doses of antipsychotics, or between the degree of blockade of the alpha-1 adrenoceptor or histamine-1 receptor and risk of fractures. The lack of association with the risk of fractures is perhaps explained by the alpha-1 blocking effect of antipsychotics not being as strong as alpha-1 adrenergic blockers used in the treatment of hypertension or benign prostate hyperplasia,[30] for which the cardiovascular effects are well known. Also, no association between dosing, and no association for the strength of the histamine-1 blocking effect and risk of fractures was found. The lack of association can perhaps be explained by patients being treated with multiple medications, with sedative effects.

To our knowledge, there has been no other systematic study of the association between fractures and long-term use of antipsychotics, although concern for this topic has been raised.[13] Multiple lines of evidence suggest dopamine, which is secreted by the tuberoinfundibular dopaminergic neurons into the portal hypophyseal vessels, is the primary prolactin-inhibiting factor.[31] Hyperprolactinaemia is associated with reduced bone mineral density, which is

probably mediated by the inhibition exerted by prolactin on the hypothalamic-pituitary-gonadal axis and the resulting hypogonadism.[32] Patients with tumors that secrete prolactin, have reduced bone densities at vulnerable sites.[33,34] Bone demineralisation could lead to a higher risk of fractures with long-term use. Recently, Meaney et al. found reduced bone mineral density after long-term prolactin-raising antipsychotic medication.[14] In our study the long-term use of antipsychotics was indeed associated with an increased risk of hip/femur fracture. Which is probably caused by the effect of antipsychotics on decreasing bone mineralisation, leading to weaker bones.[9-14] This will result in a higher probability that a fall will result in a fracture, increasing the risk of fractures.

We found an increased risk for hip/femur fractures in prior users of antipsychotics. Since our 'prior users' of antipsychotics ended their most recent prescription seven or more days before the index date, no significant amount of antipsychotic would be present in the patient. The increased risk can probably be explained by the fact that damage done to the bone structure is irreversible.[35] Although there are effective bone resorption inhibitors for osteoporosis (bisphosphonates, estrogen and calcitonin), these drugs essentially stabilise bone mass and do not cause substantial increases in bone mass or restore trabecular bone microarchitecture.[36] Damage to the bone structure caused by antipsychotics is probably also irreversible.

There are some limitations to this study. Drug treatment in observational studies is not randomised and is vulnerable to bias and confounding. In our analysis, we controlled for a range of medical conditions and prescription drugs that are associated with an increased risk of hip/femur fracture. However, we cannot rule out the possibility that residual confounding occurred or that alternative causes for our findings exist. Psychiatric patients are exposed to other risks to bone health, particularly excessive nicotine and alcohol consumption.[37,38] To overcome this, we adjusted for weight and smoking. But this study cannot address with certainty the aetiology of the increased risk of fracture in patients using antipsychotics. There remains the possibility that a higher risk of fractures is caused by the underlying disease (e.g. psychosis). Kuruvilla et al. found that prolactin levels in patients with schizophrenia are generally within the normal range prior to treatment for psychosis; schizophrenia itself does not appear to affect prolactin levels.[39]

Furthermore, we found no differences in the association between antipsychotic use and the occurrence of hip/femur fractures in patients with and without psychotic disorders, reinforcing the idea that hip/femur fractures are associated with antipsychotic use rather than the underlying disease .

Typical antipsychotics and risperidone raise prolactin levels, but clozapine, quetiapine and olanzapine are not associated with significant prolactin increase because they spare dopamine blockade within the tuberoinfundibular tract.[40] Unfortunately, we did not have enough patients who were treated solely with these atypical antipsychotics.

In conclusion, our findings suggest that use of antipsychotics is associated with a small increased risk of hip/femur fractures. This risk increases with long-term use of antipsychotics. The clinical implication is that patients starting treatment with antipsychotics have a higher risk of hip/femur fractures, regardless of the antipsychotic prescribed.

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Appendix *Antipsychotics categorised according to the affinity for the alpha-1 adrenoceptor and the histamine-1 receptor*

Drug	Alpha-1 receptor	Histamine-1 receptor
Amisulpride	Low	Low
Benperidol	Low	Intermediate
Chlorpromazine	High	Intermediate
Clozapine	High	High
Flupentixol	Unknown	Unknown
Fluphenazine	Intermediate	Low
Fluspirilene	Unknown	Unknown
Haloperidol	Intermediate	Low
Levomepromazine	High	High
Loxapine	High	High
Olanzapine	Intermediate	High
Pericyazine	Unknown	Intermediate
Perphenazine	Intermediate	High
Pimozide	High	Low
Pipothiazine	Unknown	Unknown
Promazine	High	High
Quetiapine	Intermediate	High
Risperidone	High	Intermediate
Sertindole	High	Low
Sulpiride	Low	Low
Thioridazine	High	Low
Trifluoperazine	High	Low
Zotepine	High	High
Zuclopenthixol	Intermediate	Intermediate

Adapted from Bazire[20]

[9]

Concomitant use of antidiabetic drugs in patients using antipsychotics: a comparison between inpatient and outpatient settings

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SUMMARY

Background There are marked differences between observational studies into the association between use of antipsychotic drugs and diabetes with respect to design, setting and outcome measurement.

Objective To compare the prevalence of antidiabetic use in an inpatient and an outpatient population of users of antipsychotics.

Methods Data on inpatients and outpatients were retrospectively collected. Patients that had started antipsychotic use in a two-year period between 2000 and 2002 were included. Both in the inpatient as well as in the outpatient setting, patients were defined as being treated with antidiabetics when they had received at least one prescription of an antidiabetic during the study period. Prevalence of antidiabetic use in both inpatients and outpatients treated with antipsychotics was ascertained. The age-standardised prevalences for both populations were calculated.

Results The age-standardised prevalence of antidiabetic use was 6.6% (RR=1.45; 95% CI=1.20-1.76) in inpatient antipsychotic users, 5.7% (RR=1.27; 95% CI= 1.05-1.52) in inpatient non-antipsychotic users and 4.5% (reference) in outpatient antipsychotic users.

Conclusions The prevalence of antidiabetic use differs between inpatients and outpatients, which may be explained by differences in the intensity of blood glucose monitoring between the two settings. Investigators performing observational studies on the association between antipsychotic use and diabetes mellitus need to be aware of the potential selection and detection bias resulting from the choice of setting.

INTRODUCTION

The prevalence of impaired glucose tolerance and diabetes is 2-3 times higher in schizophrenic patients compared to non-psychiatric patients.[1,2] Schizophrenia itself is associated with an increased risk of disturbed glucose homeostasis through a thus far unknown mechanism,[3] and the use of antipsychotic drugs seems to further increase this risk. Several pharmacoepidemiological studies have shown that this risk may be more increased in users of atypical antipsychotics than in users of typical antipsychotics.[3-5] Especially the use of olanzapine or clozapine is associated with a 34-41% increase in the development of diabetes type 2.[6,7]

There are marked differences between observational studies into the association between antipsychotic use and the risk of diabetes with respect to design, setting and outcome measurement. Studies have been performed in inpatients[8,9] and outpatients.[5,10,11] Some studies have used routinely collected data (i.e. as part of regular patient care) to operationalise the incidence or prevalence of diabetes, including medical history,[6,12] laboratory blood glucose measurements[13,14] and antidiabetic drug use.[15] In other studies a standard diagnostic test set for diabetes was performed as part of the protocol.[13,14]

Especially in studies in which estimates of the prevalence or incidence of diabetes are based on routinely gathered data, the setting in which the study is performed may greatly affect the outcome.

The aim of this study is to investigate the differences in the prevalence of antidiabetic use among patients using antipsychotics in an inpatient and an outpatient setting.

METHODS

Inpatient setting: study population

Data on inpatients of 15 years and older were retrospectively collected at three psychiatric hospitals that are part of Altrecht Institute for Mental Health Care, serving a catchment area of about 720,000 inhabitants in the centre of the Netherlands. All data on hospitalised patients, including their characteristics

and medication use, were collected from the hospital pharmacy drug use database. We included all hospitalised patients with sufficient follow-up data, i.e. their admission lasted for at least 28 days or they had more than one admission during the study period. Antipsychotic users were defined as patients with a first prescription of an antipsychotic during the study period of 2001-2002. Data were collected back to 1994, to be able to exclude patients who had a prescription of any antipsychotic before entering the study. Patients were defined as non-antipsychotic users when they had no prescription of an antipsychotic during any admission since 1994.

Outpatient setting: study population

Data on the outpatient population were collected from the PHARMO record linkage system. PHARMO includes pharmacy dispensing records from community pharmacies of all 950,000 community-dwelling residents of 25 population-defined areas in the Netherlands. Since almost all patients in the Netherlands are registered with a single community pharmacy, independent of prescriber, pharmacy records are virtually complete with regard to prescription drugs. The computerised drug dispensing histories contain information on the dispensed drug, dispensing date, the prescriber, amount dispensed, prescribed dosage regimen and the estimated duration of use. We selected all patients that had started antipsychotic use during the study period of 2000-2001. Data were collected back to 1994, to be able to exclude patients with previous prescriptions of any antipsychotic before entering the study period.

Antidiabetic use

Both in the inpatient as well as in the outpatient setting, patients were defined as being treated with antidiabetics when they had received at least one prescription of an oral antidiabetic or insulin during the study period.

Data analysis

Prevalence of antidiabetic use was calculated in inpatient antipsychotic users, inpatients with no antipsychotic use and in outpatient antipsychotic users. Prevalences standardised for the age-distribution of the general population in the Netherlands were calculated using the standard population constructed by Netherlands Statistics for the year 2004.[16] The age of the patients was defined as the age at the first prescription of an antipsychotic during the study period. Patients were stratified towards their age group; 15-19; 20-29; 30-39; 40-49; 50-59; 60-69 and 70 years or older. We calculated relative risks (RR) with corresponding 95 percent confidence interval (95% CI) for use of an antidiabetic using the standardised prevalences with the outpatients as a reference group.

RESULTS

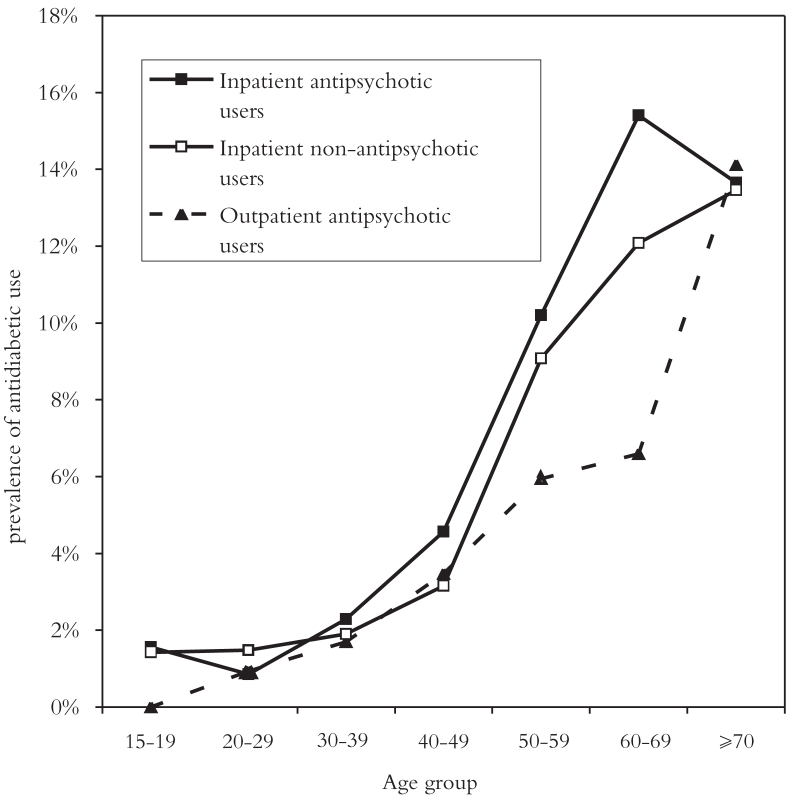
Of the 11,192 inpatients that had an admission during the study period, 4,489 patients had started with an antipsychotic. Of these, 299 (6.7%) also used an antidiabetic. Of the 6,703 inpatients who had not started with an antipsychotic 324 (4.8%) had used an antidiabetic. In outpatients, we identified 3,243 patients who used an antipsychotic, of whom 232 (7.2%) used an antidiabetic drug (Table 1). While the overall prevalence of antidiabetic drug use was comparable between inpatients and outpatients on antipsychotics, the prevalence was markedly lower in outpatients aged 40 to 70 (Figure 1).

The age-standardised prevalence of antidiabetic use was 6.6% (RR=1.45; 95% CI=1.20-1.76) in inpatient antipsychotic users, 5.7% (RR=1.27; 95% CI= 1.05-1.52) in inpatient non-antipsychotic users and 4.5% (reference) in outpatient antipsychotic users.

Table 1 *Characteristics of the patients*

Characteristics	Inpatient antipsychotic users N =4,489 (%)	Inpatient non-antipsychotic users N=6,703 (%)	Outpatient antipsychotic users N=3,243 (%)
Age (years)			
15-40	1,927 (43%)	3,149 (47%)	1,079 (33%)
40-60	1,316 (29%	2,480 (37%)	672 (21%)
≥60	1,246 (28%)	1,074 (16%)	1,492 (46%)
Female gender	2,352 (52%)	4,272 (64%)	1,639 (51%)
Antidiabetic use			
Oral antidiabetic	235 (5.2%)	251 (3.7%)	166 (5.1%)
Insulin	120 (2.7%)	146 (2.2%)	100 (3.1%)
Any antidiabetic	299 (6.7%)	324 (4.8%)	232 (7.2%)

Figure 1 *Prevalence of antidiabetic use*



DISCUSSION

We found that the prevalence of antidiabetic use differed between inpatients and outpatients, especially for patients aged 40-70. If antidiabetic use is used to estimate the prevalence or onset of diabetes, marked differences may be found in a study in inpatients compared to outpatients because of detection bias. It is common practice in many psychiatric hospitals, as it is in the investigated inpatient setting, that all patients are being tested for diabetes and other somatic diseases at each admission and at regular intervals during follow-up, while most outpatients are monitored for diabetes 'on demand'.[14,17] Therefore, there is a lower probability of detecting diabetes in outpatients, resulting in an underestimation of the prevalence of diabetes. The differences in estimated prevalence of diabetes in different settings may result in biased outcomes when investigating the association between antipsychotic use and diabetes if testing conditions for diabetes differ. Not only the setting may determine bloodglucose testing frequency. Taylor et al. found that patients who are prescribed olanzapine are 40% more likely to be tested for diabetes than those prescribed typical antipsychotics.[18] In our data we find the highest prevalences of antidiabetic drug use in all inpatients and in outpatients over the age of 70, all of which have a higher probability of regular blood glucose testing.

Inpatients on antipsychotics have a higher baseline-risk on developing diabetes compared to outpatients on antipsychotics, because of more severe underlying disease, higher comorbidity, more and longer use of medication[16]; and inpatients have a higher probability of being diagnosed with and treated for diabetes because of more frequent testing.

Investigators performing observational studies on the association between antipsychotics and diabetes mellitus need to be aware of the potential selection and detection bias resulting from the choice of setting which should be taken into account when interpreting the results.

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General Discussion

INTRODUCTION

In the introductory chapter of this thesis it has been described that the knowledge and evidence about questions, relevant for daily clinical practice when a new drug becomes available on the market, is limited. This evidence gap seems to be larger for psychiatric drugs than for drugs used in other medical domains. In this thesis individual studies have been described with the objective to detect and elucidate patterns, choices and consequences of antipsychotic use in daily clinical practice thereby extending clinical trial evidence. In this final chapter the individual studies are put into perspective. Five topics will be addressed, namely 1) how observational studies can help to bridge the evidence gap between RCTs and daily clinical practice; 2) how to choose between typical and atypical antipsychotics; 3) the problem of missing data in psychopharmacoepidemiological studies; 4) how to deal with acute and late somatic side effects of antipsychotics; 5) the pathways that psychiatric patients travel through during the course of their illness and what that means for psychopharmacoepidemiology. Finally, some general recommendations for future psychopharmacoepidemiological research will be given.

OBSERVATIONAL RESEARCH ON ANTIPSYCHOTICS: BRIDGING THE EVIDENCE GAP BETWEEN RCTs AND DAILY CLINICAL PRACTICE

In this thesis several pharmacoepidemiological studies into the dynamics and outcomes of antipsychotic pharmacotherapy have been described, with the objective to complement the evidence derived from pre-approval RCTs with evidence derived from daily clinical practice with respect to the treatment of patients with antipsychotics. Over the past 15-20 years numerous new antipsychotics have been investigated and subsequently introduced. Nevertheless, after these pre-approval (i.e. registration) trials many questions relevant to daily psychiatric patient care remain unanswered. Stated even more firmly: current best evidence is often perceived by health care professionals and decision makers as not relevant to clinical practice, thereby substantially diluting its impact.[1]

RCTs are the gold standard as far as internal validity is concerned. In RCTs patients are more closely monitored on compliance, and clinical

parameters and disease outcome measures are assessed more extensively and in a more standardised and validated way.[2] However, the external validity (i.e. generalizability) can be poor, especially for patient groups that are difficult to study, such as patients with schizophrenia or other psychotic disorders. Populations participating in RCTs with psychiatric drugs differ from populations treated in daily clinical practice with respect to age (children and the elderly are often excluded), gender (women are more often excluded, pregnant women are almost always excluded), psychiatric and somatic co-morbidity, severity of disease (severely ill patient are excluded in non-acute life threatening diseases), use of co-medication (for example the use of benzodiazepines is often restricted), type of admission, treatment duration, etcetera. In clinical practice many patients, and especially psychotic patients, lack disease insight and understanding, and thus are often not willing to take medication and to participate in RCTs. It is therefore difficult to include a representative sample of schizophrenic patients in an RCT. Additionally, not only patients may not want to participate, the same may be true for clinicians, nurses and others care givers, who have their own opinions what is best for their patients. And last but not least, also institutional review boards (medical ethics review committees) often only allow RCTs under very restricted conditions. For example: performing an RCT on the efficacy of short-acting parenteral antipsychotics such as zuclopenthixol acetate in psychotic or manic patients with severe agitation or aggression (i.e. the approved indication for the use of these type of drugs) is very difficult: it is difficult to get approval from an Institutional Review Board, difficult to get clinicians ready to recruit patient, difficult to find patients who will give informed consent, and, if they have given informed consent, difficult to find patients who will reliable comply with the study regimen. Therefore, it can be questioned whether the results from RCTs can be generalised to the more severe population.

Pharmacoepidemiological research aims to depict and unravel the dynamics of drug use and its outcomes using daily clinical practice in a non-experimental way. So, observational studies into the actual use and its associated outcomes of antipsychotics in clinical practice are likely to have added value to RCTs, if only because they include populations more representative of day-to-day psychiatric practice (i.e. higher external validity). Our review into the dosages of haloperidol used in RCTs over the past decades

as comparator to atypical antipsychotics in patients with schizophrenia showed that there indeed is a difference between the dose of haloperidol in RCTs compared to the officially recommended and approved doses for haloperidol (Chapter 2). We did not study the dosing of haloperidol in daily practice, but other studies showed that it is often lower than the officially recommended doses.

Another limitation of pre-approval RCTs is that these are mostly underpowered to detect rare side effects (1 in 10,000 to 1 in 1,000) and very rare side effects (less than 1 in 10,000).[3] Before approval of a new antipsychotic by the competent regulatory authorities, rarely more than a few thousand patients have been exposed to that new chemical entity. For example, the trials conducted for the initial approval of olanzapine for the indication schizophrenia included 1,986 patients.[4-7] The number of patients needed to detect (very) rare side-effects goes far beyond the numbers of patients actually participating in pre-approval RCTs. Consequently rare side effects are usually only discovered after approval, when more and often more complex patients have been exposed and during longer time periods. Sertindole was, for example, withdrawn from the market two years after its approval due to concerns about cardiac arrhythmia and sudden cardiac death associated with its use.[8] The antidepressant nefazodone was withdrawn from the European market in 2003 (eight years after its approval), because of liver failure.[9] For the detection of such rare, but often serious, side effects one needs large numbers that usually can only be studied efficiently via observational (pharmacoepidemiological) studies. In a large GP database capturing routine care data of more than 7 million patients, we performed a case-control study into the risk of fractures associated with the use of antipsychotics (Chapter 8). We were able to include 22,500 cases with a hip/femur fracture. The use of antipsychotics was associated with a small increased risk (RR=1.8) of hip/femur fractures especially after longer periods of use. The incidence of hip/femur fractures increased from 0.09% in non-users of antipsychotics to 0.16% in patients using antipsychotics. More than 80,000 patients with long-term follow-up would have to be included in a RCT to adequately establish this effect. Although the study of adverse drug reactions is often regarded as harmful for the innovative product and its manufacturer, the evidence arising from such studies can also be useful as a key loop for the development of new chemical entities, especially

when such studies also try to unravel the mechanism by which the interaction between the molecule and the human biosystem induces the adverse drug reaction.

Another limitation of pre-approval RCTs is that they are not capable to detect side effects that appear only after long-term administration of the drug. Pre-approval RCTs can be divided in acute studies (up to three months) and maintenance studies (more than a three months). Thus, usually only short term effects of antipsychotics are detected. Tardive dyskinesia, a non-rare but late side effect of antipsychotics, is a potentially invalidating side-effect of antipsychotics. Based on long-term observations of patients receiving antipsychotics, Schönecker described the syndrome in 1957 and may have been the first to recognise its widespread significance.[10] It was never detected in the pre-approval acute trials. In our study on risk of fractures associated with the use of antipsychotics (Chapter 8), we found that the risk on fractures was especially increased after long-term use.

Another strength of pharmacoepidemiological research is that it can reveal the dynamics of drug prescription and its outcomes in daily clinical practice. The dynamics in daily clinical practice is expected to differ from the strict conditions of RCTs. However, after introduction to the market we have to deal with less strict conditions and more severely ill patients. We performed two studies on the effect of the initial choice in antipsychotic therapy on subsequent treatment choice (Chapter 4 & 5). Both studies showed that the choice for the initial, acute treatment drove the choice for a typical or an atypical antipsychotic as follow-up treatment. The understanding of such choices is important knowledge for medical as well as marketing departments of the innovative pharmaceutical industry. Our study on switching (Chapter 6) revealed that atypical antipsychotics are less frequently associated with switching in comparison with typical antipsychotics. Switching from one to another antipsychotic may be seen as an overall expression of unsatisfactory response to treatment, including both treatment failure and unacceptable adverse effects.[11] In our study on reasons for switching (Chapter 7) we found that when switching occurred, atypical antipsychotics were more often switched because of weight gain and typical antipsychotics more often because

of extrapyramidal side effects. Both studies give insight in the dynamics of switching of an unselected clinical population.

Recommendations

After introduction on the market, each new psychotropic drug (i.e. new chemical entity) should be closely monitored with respect to their impact on patient care. Observational psychopharmacoepidemiological studies should be conducted after approval as they add important information and extend clinical trial pre-approval evidence. Such studies may be initiated by a Drugs and Therapeutics committee of a (psychiatric) hospital and its results be used by the committee in the positioning of the drug in the psychiatric 'arsenal'. These practice based studies in which new drugs are compared with other new or longer available drugs can focus on questions like reasons for choosing the new drug, characterization of the population using the new drug, time on drug, and reasons for switching and stopping.

THE CHOICE BETWEEN TYPICAL AND ATYPICAL ANTIPSYCHOTICS

In our study of incidence and prevalence of use of antipsychotics over a 10-year period (Chapter 3) a large increase in the use of atypical antipsychotics was found. This indicates that atypical antipsychotics are increasingly preferred as first choice medication over typical antipsychotics by prescribing physicians. According to the recent guidelines on the treatment of schizophrenia by the British National Institute for Clinical Excellence (NICE)[12] and the American Psychiatric Association, atypical antipsychotics should be considered as first-choice medication for patients in the acute phase of schizophrenia, mainly because of the decreased risk of extrapyramidal side effects compared to the typical antipsychotics.[13] According to the Dutch guideline on the treatment of schizophrenia, atypical antipsychotics have a better subjective acceptability.[14] However, this guideline also mentions that the atypical antipsychotics were compared to relatively high doses of typical antipsychotics. Therefore, also typical antipsychotics can be first choice treatment, and the guideline recommends taking into account individual factors of the patients.

In the nineties, the discussion on differences between typical and atypical antipsychotics was focussed on EPS. Both the lower risk on parkinsonism and other acute EPS as well as the lower risk on tardive dyskinesia led to a preference for atypical antipsychotics. However, recently other long-term side effects have also got attention, especially metabolic effects like weight gain[15,16] and disturbance of glucose metabolism[17,18] including the risk of diabetes. The Food and Drug Administration (FDA) has recently requested all manufacturers of atypical antipsychotic medications to include a warning in their product labelling regarding hyperglycaemia and diabetes mellitus.[19] The guidelines do not report how to weigh the risks and consequences of these other side effects with the risk of EPS. Why should we follow the UK and USA guideline which suggest that EPS is more relevant than weight gain and diabetes? EPS can be invalidating, but diabetes may kill. Moreover, the evidence that all atypical antipsychotics give less EPS was based upon RCTs that used inadequate high doses of haloperidol (Chapter 2).

An important point for the future is to incorporate the opinion of patients treated with antipsychotics in the weighing of (side-)effects, although this may be very difficult in this patient group. The opinion of patients is partly reflected by the results of our switching study (Chapter 6), where we found that atypical antipsychotics are less frequently associated with switching in comparison with typical antipsychotics, suggesting overall better satisfaction with these drugs.

The future will show whether choosing on a population level between one class or another is still a relevant question, or that the individual patient profile, including genetic make-up, may be highly predictive for the response to a given antipsychotic and therefore the primary determinant for choosing for a specific antipsychotic. In that scenario, the question arises which individual patient best to treat with which antipsychotic: 'tailor made' psychopharmacotherapy.

Recommendations

In order to get more information that can help to choose between atypical and typical antipsychotics, we need more RCTs in which atypical antipsychotics are

directly compared with typical antipsychotics at doses according to the official recommendations. There is a need for RCTs in which atypical antipsychotics are compared directly with each other, since the group of atypical antipsychotics is composed of substances that have different pharmacological profiles and side effects. If possible, RCTs should be adjusted to answer questions relevant for decision making in daily clinical practice (i.e. so called practice trials). In addition, more observational research is needed. In consideration of the variety of side-effects of typical and atypical antipsychotics and different resulting effects for compliance and prognosis of schizophrenia, it seems necessary to strengthen patients' perspective and patients' involvement as an important outcome criterion of antipsychotic treatment.

THE PROBLEM OF MISSING DATA IN PSYCHIATRIC PHARMACO-EPIDEMIOLOGY

Since in observational studies no randomisation takes place, information on other variables is needed in order to eliminate confounding. These variables include demographics, diagnosis, illness and treatment history. In daily clinical practice, many of these data are not systematically measured or registered. In addition, when it has been properly measured and registered, it may not be available for research purposes (Table 1).

Exposure to medication

Although information on exposure to medication is readily available in the Netherlands, some important aspects are missing. In clinical trial conditions patients are closely monitored on compliance. However, in daily clinical practice compliance is low especially among patients with psychiatric disorders such as schizophrenia.[20,21]

In inpatient settings, medication is dispensed by the nursing staff, so compliance is expected to be higher in inpatient settings, especially when patients agreed to be included in an RCT. However, even in inpatient setting, detailed information on actual use of 'as needed' prescription is important in whether the 'as needed' medication was actually used e.g. for elevating acute problems (agitation etc.).[22]

Patient characteristics

Patient characteristics are important in observational studies to adjust for possible confounders. Age and gender are available most of the time. Weight at start of the therapy is important, since weight gain is a common side effect of atypical antipsychotics. Data on length and weight should be expected, but are often absent or registered elsewhere. Moreover, many other patient characteristics like diagnoses (including psychiatric as well as somatic co-morbidity) are often also not systematically registered. For instance: a not-registration of substance abuse may mean that there is indeed no (co-morbid) substance abuse, but also that it was present but not assessed or not registered properly. Information on genetic profile can be important if the genotype predicts a certain outcome. It is expected to help us predict if patients will react on certain medication or will suffer from specific side effects. For example, polymorphism of cytochrome P450 2D6 which is responsible for metabolising many antipsychotics[23], and polymorphism of 5HT2c, which is related to the development of weight gain.[24]

Outcomes

Data on outcomes like severity ratings on specific symptom scales or systematic registration of side effects are often missing. Therefore, one has to rely on proxy outcome measures. One option is a global rating, such as a GAF or GAS score. In the study on switching (Chapter 7), switching from one to another antipsychotic was studied, since switching may be seen as an overall expression of unsatisfactory response to treatment, including both treatment failure as well as unacceptable side effects.[11] Information on the somatic side effects of antipsychotics is also important, since these side effects are not often recognised as side-effects and because they have an important impact of the health and well being of patients.

Quality of life and the patients' perspective on the perception of the disease and medication could be an important parameter in predicting success criteria of antipsychotic treatment. To gather information in this, patients should have the opportunity to comment in a structured way towards their medication.

Table 1 *Examples of missing data and possible solutions*

	Data	Problem	Possible solutions
Exposure to medication			
Unknown or not properly measured	Actual drug intake / compliance	In many cases actual drug intake by patients is unknown, especially in ambulant care	Electronic monitoring of medicine intake
Not properly registered	Medication 'as needed'	Medication dispensed 'as needed' at the wards is not always registered properly	Electronic detection of dispensing, linked to the stock of medication in the ward
Properly measured and registered, but not available	Drug prescribing in institutionalised or in ambulant patients	Drug prescription and dispensing is often registered for administration and medication surveillance, but not always available on patient level for research purposes	Linkage of medication databases to patient characteristics
Patient characteristics			
Unknown or not properly measured	Weight and length	Although easy to measure, and weight gain is an important side-effect, not measured	Give psychiatrist measure equipment or let weight and length be measured by laboratory
	Genetics	Genetics only detected after numerous medication problems	
Not properly registered	Diagnosis Somatic and psychiatric comorbidity Ethnicity	Only available in written patient files or inaccessible data on file	Electronic patient file
Properly measured and registered, but not available	Blood level Clinical chemical parameters	Often only on paper, laboratory is often external organisation	Unique registration number for all patients
Outcomes			
Unknown or not properly measured	Quality of life Patient satisfaction	Subjective classification	Regular use of validated scale
Not properly registered	Side-effects	If discussed with psychiatrist, only written in patient file	Electronic prescription system with possibility to code medication related information
Properly measured and registered, but not available	Effectiveness	Specialised wards use their own system measuring scales	Introduce validated scales for regular evaluation of the patients

Recommendations

To get a better insight in patient care including treatment with psychotropics and eventually to improve it, registration of patient characteristics, exposure to treatments, and treatment outcomes should become more common and standardised. Future electronic medical records where information is well structured and accessible are urgently needed and linking this information may facilitate this process. In such registrations, also the perspective of the patient should be included: quality of life assessments as well as evaluation of subjective well-being. Schizophrenic patients are indeed able to fill out self reports consistently and reliably and it has been shown that their perspective differs enormously from the evaluation of psychiatrists with regard to antipsychotic treatment.[25] Information should be stored in such a way that the privacy of the patients is not compromised.

ACUTE AND LATE SOMATIC SIDE EFFECTS OF ANTIPSYCHOTICS

As already mentioned before, side effects of antipsychotic do not only occur as acute side effects early in treatment, but can also occur as late side effects, i.e. after months or even years of long-term treatment. Some of these side effects are not easily recognised by psychiatrists since they are somatic in nature i.e. not part of regular psychiatric thinking and care.

Extrapyramidal side effects

Extrapyramidal side effects (EPS) are well known side effects of antipsychotics, especially the typical antipsychotics and risperidone. Yet the impact of EPS, both acute EPS and late EPS (TD) is far from clear. In our study on reason for switching (Chapter 7), we found that when switching occurred, typical antipsychotics were most often switched for this side effect.

Diabetes

The finding of an association of increased prevalence and incidence of diabetes mellitus and schizophrenia predates the introduction of antipsychotics.[26] However, recent studies have shown that the prevalence of impaired glucose

tolerance and diabetes is 2-3 times higher in individuals with schizophrenia compared to the general population.[27] It has been suggested that this increase was caused by the chronic use of antipsychotics, especially atypical antipsychotics.[28-30] There is also evidence that antipsychotics (and especially atypical antipsychotics) worsen the development of diabetes.[31] The most compelling evidence suggesting a true drug-induced effect comes from a 5-year naturalistic study of patients using clozapine. One third (37%) of the study group became diagnosed with diabetes during the study.[32]

Researching the correlation between the use of antipsychotics and the occurrence of diabetes is difficult to establish, since the prevalence will be influenced by many factors. It is also difficult to find out if diabetes or weight gain is related to specific antipsychotics, since patients frequently switch from one antipsychotic to another[33], often because of adverse effects including weight gain or the development of glucose disturbances.[34]

Lipids

Long-term use of atypical antipsychotics has also been associated with an increase in serum lipids. In a study comparing clozapine and haloperidol, age, weight, gender, daily antipsychotic dose, total cholesterol level, serum triglyceride level, and concurrent medications were recorded. Clozapine-treated men had significantly higher follow-up serum triglyceride concentrations over baseline than did haloperidol-treated men.[35] Olanzapine is also associated with increased triglycerides.[36] Several cases of acute pancreatitis are linked to the use of clozapine and olanzapine probably as a result of hypertriglyceridemia.[37,38] Owing to its potential for fatal deterioration and chronic complications, and because pancreatitis may improve upon discontinuation of clozapine and olanzapine, psychiatrists should be alert to this adverse effect.

Weight gain

In our study on the reason for switching antipsychotic therapy (Chapter 7) weight gain was a prominent reason for switching atypical antipsychotic therapy. When weight is recorded properly, the impact of antipsychotic

therapy on weight in daily clinical practice can be measured and also the influence of possible interventions, like diet, health exercise and medication switching.

Fractures

A hip/femur fracture is a devastating event, especially for the elderly. The 1-year mortality after hip/femur fracture is about 20%, and 20% of those living in the community at the time of their hip/femur fracture have to be admitted to a nursing home.[39] Of those returning to living in the community, the majority will never regain their pre-fracture levels of physical and social activities.[39]

It has been postulated that the use of antipsychotics may lead to an increased tendency to fall as result of orthostatic hypotension or sedation.[40-45] Furthermore, long-term use of antipsychotics has been associated with decreased bone mineralization leading to weaker bones,[46-51] and a higher probability that a fall will result in a fracture. Our study on fractures (Chapter 8), suggest that acute as well as long-term use of antipsychotics is associated with a small increased risk of hip/femur fractures.

Recommendations

Psychiatrists have to deal not only with psychiatric outcomes but also with many side effects of the psychotropics they are prescribing, including late somatic side effects which made it necessary that psychiatrists 'think out of the box'. Regular physical checks and a standard set of biochemical analysis should be performed on all patients. The result of observational studies should be discussed in a multidisciplinary setting, to improve patient care in daily practice.

PSYCHIATRIC PATHWAYS

The treatment of schizophrenia is always long-term and often complex. In daily clinical practice it is very difficult to have an easy and comprehensible access to all relevant information regarding individual patients: how long is he/she ill. How was his/her course of illness? Which treatments have been

tried, how long, at what dosages en with which result? And when drugs were prescribed: was the patient compliant? Did he/she stop treatment? Did stopping treatment result in a relapse or was an emerging relapse the reason why the patient stopped treatment? How were treatments tolerated? Did acute side effects occur? Did long-term side affects occur? In many if not most patients it is very difficult to get answers on these so apparent relevant questions in daily clinical practice. One of the major reasons is that relevantinformation is not properly measured and/or registered. Another major reason is that many patients have contact with many different health care providers: primary care, psychiatric institutions (and often more than one and with various settings such as inpatient units, outpatients units and day hospitals), specialised institutions (e.g. addiction clinics) etcetera. And finally, each provider (and setting) has many different professionals: psychiatrists, residents, psychologists, somatic physicians, pharmacists, nursing staff etc.

Most health care providers have their own system of recording information. In general, healthcare professionals keep their own records up-to-date, but do not have full access to the information of other healthcare providers. At its best they have copies of discharge letters, with often only global, general information and not the detailed information as described above. Moreover, when patients move between healthcare providers or from one to another setting, data get lost. The consequences are that much relevant information is missing when clinical decisions have to be made, e.g. on initiating new medications. It is always possible that these medications have been tried in the past while relevant information about doses, response and the occurrence of side effects is incomplete or even missing.

To improve care, a comprehensive knowledge on what happens to patients, including a good insight into the dynamics of patient populations is required. The enormous diversity of unabridged islands with sometimes very relevant data should become available, also between professionals, between different settings of the same provider and between different providers. Therefore, data should be properly assessed, properly registered and made accessible for each other. Linking the information between healthcare providers and between settings is crucial for improving care.

A link was performed between a drug use database and a clinical database of Altrecht Institute for Mental Health Care anonymously through record linkage methodology based on date of birth, gender and day of admission.[52] Then, medication use could be linked to clinical outcomes like diagnoses, coded according to criteria based on the 'Diagnostic and Statistical Manual', (DSM)-IV and the 'Global Assessment of Functioning' scores (GAF).[53] Several studies were performed with these linked databases (Chapter 4, 5 and 7). Most research is done on databases that contain data on a specific setting, like an admission to a hospital. In these settings, numerous databases exist that contain patient information. During a clinical admission, patient characteristics, admission dates and diagnoses are recorded in the hospital database. Medication use is recorded in the hospital pharmacy database, the somatic physician and the physiotherapist record information on somatic disease and the laboratory records clinical chemical data. Our study on incidence and prevalence of use of antipsychotics (Chapter 3) could not be performed with our clinical database. Community pharmacy data were used to investigate this.

Recommendations

When we succeed in giving insight in the pathways of patient and data transfer, we can investigate what happens to patients in a real world situation, including a transfer to another setting and for a long period of time. This research should give a positive impulse in increasing patients care. Not only in one setting or with one health care provider, but during the whole course of the disease.

FUTURE PERSPECTIVE

Psychiatric pharmacoepidemiology aims at reducing clinical uncertainty in the use of (new) psychotropics in daily clinical patient care. For this, the current RCT (pre)approval evidence (Evidence Based Evidence) needs to be complemented with evidence from general daily medical practice (Medical Based Evidence). In this thesis we performed epidemiological studies on patterns, choices and consequences of the use of antipsychotics in daily clinical psychiatric practice that extended knowledge on antipsychotics, beyond what

is known from the laboratory conditions of RCTs. For the further development of pharmacoepidemiology, we need to focus on:

- The systematic registration, collection and linking of all available data (e.g. from clinical records, GPs, pharmacy, laboratory) gathered in the process of routine patient care;
- The design of a system that enables us to follow the entire pathway of psychiatric patients;
- The inclusion of the patient's perspective in the design and execution of psychopharmacoepidemiogical studies and the patient's involvement as an important success criterion of antipsychotic treatment.

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Summary

The main objective of this thesis was to detect and elucidate patterns, choices and consequences of the use of antipsychotics and in particular typical versus atypical antipsychotics in daily clinical psychiatric practice in order to extend the knowledge on a drug beyond what we know from the laboratory conditions of clinical trials. Patterns of antipsychotic use are an important first step in revealing the dynamics of antipsychotic use in daily practice. Which treatment patterns are observed and can these patterns be explained and related to clinical outcomes? What is the impact of choices that have been made in daily practice, and what are the consequences of treatment with antipsychotics.

Although atypical antipsychotics are claimed to be better tolerated than haloperidol, this has been criticised because in many randomised controlled trials (RCTs) relatively high doses of haloperidol were used. In **Chapter 2** we determined the dose of haloperidol used in RCTs as comparator drug to atypical antipsychotics in patients with schizophrenia and we compared these doses with the officially recommended doses for haloperidol in the USA and the UK. We found that in all of the included studies (N=51), the midpoints of the required doses were above the midpoint of the official recommended doses in the USA and UK for moderately ill patients. In 88% (USA) and 80% (UK) they were above the upper border of the recommended dose. Compared to recommended doses for severely ill patients in both the UK and USA (range: 6-15 mg daily), in 17 studies (35%) the mean actual used dose was above the upper dose border for severe ill patients (15 mg daily). In nearly all randomised clinical trials haloperidol was used in doses which were higher than the official recommended doses for moderately or even very severely ill patients. This phenomenon hampers the interpretation of the effects of atypical antipsychotics in their comparison with haloperidol especially with respect to the occurrence of extrapyramidal side-effects.

Over 20 drugs with varying pharmacological properties are currently available for the treatment of patients with psychotic disorders. Over the years, there has been a shift in favour of the use of atypical antipsychotics compared to typical antipsychotics. In **Chapter 3** we described the dynamics of the prescription of typical and atypical antipsychotics during 1994-2003 by investigating incidence and prevalence of antipsychotic use in non-institutionalised patients. In community pharmacy dispensing records of

950,000 residents in the Netherlands (PHARMO database), the prevalence and incidence of antipsychotic use over time were calculated. The patients were stratified towards gender and age. The prevalence of antipsychotic use increased 43% from 1994 until 2003. The overall incidence of antipsychotic use did, however, not change. In 2003, the prevalence of atypical antipsychotics as a fraction of total antipsychotic use was 59% for age group 20-39 years old and 27% for 60 year and older. The increase in prevalence and decrease in incidence of use of antipsychotics over the studied time period indicate that the duration of use has increased over the years. Atypical agents were more frequently used in the younger than in the elderly, while the latter are more at risk for extrapyramidal side-effects.

There is not enough insight into prescribing patterns of antipsychotics in daily practice and into factors that affect the choice between typical and atypical antipsychotics. The objective of **Chapter 4** was to investigate which antipsychotics (typical versus atypical) were prescribed in a psychiatric hospital, and which determinants affected the choice for one of these two classes of antipsychotics in newly admitted patients. In a retrospective cohort study, 522 newly admitted patients were followed from date of admission until discharge from the hospital. In the cohort of newly admitted patients treated with an oral antipsychotic a nested case-control study was conducted considering recipients of an atypical agent as cases. Controls were all other cohort members. The association of patient characteristics and the choice between typical versus atypical antipsychotics was studied using logistic regression analysis. The same analysis was performed with adjustment for possible confounding factors (age group, gender, DSM-IV diagnoses, use of short-acting parenteral antipsychotic, GAF-score, involuntary admissions and involuntary measures). Patients treated with typical oral antipsychotics had more often previously been treated with short-acting parenteral (typical) antipsychotics than patients treated with atypical antipsychotics (40.8% vs. 15.2%) (adjusted OR=0.20 CI=0.09-0.44). No statistical significant difference was found between patients with different severities of disease. The availability of injectable forms seemed to drive the choice for oral antipsychotic agents. Future introductions of short-acting parenteral atypical antipsychotics may have a large impact on first-choice oral antipsychotic treatment.

In **Chapter 4**, we have shown that initial, short-acting parenteral treatment with typical antipsychotics determines the choice of subsequent long-term oral treatment. In **Chapter 5** we investigated whether olanzapine oro-dispersible tablets were used as a replacement for short-acting parenteral typical antipsychotics or for conventional olanzapine tablets, and also the impact of oro-dispersible olanzapine on follow-up antipsychotic therapy. In a retrospective follow-up study, 198 patients were included in the cohort of starters of oro-dispersible olanzapine, 424 in the cohort of starters of short-acting parenteral typical antipsychotics and 691 patients in the cohort of starters of conventional olanzapine tablets. Markers for severity of disease were compared. The associations with follow-up antipsychotic therapy were studied using logistic regression analysis. Of the 198 patients included in the cohort initially treated with oro-dispersible olanzapine 80% received also atypical antipsychotics as follow-up therapy, compared to 45% (adj. RR=1.72; 95% CI=1.39-2.13) in the cohort treated initially with a short-acting parenteral typical antipsychotic. Our study revealed that oro-dispersible olanzapine was used as an alternative for short-acting parenteral typical antipsychotics and its use was a major driving factor towards the follow-up therapy with atypical antipsychotic treatment.

Switching from one to another antipsychotic may be seen as an overall expression of unsatisfactory response to treatment, including both treatment failure and unacceptable adverse effects. In **Chapter 6** we investigated the extent and time of switching to another oral antipsychotic in newly admitted in-patients that started oral antipsychotic therapy. In a retrospective follow-up study of 522 newly admitted patients who started with an oral antipsychotic, we applied a case-control analysis considering patients switching to another oral antipsychotics as cases. Association between patient characteristics and switching antipsychotic medication was evaluated using logistic regression analysis. A Kaplan-Meier analysis was performed to analyse time to switch. Patients initially treated with an oral typical antipsychotic showed a twofold increased risk to switch to another antipsychotic compared to patients treated with an oral atypical antipsychotic (adjusted OR=1.79; 95% CI=1.15-2.78). The Kaplan-Meier survival analysis revealed that patients started with a typical antipsychotic switched sooner compared to patients on atypical antipsychotics. Atypical antipsychotics were less frequently associated with switching in

comparison with typical antipsychotics suggesting overall better treatment satisfaction.

Previous research revealed that atypical antipsychotics were switched less than typical antipsychotics, suggesting overall better treatment satisfaction with atypical antipsychotics. The objective of **Chapter 7** was to investigate the reasons for switching antipsychotics after initiating oral treatment with either typical or atypical antipsychotics in a clinical setting. A total of 123 patients that switched antipsychotic therapy were recruited from 17 psychiatric hospitals, of which 46% of patients switched because of insufficient effect and 45% because of adverse effects. No significant differences were found between users of atypical versus typical antipsychotics in reasons for switching (adverse events or insufficient effectiveness). In users of atypical antipsychotics extrapyramidal effects were reported less often as reason for switching (adjusted OR=0.18; 95% CI=0.07-0.51). Patients on atypical antipsychotics switched more often because of weight gain (adjusted OR=12.8; 95% CI=1.50-109). In case of switching, no difference was found between typical and atypical antipsychotics in the frequency of tolerability or reported lack of effectiveness. However, the type of side-effect as a reason for switching differed between atypical and typical antipsychotics.

A hip/femur fracture is a devastating event, especially for the elderly: the majority will never regain their pre-fracture levels of physical and social activities. In **Chapter 8** we investigated whether the use of antipsychotics was associated with hip/femur fractures and whether pharmacological differences between antipsychotics were related to the occurrence of fractures. A case-control study was conducted, in which cases were defined as patients with a hip/femur fracture. Each patient was matched to one control patient. The association between use of antipsychotics and the occurrence of hip/femur fractures was evaluated using conditional logistic regression. The study included 44,500 patients from 683 general practices from different geographical areas in the UK, registered within the General Practice Research Database (GPRD). Exposure to antipsychotics was categorised as 'no use', 'current use' and 'prior use'. Both current and prior use of antipsychotics were associated with an approximately two-fold increased risk of fractures. After adjustment for possible confounders, a small significant effect remained (Odds Ratios (OR) of

1.3). We did not find an association between dose of antipsychotics, or between the degree of blockade of the alpha-1 adrenoceptor or histamine-1 receptor and risk of fractures. The duration of antipsychotic use was significantly associated with an increased risk of hip/femur fractures. There are marked differences in observational studies into the association between antipsychotic use and diabetes, with respect to design, setting and outcome measurement. These differences may be explained by differences in type of patients, severity of disease, dosing and type of medication in the various settings. In **Chapter 9** the prevalence of antidiabetic use in an inpatient and an outpatient population of users of antipsychotics was compared. Data on inpatients and outpatients were retrospectively collected. Patients were selected that had started antipsychotic use in a two-year period between 2000 and 2002. Both in inpatients and outpatients, patients were defined as being treated with antidiabetics when they had at least one prescription of an oral antidiabetic or insulin in the study period. Prevalence of antidiabetic use in both inpatients and outpatients treated with antipsychotics was ascertained. The age-standardised prevalence of antidiabetic use was 6.6% (RR=1.45; 95% CI=1.20-1.76) in inpatient antipsychotic users, 5.7% (RR=1.27; 95% CI= 1.05-1.52) in inpatient non-antipsychotic users and 4.5% (reference) in outpatient antipsychotic users. The prevalence of antidiabetic use differs between inpatients and outpatients, which may be explained by differences in the intensity of blood glucose monitoring between the two settings. Investigators performing observational studies on the association between antipsychotic use and diabetes mellitus need to be aware of the potential selection and detection bias resulting from the choice of setting.

Finally, in **Chapter 10** the individual studies were put into perspective. Five topics are addressed. 1) How observational studies can help to bridge the gap between RCTs and daily clinical practice; 2) How to choose between typical and atypical antipsychotics; 3) The problem of missing data in psychopharmacoepidemiological studies; 4) How to deal with acute and late somatic side-effects of antipsychotics; 5) The pathways psychiatric patients travel through during the course of their illness.

Psychiatric pharmacoepidemiology aims at reducing clinical uncertainty in the use of (new) psychotropics in daily clinical patient care. For this, the

current RCT (pre)approval evidence (Evidence Based Evidence) needs to be complemented with evidence from general daily medical practice (Medical Based Evidence). In this thesis we performed epidemiological studies on patterns, choices and consequences of the use of antipsychotics in daily clinical psychiatric practice that extended knowledge on antipsychotics, beyond what is known from the laboratory conditions of RCTs. For the further development of pharmacoepidemiology, we need to focus on:

- The systematic registration, collection and linking of all available data (e.g. from clinical records, GPs, pharmacy, laboratory) gathered in the process of routine patient care;
- The design of a system that enables us to follow the entire pathway of psychiatric patients;
- The inclusion of the patient's perspective in the design and execution of psychopharmacoepidemiogical studies and the patient's involvement as an important success criterion of antipsychotic treatment.

Samenvatting

Het doel van dit proefschrift was het detecteren en ontrafelen van patronen, keuzes en consequenties van het gebruik van antipsychotica in de dagelijkse klinische praktijk, om hiermee de kennis te vergroten op gebieden die niet naar voren zijn gekomen uit gerandomiseerde klinische onderzoeken (RCTs). Patronen van antipsychoticagebruik zijn een belangrijke eerste stap in het ontrafelen van de dynamiek van het antipsychoticagebruik in de dagelijkse praktijk. Welke behandelpatronen werden onderzocht en konden deze patronen verklaard en gerelateerd worden aan klinische uitkomsten? Wat was de impact van een keuze die gemaakt werd in de dagelijkse praktijk en wat zijn de consequenties van een behandeling met antipsychotica?

Hoewel van atypische antipsychotica geclaimd wordt dat ze beter verdragen worden dan haloperidol, wordt deze mening soms bekritiseerd omdat in veel RCT's relatief hoge doseringen haloperidol als vergelijkend antipsychoticum worden gebruikt. In **Hoofdstuk 2** hebben we onderzoek gedaan naar de dosering haloperidol, in RCTs met atypische antipsychotica, waarin patiënten behandeld werden vanwege schizofrenie. Deze doseringen hebben we vergeleken met officiële richtlijnen voor het doseren van haloperidol in de Verenigde Staten en het Verenigd Koninkrijk. We vonden dat in alle geïncludeerde onderzoeken (N=51), het midden van de doseringsrange boven het midden van de doseringsrange van de officiële aanbevolen doseringen in de Verenigde Staten en het Verenigd Koninkrijk uitkwam. In 88% (vergeleken met de richtlijnen van de Verenigde Staten) en 80% (vergeleken met de richtlijnen van het Verenigd Koninkrijk) waren de doseringen boven de bovengrens van de aanbevolen dosering. Vergeleken met de aanbevolen dosering voor zeer ernstig zieke patiënten van zowel de Verenigde Staten als van het Verenigd Koninkrijk (range: 6-15 mg per dag), was de gemiddeld gebruikte dosering in 17 onderzoeken (35%) boven die bovengrens (15 mg per dag). In bijna alle RCTs werd haloperidol gebruikt in doseringen die hoger waren dan de officieel geregistreerde doseringen voor matig of zeer ernstig zieke patiënten. Hierdoor is de extrapolatie van de effecten van atypische antipsychotica zoals gevonden in RCT's in vergelijking met haloperidol moeilijk, vooral met betrekking tot extrapyramidale bijwerkingen.

Meer dan 20 antipsychotica, met verschillende farmacologische profielen, zijn op dit moment beschikbaar voor de behandeling van patiënten met psychotische stoornissen. In de loop der jaren is er een verschuiving opgetreden ten gunste van de atypische antipsychotica, in vergelijking met de klassieke antipsychotica. In **Hoofdstuk 3** beschrijven we de dynamiek van het voorschrijven van klassieke en atypische antipsychotica in de periode 1994-2003 door de incidentie en prevalentie van antipsychoticagebruik in een ambulante patiëntenpopulatie te onderzoeken. De prevalentie en incidentie van antipsychoticagebruik zijn per jaar berekend, waarbij de patiënten tevens zijn ingedeeld naar geslacht en leeftijd. De prevalentie van het totale antipsychoticagebruik steeg gedurende 1994 tot 2003 met 43%. De totale incidentie daalde enigszins in dezelfde periode. In 2003 was de prevalentie van het gebruik van atypische antipsychotica, berekend als fractie van het totale antipsychoticagebruik, 59% voor de leeftijdsgroep 20-39 jaar en 27% voor de leeftijdsgroep van 60 jaar en ouder. De stijging van de prevalentie en daling van de incidentie van antipsychoticagebruik gedurende de onderzoeksperiode wijzen er op dat de duur van het gebruik is toegenomen over de jaren. Opvallend was daarnaast dat de atypische antipsychotica vaker werden voorgeschreven aan jongeren dan aan ouderen, terwijl de ouderen meer baat zouden hebben bij een kleiner risico op extrapyramidale bijwerkingen.

Er bestaat onvoldoende inzicht in voorschrijfpatronen van antipsychotica in de dagelijkse klinische praktijk en in factoren die van invloed zijn op de keuze tussen klassieke en atypische antipsychotica. Het doel van **Hoofdstuk 4** was te onderzoeken welke antipsychotica (klassiek of atypisch) voorgeschreven worden in psychiatrische ziekenhuizen, en welke determinanten de keuze beïnvloeden voor één van beide klassen antipsychotica bij nieuw opgenomen patiënten. In een retrospectief cohort onderzoek werden 522 nieuw opgenomen patiënten gevolgd vanaf de dag van opname tot ontslag uit het ziekenhuis. In het cohort van nieuw opgenomen patiënten, die behandeld werden met een antipsychoticum is een genest patiënt-controle ('case-controle') onderzoek uitgevoerd waarbij patiënten die behandeld werden met een atypisch antipsychoticum beschouwd werden als 'cases'. De controlegroep bestond uit alle andere patiënten. De associatie tussen patiëntkarakteristieken en de keuze voor atypische antipsychotica werd berekend met behulp van logistische regressie. Dezelfde analyse is uitgevoerd met een correctie voor

mogelijke confounders (leeftijdsgroep, geslacht, DSM-IV diagnose, gebruik van kortwerkende parenterale antipsychotica, GAF-score, gedwongen opname en dwangbehandeling). Patiënten die behandeld werden met orale klassieke antipsychotica waren voordien vaker behandeld met kortwerkende parenterale (klassieke) antipsychotica dan patiënten die behandeld werden met atypische antipsychotica (40.8% vs. 15.2%) (gecorrigeerde OR=0.20; 95% CI=0.09-0.44). De beschikbaarheid van injecteerbare (klassieke) antipsychotica lijkt de keuze te sturen in de richting van de orale (klassieke) antipsychotica. Toekomstige introducties van kortwerkende parenterale atypische antipsychotica kunnen een grote impact hebben op de eerste keuze orale antipsychotische therapie.

In Hoofdstuk 4, hebben we laten zien dat de initiële behandeling met kortwerkende parenterale (klassieke) antipsychotica gevolgen heeft voor de keuze van de vervolgbehandeling met antipsychotica. In **Hoofdstuk 5** onderzochten we of dispergeerbare olanzapine tabletten gebruikt werden als vervanging voor kortwerkende parenterale antipsychotica of voor de conventionele olanzapine tabletten. Tevens onderzochten we de impact van de dispergeerbare tabletten op de vervolgtherapie. In een retrospectief onderzoek werden 198 patiënten geïncludeerd in het cohort met starters van dispergeerbare olanzapine tabletten, 424 patiënten werden geïncludeerd in het cohort van starters met kortwerkende parenterale antipsychotica en 691 patiënten in het cohort van starters met conventionele olanzapine tabletten. Indicatoren voor de ernst van de ziekte werden vergeleken. De associaties met de vervolgtherapie met antipsychotica werden bestudeerd met behulp van logistische regressie. Van de 198 patiënten die geïncludeerd werden in het cohort dat initieel behandeld werd met dispergeerbare olanzapine, gebruikte 80% een atypisch antipsychoticum als vervolgtherapie, vergeleken met 45% (gecorrigeerd RR=1.72; 95% CI=1.39-2.13) in het kortwerkende parenterale antipsychotica cohort. Dit onderzoek liet zien dat dispergeerbare olanzapine tabletten gebruikt werden als alternatief voor kortwerkende parenterale klassieke antipsychotica en dat het gebruik een belangrijke sturende kracht was in de richting van de behandeling met atypische antipsychotica.

Het omzetten van een patiënt van het ene naar het andere antipsychoticum zou gezien kunnen worden als een uitdrukking van ontevredenheid over de behandeling, zowel wat betreft de effectiviteit als de bijwerkingen. In

Hoofdstuk 6 hebben we onderzoek gedaan naar de snelheid en mate van omzetten van de antipsychotische therapie in nieuw opgenomen patiënten die gestart waren met een oraal antipsychoticum. In een retrospectief onderzoek werden 522 nieuw opgenomen patiënten die gestart waren met orale antipsychotische therapie gevolgd. Hierbij is een patiënt-controle onderzoek uitgevoerd waarbij patiënten die omgezet werden naar een ander antipsychoticum beschouwd werden als 'cases'. De associatie tussen patiëntkarakteristieken en het omzetten van een patiënt naar een ander antipsychoticum werd onderzocht met behulp van logistische regressie. Een Kaplan-Meier analyse is uitgevoerd om de tijdsduur tot omzetten te berekenen. De patiënten die in eerste instantie behandeld werden met een oraal klassiek antipsychoticum lieten een bijna tweevoudig verhoogd risico zien om omgezet te worden naar een ander antipsychoticum, in vergelijking met patiënten die met een atypisch antipsychoticum behandeld werden (gecorrigeerde OR=1.79; 95% CI=1.15-2.78). De Kaplan-Meier analyse liet zien dat patiënten die gestart waren met een klassiek antipsychoticum sneller omgezet werden dan patiënten die behandeld werden met een atypisch antipsychoticum. Atypische antipsychotica waren minder vaak geassocieerd met omzettingen in vergelijking met klassieke antipsychotica wat suggereert dat men meer tevreden is met atypische antipsychotica.

Het onderzoek gepresenteerd in Hoofdstuk 6 heeft laten zien dat atypische antipsychotica minder vaak omgezet werden. Het doel van **Hoofdstuk 7** was te onderzoeken welke redenen van omzetten er waren nadat een therapie met orale antipsychotica was ingezet in een klinische omgeving. In totaal 123 patiënten die omgezet werden naar een ander antipsychoticum werden verzameld in 17 psychiatrische ziekenhuizen. Van de patiënten werd 46% omgezet naar een ander antipsychoticum vanwege onvoldoende effectiviteit en 45% vanwege bijwerkingen. Er werden geen significante verschillen gevonden tussen gebruikers van klassieke en atypische antipsychotica wat betreft redenen om de medicatie om te zetten: bijwerkingen dan wel te weinig effectiviteit. Bij gebruikers van atypische antipsychotica werden minder vaak extrapyramidale bijwerkingen gerapporteerd als reden van omzetten (gecorrigeerde OR=0.18; 95% CI=0.07-0.51). Patiënten die behandeld werden met atypische antipsychotica werden vaker overgezet op een ander antipsychoticum vanwege gewichtstoename (gecorrigeerde OR=12.8; 95% CI=1.50-109). Wanneer er

omgezet werd, werd geen verschil gevonden tussen klassieke en atypische antipsychotica in het voorkomen van bijwerkingen en ineffectiviteit. Echter, het type bijwerking waarom omgezet werd verschilde tussen klassieke en atypische antipsychotica.

Een heupfractuur is een zeer ingrijpende gebeurtenis, in het bijzonder voor de ouderen: de meerderheid zal nooit meer op hetzelfde niveau functioneren als in de periode voor de fractuur. In **Hoofdstuk 8** hebben wij onderzocht of het gebruik van antipsychotica was geassocieerd met heupfracturen èn of farmacologische verschillen tussen antipsychotica gerelateerd zijn aan het optreden van fracturen. Hiertoe hebben wij een onderzoek opgezet, waarbij 'cases' waren gedefinieerd als patiënten met een heupfractuur. Iedere patiënten werd 'gematched' met een controle patiënt. De associatie tussen antipsychotica en het optreden van heupfracturen werd berekend met behulp van conditionele logistische regressie. In de studie zijn 44,500 patiënten geïncludeerd die afkomstig waren uit 683 huisartsenpraktijken uit verschillende geografische regio's in het Verenigd Koninkrijk. Deze praktijken waren opgenomen in de 'General Practice Research Database' (GPRD). De blootstelling aan antipsychotica is ingedeeld in de categorieën 'geen gebruik', 'huidig gebruik' en 'voormalig gebruik'. Zowel het huidige gebruik als voormalig gebruik van antipsychotica was geassocieerd met een ongeveer tweevoudig verhoogd risico op het optreden van heupfracturen. Na correctie voor mogelijke confounders bleef een klein significant verschil over bij huidige gebruikers (OR=1.3; 95% CI: 1.1-1.5) en voormalige gebruikers (OR=1.3; 95% CI: 1.2-1.5). Wij hebben geen associatie kunnen vinden tussen de dosering van het antipsychoticum, noch tussen de mate van blokkade van alfa-1 receptor of de histamine-1 receptor en het risico op fracturen. De duur van het antipsychoticagebruik was significant geassocieerd met een verhoogd risico op heupfracturen: het risico nam toe naarmate de gebruiksduur langer was.

Er is in toenemende mate aandacht voor het ontstaan van diabetes als gevolg van het gebruik van, met name de atypische, antipsychotica. Tussen de diverse observationele onderzoeken die zijn uitgevoerd naar dit onderwerp studies naar de associatie tussen antipsychotica en diabetes bestaan grote verschillen qua ontwerp, setting en uitkomstmaten. De verschillen kunnen

wellicht verklaard worden door het type patiënt, de dosering, ernst van de ziekte en verschillen in medicatie in de verschillende settings. In **Hoofdstuk 9** is onderzocht of er verschil in prevalentie bestond tussen een opgenomen en een niet-opgenomen populatie. Hiertoe zijn gegevens over opgenomen patiënten en ambulante patiënten retrospectief verzameld. Er zijn patiënten geselecteerd die in een twee-jarige peride in 2000-2002 gestart waren met de behandeling van een antipsychoticum. De patiënten werden aangemerkt als diabetici wanneer ze tenminste één voorschrift van een oraal antidiabeticum of insuline hadden gekregen. De prevalentie van antidiabeticagebruik in zowel opgenomen als ambulante patiënten die behandeld werden met antipsychotica is vastgesteld. De leeftijd-gestandaardiseerde prevalentie van antipsychotica-gebruik was 6.6% (RR=1.45; 95% CI=1.20-1.76) in opgenomen patiënten die antipsychotica gebruikten, 5.7% (RR=1.27; 95% CI=1.05-1.52) bij opgenomen niet-antipsychoticagebruikers en 4.5% (referentie) bij ambulante antipsycho-ticagebruikers. De prevalentie van antidiabeticagebruikers verschilt tussen opgenomen en niet-opgenomen patiënten, wat wellicht verklaard zou kunnen door verschillen in intensiteit van bloed-glucose onderzoek. Onderzoekers die observationeel onderzoek uitvoeren naar de associatie tussen antipsychotica en diabetes moeten zich bewust zijn van de potentiële selectie en detectie bias als het gevolg van de keus voor de setting.

In Hoofdstuk 10 de resultaten van de individuele onderzoeken in een breder perspectief geplaatst. Er werden vijf onderwerpen nader belicht: 1) Hoe kunnen observationele studies helpen de kloof tussen RCT's en de dagelijkse praktijk te overbruggen; 2) Hoe moet er gekozen worden tussen klassieke en atypische antipsychotica; 3) Hoe gaan we om met ontbrekende gegevens in psychofarmaca-epidemiologische onderzoeken; 4) Hoe moet omgegaan worden met acute en late somatische bijwerkingen van antipsychotica; 5) Langs welke paden bewegen psychiatrisch patiënten zich tijdens de duur van hun ziekte.

De psychiatrische farmaco-epidemiologie probeert de onzekerheid te verminderen met betrekking tot het gebruik van (nieuwe) psychofarmaca in de dagelijkse patiëntenzorg. Hiervoor wordt het bewijs dat afkomstig is uit RCT's ('Evidence Based Medicine') aangevuld met bewijs uit de dagelijkse praktijk ('Medicine Based Evidence'). In dit proefschrift zijn epidemiologische studies

uitgevoerd naar patronen, keuzes en consequenties van antipsychoticagebruik in de dagelijkse klinische praktijk, waardoor de kennis hierover verder gaat dan die verkregen is onder de laboratoriumcondities van RCT's. Voor vooruitgang op het gebied van de psychofarmaco-epidemiologie moet speciale aandacht gegeven worden aan:

- De systematische registratie, verzameling en koppeling van alle beschikbare data (bijvoorbeeld patiëntendossiers, gegevens van huisartsen, apotheek en laboratorium) die verzameld zijn tijdens de reguliere patiëntenzorg;
- Een systeem om psychiatrische patiënten te kunnen volgen tijdens hun contacten met verschillende zorgverleners;
- Het perspectief en de betrokkenheid van de patiënt, als zijnde belangrijke succesfactoren gedurende de behandeling.

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Publications related to this thesis

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Curriculum vitae

CURRICULUM VITAE

Gerard Hugenholtz was born on October 29, 1964 in Amersfoort, the Netherlands. He completed secondary school (VWO) at the 'Eemland-Noord College' in Amersfoort. In 1992 he obtained his masters degree in Pharmacy at the Utrecht University, and in 1994 he became a pharmacist. He started working in St. Jansdal Hospital in Harderwijk and the Antonius Hospital in Nieuwegein. After seven months he was assigned as chief pharmacist in a large psychiatric hospital 'Altrecht Institute for Mental Health Care' located in the central region of the Netherlands. In 1998 he started his specialisation in hospital pharmacy in the Diakonessenhuis in Utrecht and graduated in 2000. In 2000 he started his PhD studies described in this thesis at the Department of Pharmacoepidemiology and Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht, the Netherlands. He continued working for Altrecht during this period.

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