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Less medication switching after initial start with atypical antipsychotics

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Abstract

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

Keywords: Antipsychotic; Switch; Epidemiology; Pharmacoepidemiology

1. Introduction

Antipsychotics are indicated in the treatment of patients suffering from psychotic disorders in order to manage symptoms and prevent relapse (Davis et al., 1992). 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 (Anonymous, 1997). The introduction of atypical antipsychotics (clozapine, olanzapine, risperidone, sertindole and quetiapine) has broadened treatment options for psychotic disorders. There has been a shift in favour of the use of atypical antipsychotics (Sarfati et al., 1999), although the precise therapeutic value of atypical antipsychotics remains controversial (Duggan et al., 2000; Geddes et al., 2000; Kennedy et al., 2000; Srisurapanont et al., 2000; Tuunainen et al., 2000; Wahlbeck et al., 2000, 2003). The use of typical antipsychotics is associated with adverse effects including extrapiramidal symptoms (EPSs) (Owens, 1996), tardive dyskinesia (Lieberman et al., 1991) and hyperprolactinaemia (Kinon and Lieberman, 1996). Atypical antipsychotics seem to have different adverse effects such as weight gain (Geddes et al., 2000; Kinon and Lieberman, 1996) and disturbance of glucose metabolism (Meyer, 2002; Newcomer et al., 2002). 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 (Leucht et al., 1999; Meltzer, 1999; Moller, 1998).

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 (Weiden et al., 1997).

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.

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2. Methods

2.1. 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 3 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.

2.2. 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 1 January 1997 until 31 December 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 (Herings et al., 1992).

At admission, the diagnosis was established by the treating psychiatrist and coded according to DSM-IV (Anonymous, 1994). 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, was 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 (Hugenholtz et al., 2002).

Antipsychotics were classified as typical or atypical. Clozapine, olanzapine, risperidone, sertindole and quetiapine were classified as atypical antipsychotics. Other drugs starting with with the four-digit ATC-code N05A (Anonymous, 2000) were classified as typical antipsychotics. Lithium and levomepromazine also having a four-digit 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 approved the study protocol with respect to privacy aspects.

2.3. Data analyses

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% confidence interval (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 calculated 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) from the Cytel Software Corporation.

3. Results

The characteristics of the cohort are presented in Table 1. A total of 522 patients met the inclusion criteria. Most

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%)

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%).

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.

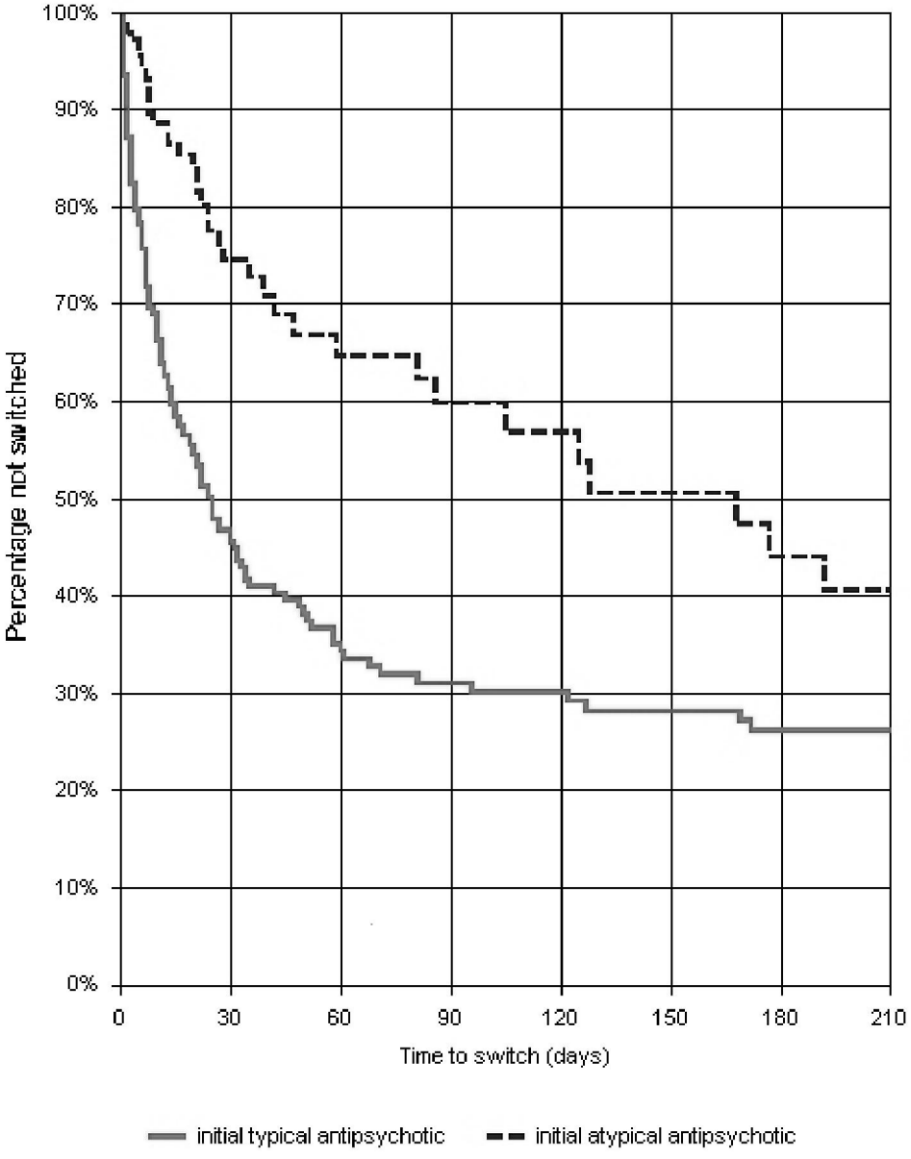

Fig. 1. Time to switch for patients on typical or atypical antipsychotics.

Table 3
Determinant for switching from one oral to another 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 may exceed 100% because of multiple diagnoses.
** Adjusted for age group, gender, diagnosis, initial short acting parenteral antipsychotics and involuntary admission and or restrictive measures.

Patients starting with an oral atypical antipsychotic switched less quickly to another antipsychotic (Fig. 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 typical oral antipsychotics, patients starting with an atypical oral antipsychotic have a lower risk to switch to another antipsychotic [adjusted Odds ratio (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).

4. 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 (RCTs). 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, etc.) 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 do not know if and how patients were treated with antipsychotics before treatment. Negative experiences with antipsychotic treatment before admission may influence the future choice for an antipsychotic after admission.

In our clinical setting medication to be preferred is included in a local formulary. With the exception of clozapine, this formulary did not contain atypical antipsychotics until 1999. However, their use was not restricted in any way. Many psychiatrists asked for their opinion on the use of atypical antipsychotics, had the impression that the newer antipsychotics were less potent in treating psychotic disorders in the acute clinical setting. Although we do not 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 12 months of therapy (Williams et al., 1999). 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 (Leslie and Rosenheck, 2002). 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 less frequently associated with switching in comparison with typical antipsychotics suggesting overall better treatment satisfaction.

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