Pharmacy data as a tool for assessing antipsychotic drug use
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Chapter 7

ANTIPSYCHOTIC DRUG USE AND PSYCHOTROPIC COMEDICATION AT A LONG-STAY WARD

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Abstract

OBJECTIVE Polypharmacy at in-patient services for psychosis may consist of either concomitant use of several antipsychotic drugs or of concurrent use of different types of psychototropic drugs. Prevalence figures of concomitant psychotropic drug use beside atypical antipsychotic treatment are scarce. In this study, concomitant psychotropic drug use at an in-patient ward for schizophrenia was investigated.

METHOD For 71 adult patients of a long-stay ward, we performed three cross-sectional inventories of psychotropic drug use (1998, 1999, 2000), using both medical records and prescription databases. Antipsychotic dosages were calculated by using Prescribed Daily Dosages and were stratified to classic or atypical. Per stratum concomitant benzodiazepine and antidepressant use was determined.

RESULTS More than 80% of our subjects had a diagnosis in the schizophrenia spectrum. During the study period we could not establish differences in distribution between classic and atypical antipsychotic use (both 40%). Dosages of classic antipsychotics were significantly lower, compared to atypical drugs. Anticholinergics were significantly more often used with classic antipsychotics ($\chi^2$, $p < 0.04$). Antidepressant comedication occurred less often with atypical treatment, while benzodiazepine use was seen in equal amount of cases (50-60%) with both types of antipsychotics.

CONCLUSION Polypharmacy with psychotropic comedication at a long-stay ward occurs equally with classic and atypical antipsychotic drug use.
Introduction

In most psychiatric hospitals in the Netherlands, medical treatment of schizophrenic psychosis complies with the guidelines Antipsychotic Drug Use in Schizophrenic Psychosis of the Dutch Society for Psychiatry [1], which is based on the guideline of the American Psychiatric Association [2]. Following this guideline aims to relieve symptoms of psychosis and to improve long-term prognosis. However, when treating chronically ill patients, following the guideline is not always possible and this may lead to apparently irrational prescribing behaviour [3].

During treatment of chronically psychotic patients, a supplemental psychotropic drug is often added to the antipsychotic therapy in order to create a stable treatment situation, to cure side effects or to deal with comorbidities. This polypyschopharmacology can consist of simultaneous use of several antipsychotic drugs and of concurrent use of different psychotropic drugs. Nevertheless, polypharmacy can give cause for several complications during treatment. Interactions between psychotropic drugs may increase chances on the occurrence of adverse effects, which may effect compliance and quality of life [4]. On the other hand, addition of a psychotropic drug may reduce required antipsychotic doses, which, for example, may prevent occurrence of extrapyramidal side effects [1].

Literature concerning atypical antipsychotics suggests an improved effectiveness towards typical antipsychotics on positive, negative and depressive symptoms and a decreased incidence of locomotory side effects [5-7]. However, the actual surplus value in daily practice of atypical antipsychotics needs to be elaborately proved in future systematic research [8]. The impact of type of antipsychotic drug on the use of psychotropic comedication is not yet clearly investigated.

The aim of this explorative survey is to determine total psychotropic drug use at a long-stay inpatient ward for schizophrenia.

Methods

Design

This study is performed at a long-stay inpatient ward for patients with schizophrenia at the Psychosis Unit of the Psychiatric Hospital Drenthe, the Netherlands. Preceding to this study, the research protocol has been approved by a medical ethics committee. In a retrospective drug utilisation study, psychotropic drug use at the long-stay ward is determined at three points of time (1998, 1999 and 2000). All patients (n = 71) are included.
Data concerning date of birth, sex and diagnosis are collected by examining medical records. Additional data concerning antipsychotic drug use, psychotropic and anticholinergic comedication and prescribed daily doses are extracted out of the prescription database of the hospital pharmacy.

Data analysis

Between 1998 and 2000, we made an inventory of current antipsychotic drug use. Because most long-stay patients are chronically hospitalised, but do not have equal duration and history of disease, cross-sectional data analysis is performed by calculation of the point prevalence at the first of January of 1998, 1999 and 2000.

Antipsychotic dosages are expressed in Prescribed Daily Dosages (PDD). The PDD is the prescribed daily dose, expressed as an amount of the Defined Daily Dose (DDD). The DDD is derived from scientific studies and reflects a specific quantity of drug, which an average adult would need to treat the primary registered indication of the drug.

DDD-values can be obtained from the Informatorium Medicamentorum [9] or at the WHO [10]. Because DDD-values concern the total working profile of the antipsychotic drug, while chlorpromazine-equivalency is mainly restricted to D2-antagonism, comparison with DDD-values may be more reliable. This may apply especially for atypical antipsychotics, which possess a range of different receptor affinities [11]. A DDD of haloperidol (= 8 mg) corresponds in effectiveness and safety with 1 DDD of risperidone (= 5 mg). If a patient is using a daily dose of 10 mg haloperidol, it implies that this person uses a PDD of $10/8 = 1.25$. Per patient a PDD of the antipsychotic drug is calculated of the actual prescription at each three points in time. Data are categorised per sex and per type of antipsychotic (typical or atypical). Depot medication is excluded from PDD calculations, because of insufficient reliability of registered dosages in pharmacy databases. Benzodiazepines and antidepressants are defined as psychotropic comedication. Hypnotics and anxiolytics are combined in one category of benzodiazepines, since separate categorisation would lead to group minimisation. Bipiridene is classified as anticholinergic comedication.

Statistical analysis was performed with SPSS 10. Proportions were compared using Chi-square tests and Fisher Exact tests (95% CI).
Results

The study population consisted of 45 men and 26 women, whereof more than 80% had a primary diagnosis in the schizophrenia spectrum. Alternative diagnoses were chronic psychotic depression, mentally retardation and bipolar disorder. The mean age of the male individuals was 49.6 years (range: 32 – 73) and of the females 49.3 years (range: 31 – 72).

Antipsychotic drug use is represented in table 1. During the study period, proportions of classic and atypical antipsychotic drug users did not substantially change. Polypharmacy with two or more antipsychotics occurred in 10% of patients.

<table>
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<tr>
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<tbody>
<tr>
<td></td>
<td>M  F  Tot</td>
<td>M  F  Tot</td>
<td>M  F  Tot</td>
</tr>
<tr>
<td>Classic Antipsychotic*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depot</td>
<td>6  5  11</td>
<td>5  4  9</td>
<td>3  4  7</td>
</tr>
<tr>
<td>Atypical Antipsychotic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clozapine</td>
<td>11  3  14</td>
<td>11  5  16</td>
<td>10  4  14</td>
</tr>
<tr>
<td>Risperidon</td>
<td>3   4  7</td>
<td>4   4  8</td>
<td>3  4  7</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>5   1  6</td>
<td>3   1  4</td>
<td>4  2  6</td>
</tr>
<tr>
<td>Concom. Cl&amp;Atyp Antipsychotic</td>
<td>5  1  6  8</td>
<td>6  1  7  10</td>
<td>6  1  7  10</td>
</tr>
<tr>
<td>No Antipsychotic†</td>
<td>5   6  11  16</td>
<td>4   6  11  15</td>
<td>4  4  8  12</td>
</tr>
</tbody>
</table>

*: Levomepromazine, Flufenazine, Trifluoperazine, Haloperidol, Pipamperon, Broomperidol, Flupentixol, Chloorprotixeen, Zuclopentixol, Pimozide, Penfluridol or Sulpiride.
†: at later moment in study period known with antipsychotic drug use
While the dose difference in males between classic and atypical antipsychotics was significant during the total study period (Chi-square, \( p < 0.05 \)), we were not able to show this difference in females (Table 2).

Mean classic PDDs of the total study population were 0.96, 0.97 and 0.87 in 1998, 1999 en 2000 respectively. Mean atypical PDDs of the total study population were 1.48, 1.37 and 1.34 in 1998, 1999 en 2000 respectively. All atypical PDDs were significantly higher, compared to classic doses (Chi-square, \( p < 0.05 \)). During the study period, there was no dose difference between males and females in general (at all moments \( p > 0.2 \)).

Table 2: Mean Prescribed Daily Dose*/person per type of antipsychotic drug

<table>
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<tbody>
<tr>
<td></td>
<td>M</td>
<td>F</td>
<td>M</td>
</tr>
<tr>
<td>n</td>
<td>PDD</td>
<td>n</td>
<td>PDD</td>
</tr>
<tr>
<td><strong>Classic Antipsychotic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>1.05</td>
<td>6</td>
<td>0.82</td>
</tr>
<tr>
<td><strong>Atypical Antipsychotic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>1.55</td>
<td>8</td>
<td>1.34</td>
</tr>
<tr>
<td>Clozapine</td>
<td>11</td>
<td>1.62</td>
<td>3</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>5</td>
<td>1.78</td>
<td>1</td>
</tr>
<tr>
<td>Risperidone</td>
<td>3</td>
<td>0.92</td>
<td>4</td>
</tr>
</tbody>
</table>

* = quotient of prescribed amount of antipsychotic and recommended daily dose
† = depot preparations excluded
Both anticholinergic and general psychotropic comedication was more prevalent with classic antipsychotic drug use, compared to prevalence with atypical antipsychotics. (table 3). Anticholinergic comedication occurred al all points in time significantly more often with classic antipsychotic drug use. (Chi-square, \( p = 0.01, 0.04 \) en 0.01, respectively).

Antidepressants were more often seen with classic antipsychotic drug use, however, this difference was not significant at all three points in time. Benzodiazepines were most prevalent as additive psychotropic drug, although we could not establish a difference in percentage of benzodiazepine use between classic and atypical antipsychotic drug users.

Table 3: Anticholinergic (AC), antidepressant (AD) en benzodiazepine (BD) comedication* per type of antipsychotic drug

<table>
<thead>
<tr>
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<tbody>
<tr>
<td></td>
<td>AC</td>
<td>AD</td>
<td>BD</td>
</tr>
<tr>
<td>Classic Antipsych</td>
<td>7 (26%)</td>
<td>12 (44%)</td>
<td>16 (59%)</td>
</tr>
<tr>
<td>Atypical Antipsych</td>
<td>- (15%)</td>
<td>4 (15%)</td>
<td>14 (52%)</td>
</tr>
</tbody>
</table>

\[ p \text{- value}^\dagger = 0.01, 0.04, 0.58 \]  \[ p \text{- value}^\dagger = 0.04, 0.19, 0.64 \]  \[ p \text{- value}^\dagger = 0.01, 0.07, 0.45 \]

\[ CI \& Atyp = 1 (17%), - (67%), 4 (67%), 1 (14%), 1 (14%), 5 (71%), 1 (14%), 2 (29%), 7 (100%) \]

\( * = \% \) is percentage of this stratum of antipsychotic users (eg. 26% of classic antipsychotic drug users did use an anticholinergic as comedication in 1998).

\( ^\dagger = \% \) comedication classic versus \% comedication atypical. Chi-square test, 95 \% CI. Expected values < 5: Fisher Exact test.
Discussion

In this retrospective study we demonstrated that, at a long-stay ward, proportions of classic and atypical antipsychotic drug use did not change substantially between 1998 and 2000. Atypical antipsychotic doses, in comparison to classic antipsychotic doses, were significantly higher at all points in time during the study period. Furthermore, we could not establish dose differences between the sexes. Use of any psychotropic comedication was slightly elevated with classic antipsychotic use, however, this difference was not significant. In general, use of psychotropic comedication occurs frequently.

In this study we could not establish significant sex differences in antipsychotic doses. Earlier research reported contradictory results concerning this topic, both equal and lower dosing has been found [12-14]. An explanation for the equal doses in our study may be the fact that both male and female patients had a complex history of disease with a relapsing course (e.g. chronic hospitalisation need). However, women in general do suffer less from behavioural disorders and are functioning better [15], which may also be an explanation for the (although not significant) lower antipsychotic dosages.

Mean PDDs of classic antipsychotic drugs were significantly lower than atypical antipsychotics, probably in order to prevent the occurrence of extrapyramidal symptoms at high dosing of classic antipsychotic drugs. We recommend that DDDs of atypical antipsychotics in future research are compared critically with equivalent classic doses. It may occur that atypical DDDs are initially defined suboptimally, because of commercial reasons or in order to delay occurrence of extrapyramidal symptoms. However, it is remarkable that, in spite of the active marketing of atypical antipsychotics, the distribution between classic and atypical medication remained equal during the study period, again possibly due to the chronic disease-character of the population. During treatment, it is aimed to maintain a situation as stable as possible and –after a history of switching to many different antipsychotics- that may not always occur with the guideline antipsychotic drug. Nevertheless, one can expect that, because of the high risk of development of tardive dyskinesia, switching to atypical antipsychotic drug treatment would have occurred more frequently.

In spite of lower classic dosages, significantly more often anticholinergics were prescribed with classic antipsychotic drugs, which reflects the occurrence of parkinsonian adverse effects. The fact that classic substances are worse tolerated, can explain the elevated use of psychotropic comedication. If the expected effect of the antipsychotic drug is unsatisfying or serious adverse effects are arising, one can imagine that instead of increasing antipsychotic dosages, supplemental psychotropic medication can be provided in order to treat symptoms like anxiety, agitation and depression [1].

Antidepressant use seems to occur less frequently with atypical antipsychotic use. This may be explained by the theory of the beneficial working
profile of atypical antipsychotics on negative symptomatology, which may be responsible for a better treatment of depression. This will make antidepressant comedication less necessary [7;16].

On the contrary, benzodiazepine use occurs equally in both classic and atypical antipsychotic drug use. Preferably, benzodiazepines should be restricted to the treatment of anxiety and agitation in the acute phase of schizophrenic psychosis, because of the risk of addiction and the occurrence of adverse effects like cognition decrease. Because of the patient characteristics, minimal benzodiazepine use may be considered as rational, however, only in acute situations. This raises questions regarding the evaluation of the medication policy at long-stay wards. Especially, consistent switching to different antipsychotic medication should be reviewed frequently enough, since inconsistent withdrawing of medication can lead to long-term overconsumption. This may explain the relatively high percentage of patients (10%) in this study that concurrently use several antipsychotic drugs.

A limitation of data-analysis by investigation of medical records is the fact that several patient data are documented subjectively by the treating psychiatrist. However, in this study only diagnosis as subjective observation is extracted out of the medical record, which may be considered as stable in chronic patients. The mean age of 49 years reflects the fact that patients probably are in treatment for a long time, since in general psychotic symptomatology begins between the age of 15 and 30 [17]. A further limitation of this study design is that because of the small amount of patients and the regional setting, the results can not directly be extrapolated to the entire Dutch situation. However, for an explorative study to medication use, it is recommendable to analyse a small population qualitatively, instead of using a database of medication records whereof qualitative data are lacking.

This study indicates that, if in a future adjustment of the guideline “treatment of schizophrenic psychosis” a choice should be made between classic and atypical antipsychotic drug use, elaborate research should be conducted to the actual place of both drugs in the spectrum of medical treatment possibilities. Because of the high percentage of psychotropic comedication with atypical antipsychotic drug use, further studies are necessary to the actual surplus value of the atypical drugs.

This study is part of a project to efficient prescribing of antipsychotics in Dutch intramural settings, which was funded by the Committee of Drug Policy Research of the Dutch Board of Health Insurance.


Chapter 7

Reference list


