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# Trends in the pharmacological treatment of patients with schizophrenia over a 12 year observation period

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**Abstract**

In this study we evaluated whether our efforts to promote evidence-based guidelines for the psychopharmacological treatment of patients with schizophrenia have led to measurable changes of treatment practice in our hospital by investigating three primary hypotheses: 1) Polypharmacy has become less common in recent years, 2) Conventional neuroleptics have been replaced by second generation antipsychotics; and 3) Dosing regimes have changed towards lower doses. We have therefore collected data from the clinical records of all in-patients with ICD-9/ICD-10 diagnoses of schizophrenia hospitalized at the Department of Psychiatry of the Medical University Innsbruck in the years 1989, 1995, 1998 and 2001. Data from 1989 to 1998 showed a significant decrease in the use of two or more antipsychotics given simultaneously. Contrary to our hypothesis, there was a significant increase in polypharmacy between 1998 and 2001. The predominant use of second generation antipsychotics became standard in schizophrenia treatment. In this context the decrease of concomitant anticholinergic medication is notable. Doses of conventional antipsychotics like haloperidol as well as doses of risperidone decreased whereas doses of other second generation antipsychotics increased. All in all, the pharmacological management of schizophrenia patients is increasingly in tune with current treatment guidelines.


*Keywords:* Schizophrenia; Pharmacotherapy; In-patient treatment; Antipsychotics; Guidelines; Follow up; Neuroleptics

## 1. Introduction

During the last decade many efforts have been made towards improving strategies concerning the pharmacological treatment of patients with schizophrenia. The development of new antipsychotics and the international scientific consensus in particular about duration of treatment, dose recommendations and preference of antipsychotic monotherapy (American Psychiatric Association, 2004; Lehman and Steinwachs, 1998a, 2004; Kissling, 1991) have been the most relevant steps in this undertaking.

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However, the Schizophrenia Patient Outcome Research Team (PORT) data indicate discouragingly little effect of clinical guidelines for the treatment of schizophrenia in the U.S. (Lehman and Steinwachs, 1998b).

There are a number of differences between psychiatric care in Europe and in the U.S. These differences pertain mostly to resources and accessibility, especially in so far as national health care systems in Europe generally have less restrictions with regard to length of hospital stay. More different antipsychotics are available which seem to be used in combination treatments, and clozapine is prescribed in lower dosage in some European countries than in the U.S. (Fleischhacker et al., 1994). But, also within Europe, treatment strategies differ markedly (Kiivet et al., 1995; Bowers et al., 2004).

Just as Lehmann and Steinwachs (1998b) in the U.S., an earlier Austrian study (Meise et al., 1994) reflected clear discrepancies between treatment recommendations and clinical practice. As the latter was a postal survey with all the inherent limitations of this type of research, a tendency to give answers in a biased way could not be excluded.

We therefore decided to study actual clinical practice in our own hospital where treatment guidelines are an essential part of education and residency training. A preliminary analysis of data from 1989, 1995 and 1998 demonstrated an encouraging outcome concerning the efforts towards implementation of modern pharmacological schizophrenia treatment (Kurz et al., 2003). With the further investigation of more recent admissions we wanted to prove if newly registered antipsychotics influence the choice of medication, if antipsychotic dose continues to decrease and if polypharmacy becomes yet less popular, thereby lending credence to our assumption that this was indeed indicative of a continuing change towards evidence-based treatment.

## 2. Methods

We collected data from the clinical records of all in-patients with an undisputed ICD-9/ICD-10 diagnosis of schizophrenia hospitalized at the Department of Psychiatry of the Medical University Innsbruck in the years 1989, 1995, 1998 and 2001.

Next to socio-demographic data, clinical features and antipsychotic prescription schedules (choice of medication, timing and dose, route of administration, change of medication or simultaneous prescription of two or more antipsychotics) during hospital treatment and at time of discharge were obtained. Daily doses of long acting injectable depot medications were calculated by dividing the single dose by the number of days within the application intervals. Comedication was categorized into antidepressants, low-potency antipsychotics, benzodiazepines, anticholinergic agents, beta-blockers and other drugs, which include mood stabilizers and non-psychopharmacological pharmaceuticals. The frequencies of comedication were obtained in days on medication during the hospital stay.

Statistical analyses were performed using SPSS for Windows, Version 11. For comparing the four years (1989, 1995, 1998 and 2001) with respect to binary dependent variables (e.g., use of a certain antipsychotic [yes/no]) the chi-square test was applied for an overall assessment of differences between the years. In case of a significant result ($p \leq 0.05$), post hoc pair wise comparisons were performed using Fisher's exact test. Similarly, for comparisons with respect to numerical dependent variables (e.g., dose of a certain antipsychotic) the Kruskal–Wallis test was used for an overall evaluation; non-parametric rather than parametric tests were used because most numerical variables showed a non-normal distribution. If the Kruskal–Wallis test yielded a $p$-value $\leq 0.05$, Mann–Whitney $U$-tests were conducted subsequently for comparing pairs of years. In order to discover time trends with gradually increasing or decreasing values, the analyses were complemented by Spearman rank correlation analyses in which the dependent variable was correlated with the ordinal variable year.

## 3. Results

### 3.1. Sample description

Overall, 333 (1989: 58, 1995: 80, 1998: 98, 2001: 97) patients were entered into the analysis. Demographic and clinical data are shown in Table 1. The four groups were very similar concerning age, sex

Table 1
Demographic and clinical data

| | 1989 ($n=58$) | | 1995 ($n=80$) | | 1998 ($n=98$) | | 2001 ($n=97$) | |
|---|---|---|---|---|---|---|---|---|
| Male patients (%) | 67.2 | | 67.5 | | 58.2 | | 63.9 | |
| First-episode patients (%) | 15.5 | | 17.5 | | 18.4 | | 7.2 | |
| | | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| Age (years) | M | 31.4 | 10.3 | 33.3 | 10.5 | 34.7 | 11.2 | 35.1 | 11.1 |
| | F | 38.1 | 14.3 | 33.9 | 10.6 | 40.9 | 14.6 | 41.9 | 15.4 |
| | All | 33.6 | 12.1 | 33.5 | 10.5 | 37.3 | 13.0 | 37.1 | 13.1 |
| | | Mean/median | | Mean/median | | Mean/median | | Mean/median | |
| Duration of illness (months) | M | 92.2/53.5 | | 86.0/48.0 | | 107.9/90.0 | | 96.3/58.0 | |
| | F | 104.2/91.0 | | 103.7/72.0 | | 123.3/102.0 | | 165.4/120.0 | |
| | All | 96.1/68.5 | | 92.0/60.0 | | 114.4/96.0 | | 121.7/72.0 | |
| Duration of hospitalization (days) | M | 36.9/28.0 | | 39.0/26.0 | | 28.9/24.0 | | 45.9/31.5 | |
| | F | 31.0/18.0 | | 50.8/36.0 | | 37.4/29.0 | | 38.3/30.0 | |
| | All | 35.0/24.5 | | 42.8/29.0 | | 32.4/24.0 | | 43.2/30.0 | |

No significant differences between the years for any of the variables.

distribution, history of illness and percentage of first-episode patients. Patients in 1998 and 2001 had a longer duration of illness and the mean duration of hospitalization was longer in 1995 and in 2001 in comparison to the other years, yet without being significantly different.

### 3.2. Frequency, dose and treatment duration of antipsychotics

Different antipsychotics used as first-line medication during in-patient treatment are listed in Table 2a. While risperidone was not available in 1989, it was the most frequently used first-choice antipsychotic in the 1995 patient group (31.3%) with a subsequent significant decrease until 2001. Haloperidol and clozapine lost their leading positions from 1989, with a statistically significant decrease in the frequency of haloperidol use (25%) between 1989 and 1995, another 15% loss from 1995 to 2001. Clozapine used as first-line agent decreased by 20% from 1989 to 1998. In 1998 as well as in 2001, first-line prescriptions of second generation antipsychotics (excluding clozapine) amounted to two-thirds of the patients. Other antipsychotics like fluphenazine, sulpiride or perphenazine (not specified in table) were of little importance throughout.

Daily doses of haloperidol and risperidone were generally found to decrease from 1989 to 2001 (Table 2b). Doses of olanzapine on the other hand increased from 1998 to 2001 ($p=0.009$). Patients treated with clozapine received a mean of 345 mg/day in 2001, which was higher than in previous years.

No significant differences were found concerning duration of antipsychotic treatment (between 12 and

Table 2a
First-choice antipsychotics

| | 1989 | | 1995 | | 1998 | | 2001 | |
|---|---|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | *n* | % | *n* | % |
| Haloperidol [a] | 29 | 50.0 | 20 | 25.0 | 14 | 14.3 | 9 | 9.3 |
| Risperidone [b] | – | – | 25 | 31.3 | 24 | 24.5 | 8 | 8.2 |
| Clozapine [c] | 19 | 32.8 | 15 | 18.8 | 13 | 13.3 | 22 | 22.7 |
| Olanzapine [d] | – | – | – | – | 15 | 15.3 | 32 | 33.0 |
| Sertindole [e] | – | – | – | – | 11 | 11.1 | 0 | 0.0 |
| Zotepine | – | – | – | – | 6 | 6.1 | 2 | 2.1 |
| Amisulpride | – | – | – | – | – | – | 11 | 11.3 |
| Quetiapine | – | – | – | – | – | – | 4 | 4.1 |
| Experimental study-medication | 5 | 8.6 | 6 | 7.5 | 5 | 5.1 | 3 | 3.1 |
| Others | 4 | 6.9 | 12 | 15.0 | 10 | 10.1 | 5 | 5.2 |

One patient in 1989, 1995 and 2001 received no antipsychotic.
[a] Overall: $p<0.001$; 1989 vs. 1995: $p=0.002$; 1989 vs. 1998, 2001: $p<0.001$; 1995 vs. 2001: $p=0.007$.
[b] Overall: $p<0.001$; 1995 vs. 2001: $p<0.001$; 1998 vs. 2001: $p=0.003$.
[c] Overall: $p=0.031$; 1989 vs. 1998: $p=0.004$.
[d] 1998 vs. 2001: $p=0.004$.
[e] 1998 vs. 2001: $p<0.001$.

Table 2b
Daily dose, mean (mg/d)

| | 1989 | | 1995 | | 1998 | | 2001 | |
|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| Haloperidol[a] | 23.9 | 18.5 | 15.1 | 12.1 | 10.4 | 6.4 | 7.2 | 3.0 |
| Risperidone[b] | – | – | 5.8 | 2.7 | 4.0 | 2.0 | 3.3 | 1.0 |
| Clozapine | 285.2 | 184.7 | 261.9 | 148.6 | 279.1 | 141.5 | 344.5 | 127.3 |
| Olanzapin[c] | – | – | – | – | 12.1 | 4.5 | 16.0 | 5.7 |
| Sertindole | – | – | – | – | 11.8 | 5.3 | – | – |
| Zotepine | – | – | – | – | 114.3 | 84.2 | 160.3 | 25.8 |
| Amisulpride | – | – | – | – | – | – | 436.0 | 110.5 |
| Quetiapine | – | – | – | – | – | – | 555.6 | 152.4 |

[a] Ordinal time trend (Spearman correlation between dose and year): $r=-0.31$, $p=0.009$; 1989 vs. 2001: $p=0.045$.
[b] Overall: $p=0.009$; 1995 vs. 1998: $p=0.015$, 1995 vs. 2001: $p=0.005$.
[c] 1998 vs. 2001: $p=0.009$.

26 days on average), apart from clozapine, which was applied for a longer period of time (mean 44 days) in 2001.

### 3.3. Number of antipsychotics per patient

In 1989, 1995 and 2001 only a single patient each with no antipsychotic medication at all was detected. About 60% of the patients in the years 1989, 1995 and 1998, and 50% in 2001 were treated with a single antipsychotic agent during their entire hospitalization period. About 25% of the patients received two antipsychotics consecutively in all observation years and 12–23.7% received three or more antipsychotics while being treated as in-patients. Overall, there were no statistically significant differences between the four years regarding the number of consecutively prescribed antipsychotics.

The parallel use of two high-potency antipsychotics was not very common. Table 3 summarizes the percentages of patients on two simultaneous antipsychotic agents for at least 7 days. Compared to former years of observation there was a significantly higher percentage of patients on antipsychotic polypharmacy in 2001.

### 3.4. Non-antipsychotic comedication

Any use of concomitant medication per patient at any time during in-patient treatment is listed on Table 4. The use of benzodiazepines increased significantly over the observation period. In contrast, the prescription of low-potency neuroleptics, generally used as sedatives, decreased significantly from 1989 to 2001. Simultaneously, anticholinergic substances were used with decreasing frequency over the years. Beta-blockers were more commonly prescribed in 1995 compared to all other years. The category "others" subsumes non-psychopharmacological medication and mood stabilizers, the latter contributing a very small amount. In 2001 only three patients received adjunct valproate.

### 3.5. Route of drug administration

The route of drug administration (oral, intravenous or depot application) was oral in 58.6% of all antipsychotic prescriptions in 1989 over all of the in-patient treatments. This percentage was 81.3% in

Table 3
Number of high-potency antipsychotics per patient

| | 1989 | | 1995 | | 1998 | | 2001 | |
|---|---|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | *n* | % | *n* | % |
| Subjects receiving two APs in parallel for at least 7 days[a] | 4 | 6.9 | 3 | 3.8 | 3 | 3.1 | 14 | 14.4 |
| Period of time during which subjects received two APs[b,c] | 6.1% | | 3.4% | | 2.7% | | 10.8% | |

[a] Overall comparison: $p=0.009$; 1989 vs. 1998: $p=0.020$, 1998 vs. 2001: $p=0.010$.
[b] Expressed as a percentage of the total length of the hospital stay. A subject never receiving two APs counts 0%, a subject receiving two APs for one week out of four counts 25%, etc. Values shown are mean percentages.
[c] Overall comparison: $p=0.001$; 1989 vs. 1995: $p=0.014$, 1989 vs. 1998: $p=0.024$, 1995 and 1998 vs. 2001: $p<0.001$.

Table 4
Comedication

| | 1989 | | 1995 | | 1998 | | 2001 | |
|---|---|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | *n* | % | *n* | % |
| Benzodiazepines[a] | 44 | 75.9 | 63 | 78.8 | 79 | 80.6 | 87 | 89.7 |
| Low-potency antipsychotics[b] | 27 | 46.6 | 25 | 31.3 | 18 | 18.4 | 13 | 13.4 |
| Anticholinergics[c] | 28 | 48.3 | 33 | 41.3 | 21 | 21.4 | 14 | 14.4 |
| Beta-blockers[d] | 5 | 8.6 | 19 | 23.8 | 9 | 9.2 | 12 | 12.4 |
| Antidepressants | 7 | 12.1 | 6 | 7.5 | 18 | 18.4 | 16 | 16.5 |
| Others | 20 | 34.5 | 27 | 33.8 | 29 | 29.6 | 45 | 46.4 |

[a] Ordinal trend in the time course: $r$ Spearman=0.18, $p=0.030$; 1989 vs. 2001: $p=0.037$.
[b] Overall: $p<0.001$; 1989 vs. 1998, 2001: $p<0.001$; 1995 vs. 2001: $p=0.004$.
[c] Overall: $p<0.001$; 1995 vs. 1998: $p=0.005$; 1989 vs. 1998: $p=0.001$; 1989, 1995 vs. 2001: $p<0.001$.
[d] Overall: $p=0.018$; 1989 vs. 1995: $p=0.023$; 1995 vs. 1998: $p=0.012$.

1995, 79.6% in 1998 and 82,3% in 2001. In 1989, 31.0% of patients were treated with intravenous medications as opposed to 11.3% of patients in 1995, 14.3% in 1998 and 7.3% in 2001 ($p<0.001$, 1989 versus all other years). Duration of intravenous treatment was mostly few days only, lasting for one week at most.

Depot medication–at any time during hospitalization–was not used frequently among in-patients, especially in the years 1995 (10.0%), 1998 (9.2%) and 2001 (12.5%). In 1989, 19% of patients were treated with depot antipsychotics during their in-patient stay.

### 3.6. Discharge prescriptions

Prescriptions at the time of hospital discharge are summarized on Table 5a. Patients were discharged on haloperidol significantly more often in 1989 than in later years, notably in 2001 when only 5% of all patients had haloperidol among their antipsychotic discharge medications. Risperidone was the most common antipsychotic at discharge in 1995, but the number of patients diminished in more recent years. The use of clozapine remained fairly stable over time. Beyond risperidone and clozapine, the majority of prescriptions at discharge in 1998 were written for the then newly available antipsychotics, olanzapine and sertindole, whereas by 2001 this shifted to olanzapine and amisulpride.

Doses of antipsychotic medication at discharge varied widely across years, but were almost the same as during in-patient treatment. Haloperidol dose decreased from a mean of 20.5 mg per day in 1989 to 7.5 mg in 2001. From 1995 to 1998, the dose of risperidone decreased by 2.5 mg/day. It stayed at a similar level until 2001. The dose of clozapine increased significantly in 2001 compared to 1995 and 1998, as did the dose of olanzapine from 1998 to 2001.

Only two patients from the 1989 sample received two different antipsychotics simultaneously when

Table 5
Discharge prescription

| | 1989 | | 1995 | | 1998 | | 2001 | |
|---|---|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | *n* | % | *n* | % |
| *a) Antipsychotics* | | | | | | | | |
| Haloperidol[a] | 22 | 39.3 | 13 | 16.9 | 5 | 5.1 | 5 | 5.2 |
| Risperidone [b] | – | – | 23 | 29.9 | 20 | 20.4 | 6 | 6.2 |
| Clozapine | 15 | 26.8 | 21 | 27.3 | 20 | 20.4 | 33 | 34.0 |
| Olanzapine | – | – | – | – | 15 | 15.3 | 23 | 23.7 |
| Sertindole [c] | – | – | – | – | 11 | 11.2 | 0 | 0.0 |
| Zotepine | – | – | – | – | 10 | 10.2 | 4 | 4.1 |
| Amisulpride | – | – | – | – | – | – | 23 | 23.7 |
| Quetiapine | – | – | – | – | – | – | 2 | 2.1 |
| Fluphenazine | 4 | 7.1 | 7 | 9.1 | 1 | 1.0 | 5 | 5.2 |
| Experimental study-medication | 7 | 12.5 | 2 | 2.6 | 4 | 4.1 | 2 | 2.1 |
| Others | 8 | 14.3 | 11 | 14.3 | 12 | 12.2 | 2 | 2.1 |
| Two antipsychotics | 2 | 3.4 | 0 | 0.0 | 2 | 2.0 | 12 | 12.4 |
| None | 2 | 3.4 | 2 | 2.6 | 0 | 0.0 | 4 | 4.1 |
| *b) Comedication* | | | | | | | | |
| Benzodiazepines[d] | 16 | 27.6 | 18 | 22.5 | 30 | 30.6 | 43 | 44.3 |
| Anticholinergics[e] | 17 | 29.3 | 19 | 23.8 | 9 | 9.2 | 9 | 9.3 |
| Low-potency antipsychotics[f] | 13 | 22.4 | 9 | 11.3 | 5 | 5.1 | 2 | 2.1 |
| Beta-blockers[g] | 4 | 6.9 | 13 | 16.3 | 4 | 4.8 | 8 | 8.2 |
| Antidepressants | 4 | 6.9 | 4 | 5.0 | 12 | 12.2 | 9 | 9.3 |
| Others | 15 | 25.9 | 18 | 22.5 | 22 | 22.4 | 31 | 32.0 |

[a] Overall: $p<0.001$; 1989 vs. 1995: $p=0.004$; 1989 vs. 1998, 2001: $p<0.001$; 1995 vs. 1998: $p=0.022$; 1995 vs. 2001: $p=0.023$.
[b] Overall: $p<0.001$; 1995 vs. 2001: $p<0.001$, 1998 vs. 2001: $p=0.001$.
[c] 1998 vs. 2001: $p<0.001$.
[d] Overall: $p=0.014$; 1989 vs. 2001: $p=0.042$, 1995 vs. 2001: $p=0.003$.
[e] Overall: $p=0.001$; 1989 vs. 1998, 2001: $p=0.001$; 1995 vs. 1998, 2001: $p=0.012$.
[f] Overall: $p<0.001$; 1989 vs. 1998: $p=0.002$, 1989 vs. 2001: $p<0.001$, 1995 vs. 2001: $p=0.024$.
[g] Overall: $p=0.035$; 1995 vs. 1998: $p=0.006$.

discharged, both were on clozapine first-line with add-on depot medication (haloperidol, flupenthixol). In 1998, two patients were prescribed two different antipsychotics, both were on clozapine combined with olanzapine and orally administered flupenthixol, respectively. Twelve patients (12.4%) were referred to outpatient treatment with two antipsychotics in 2001, significantly more than in former years. Most patients (10) received clozapine with an additional antipsychotic (5 amisulpride, 2 haloperidol, 2 fluphenazine, 1 flupenthixol). The other combinations were amisulpride with olanzapine and zotepine with fluphenazine.

Injectable depot antipsychotics were infrequently prescribed at hospital discharge (1989: 8.6%, 1995: 5.0%, 1998: 6.1%, 2001: 7.2%).

Prescriptions of non-antipsychotic comedication at discharge followed a similar pattern as during in-patient treatment (Table 5b): Benzodiazepine use increased over the years from 27.6% in 1989 to 44.3% in 2001. Anticholinergic prescriptions decreased by 20% from 1989 to 1998 and 2001, as did the use of low-potency antipsychotics.

## 4. Discussion

### 4.1. Choice of antipsychotic medication

Second generation antipsychotics (except for clozapine, which has been available since the early 1970s) were registered in Austria in 1993 (risperidone, zotepine), 1994 (amisulpride), 1996 (olanzapine, sertindole) and 2000 (quetiapine) respectively. As our hospital includes an academic schizophrenia research centre each of these drugs was evaluated in the framework of phase II/III clinical trials before registration. For the same reason, advertising tends to be equally balanced between all producers of antipsychotics. Therefore differences in the frequency of prescriptions are unlikely to be due to particular drug company promotion.

The change in first-line medication from conventional to second generation antipsychotics as commonly recommended internationally (American Psychiatric Association, 2004; NICE clinical guidelines, 2002) and in an Austrian recommendation (Katschnig et al., 2002) apparently gained momentum in our clinic over the years observed (see Fig. 1). In

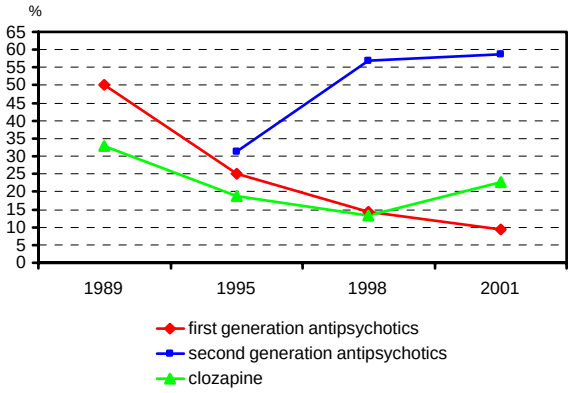


Fig. 1. First-choice antipsychotics.

2001, as well as in 1995 and 1998, the majority of patients were treated with second generation antipsychotic monotherapy. In 1995 risperidone was the most commonly prescribed novel antipsychotic, later losing this position to clozapine and olanzapine. The prominent role of olanzapine has also been demonstrated in other European (Bowers et al., 2004), American (Centorrino et al., 2002) and Australian (Galletly, 1999) reports. In 2001 almost a fourth of patients received clozapine during in-patient treatment and at discharge 34% of our patients were on clozapine. Some years earlier a new specialized outpatient clinic for schizophrenia patients was installed at our department. With increasing emphasis on outpatient treatment even in the case of exacerbation, more critically ill, chronic and therapy resistant patients were admitted which may in part explain higher rates of clozapine use. In contrast, Weissman (2002) has reported a low utilization of clozapine (1% of schizophrenia patients) for the New York metropolitan region of the Veterans Integrated Service Network, a fact discussed very critically in this paper. This may be related to regular blood counts, which were still mandatory weekly throughout treatment in the U.S. at the time of this study, while many European countries loosen blood count monitoring after 4 months of treatment. In addition, clozapine has been available without interruption in Austria since the 1970s, making it a drug which many psychiatrists have lots of experiences with.

### 4.2. Dose of antipsychotic medication

Clozapine was administered in comparable doses during in-patient treatment, but at time of discharge in

the year 2001, dose was significantly higher than in previous years (mean 350 mg/day). Overall, in Austria and Germany, another country with a long clozapine tradition (Naber and Hippius, 1990), lower dose rates of clozapine are prescribed in contrast to the United States, as reported elsewhere (Fleischhacker et al., 1994; Pollack et al., 1995). The dose increase in recent years could be attributed to the change in service provision described in the previous paragraph.

Doses of the newer second generation antipsychotics, especially olanzapine, also increased by 2001, but still remained within recommended limits. This may be due to more experience with these substances over the years and the aim to reach optimal therapeutic dosing with a single antipsychotic. The generally better side-effect profile of second generation antipsychotics permits this, as higher doses are usually also well tolerated (Tandon, 2002). In addition, higher doses of novel antipsychotics have been reported to correlate with greater clinical improvement during hospital stay (Centorrino et al., 2002). A significant dose reduction could be seen with risperidone and most clearly with haloperidol: The mean daily dose of the latter was 23.9 mg in 1989 and 7.2 mg in 2001. Risperidone dose decreased from 5.8 mg in 1995 to 3.3 mg in 2001. This is in line with recent dosing recommendation of these drugs (Davis and Chen, 2004).

The use of depot antipsychotics during in-patient treatment remained stable over the years, while the intravenous and intramuscular administration of antipsychotics in the management of acute psychosis decreased steadily over the 12 year observation period. The latter may be interpreted as the consequence of the increasing popularity and success of concomitant benzodiazepines in acutely ill schizophrenia patients.

### 4.3. Duration of antipsychotic monotherapy

One third to half of our patients received two or more antipsychotics consecutively during hospitalization. The mean duration of hospitalization was between 32.4 and 43.2 days and all antipsychotics, except clozapine, were used for a maximum of four weeks, which indicates that the recommended treatment time of a minimum of 4 to 6 weeks before changing medication (American Psychiatric Association, 2004) is seldomly observed. Clozapine was used for longer periods in 2001 (mean 44.6 days) compared to former years, which may be related to its status as third-line medication when other possibilities are exhausted and to the fact that treatment trials with clozapine have been suggested to have to last for three to six months (Conley et al., 1999; Fleischhacker, 1999; Kane et al., 2001; Kurz et al., 1995; Marder et al., 2002).

### 4.4. Polypharmacy

Our data show that the parallel use of two (or more) high-potency antipsychotics is not very common in our hospital, which is in line with recent national and international treatment guidelines for schizophrenia (Katschnig et al., 2002; American Psychiatric Association, 2004; NICE clinical guidelines, 2002). In 2001 significantly more patients were on two different antipsychotics than in previous years. At time of discharge this amounted to 12.4%, which concurs with findings from the U.S. (Centorrino et al., 2002; Wang et al., 2000). In contrast to most recommendations antipsychotic polypharmacy has been shown to be a common phenomena in a number of surveys. Figures range from 10% up to 60% of patients receiving two or more different antipsychotics (Stahl, 1999; Wilson et al., 1985; Takei and Inagaki, 2002; Procyshyn et al., 2001), but it must be mentioned that, different from our report, most authors have not differentiated between high- and low-potency antipsychotic drugs, the latter frequently used as add-on medication to control behavioral symptoms of schizophrenia, such as agitation and violence. In a retrospective observational study the overall prevalence of antipsychotic polypharmacy in patients with schizophrenia in Georgia and California increased from 32% in 1998 to 41% in 2000 (Ganguly et al., 2004). McCue et al. (2003) have compared prescribing practices for schizophrenia patients in the Woodhull Medical and Mental Health Care Center in New York and found that in 1995 no patient had been discharged on more than one antipsychotic while 16% were on treatment with two different antipsychotics in 2000, which is similar to our findings. The same authors showed that the use of polypharmacy coincided with a decrease in adverse drug reactions and was associated with indicators of a better patient

outcome. Linden et al. (1999), in a European survey, found a close correlation between the number of drugs prescribed and the severity of patient's illness. Again, we can see coherence with antipsychotic polypharmacy potentially following increasing in-patient severity of illness in the wake of setup of our schizophrenia outpatient clinic 1996.

We found clozapine to be the most frequent part of antipsychotic combination therapy, either with additional first or second generation drugs. Canadian data from 1996 to 1998 showed that nearly 30% of patients were discharged with two different antipsychotics. The most common regimen consisted of two conventional antipsychotics, the second most common combination was olanzapine with a conventional agent (Procyshyn et al., 2001). Interestingly another Canadian group found lower rates of antipsychotic polypharmacy (Remington et al., 2001), dependent on the type of hospital studied. Prescription of two or more antipsychotics was more common in peripheral than in university hospitals.

The use of low-potency antipsychotics used as sedatives sank significantly from 1989 to 2001 while benzodiazepine prescriptions rose in parallel. This follows most available practice guidelines, which advocate benzodiazepine if sedation during agitated states of the disorder becomes necessary (Wolkowitz and Pickar, 1991; Allen et al., 2001).

Up to 44.3% of patients were discharged on benzodiazepines in our hospital. Although this is only about half of the prescription rate during in-patient treatment, it remains somewhat worrisome given the risk for benzodiazepine abuse and dependency, especially in predisposed individuals (Nelson and Chouinard, 1999).

The significant decrease of anticholinergic comedication can be explained by the reduced risk of extrapyramidal motoric side-effects induced by second generation antipsychotics (Sartorius et al., 2002, 2003). In a comparison of psychotropic drug prescribing patterns in acute psychiatric wards across Europe, Finland had the highest percentage of patients on antipsychotic drugs but no anti-parkinsonian agents were prescribed there (Bowers et al., 2004). This was related to low daily doses and the predominant use of second generation antipsychotics. The PORT-recommendations (Lehmann et al., 2004) as well as a recent olanzapine/haloperidol comparison study conducted in the American Veteran's Administrative Healthcare System (Rosenheck et al., 2003) suggest the prophylactic use of anti-parkinsonian agents for patients treated with typical antipsychotics, which is in sharp contrast to World Health Organisation (1990) and non-US (Barnes, 1990; Fleischhacker and Widschwendter, 2004; Remington and Bezchlibnyk-Butler, 1996) based views on the issue. The latter publications emphasize potential adverse effects of anticholinergics (abuse, cognitive impairment, higher risk for tardive dyskinesia) and recommend to restrict their use to patients with manifest EPS, except for high risk populations.

The "excessive" use of beta-blockers in 1995 has a very simple explanation: During the early 1990s neuroleptic-induced akathisia was a specific research target in our hospital. Therefore there appears to have been a special focus on this problem. This underscores the close connection between clinical practice and science.

In contrast to common practice in the U.S. (Citrome et al., 2000) only very few of our patients received valproate, lithium or carbamazepine in addition to their antipsychotic medication.

## 5. Conclusion

As hoped and hypothesized there was a clear indication that the trend towards antipsychotic monotherapy, lower doses and an increasing utilization of modern antipsychotics could be substantiated over the observation period, which is in accordance with current treatment guidelines and recommendations. Against our expectations we could not detect relevant differences with regard to the use of depot antipsychotics as well as the duration for which antipsychotics were prescribed before switching to alternative medication in the event of unsatisfactory response. The fairly high rate of polypharmacy must be seen in the context of the fact that available pharmacological treatments are still far from meeting all the needs of the management of this complex disorder.

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