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Patterns of Drug Prescription in a Psychiatric Outpatient Care Unit
The Issue Of Polypharmacy

Bernd R. Brüggemann, Hermann Elgeti, and Marc Ziegenbein

Department of Social Psychiatry and Psychotherapy, Hannover Medical School, Germany

Corresponding author: Dr. med. Bernd Rüdiger Brüggemann M.A., Department of Social Psychiatry and Psychotherapy, Hannover Medical School, Podbielskistr. 158, D-30177 Hannover, E-mail: Brueggemann.Bernd@MH-Hannover.de

Abstract

Background: In psychiatry, polypharmacy is more the rule than the exception. The present study investigates the frequency and type of polypharmacy in various diagnostic groups amongst patients of a psychiatric outpatient care unit. Methods: Patients' medical records were used to collect data on the last psychopharmacological medication prescribed in 2005 for all patients at the outpatient care unit (N = 429). Results: Patients with an initial diagnosis of schizophrenic psychosis were most frequently treated, followed by patients with affective disorders. 57 % of the patients received at least one psychotropic drug. 20 % of the patients received monotherapy and 36 % combination therapy. Patients with a schizophrenic psychosis most frequently received a combination therapy, followed by patients with affective disorders. Atypical anti-psychotic drugs were most often prescribed. The anti-psychotic drugs held the greater importance in the combination therapy. Conclusions: The chronic and severely ill patients in our sample represent a high-risk population for whom a polypharmacy of psychotropic substances might be advisable. When polypharmacy becomes necessary, it should only be administered according to evidence-based data. Due to the widespread use of polypharmacy in psychiatric care units, we are in urgent need of controlled studies further investigating combinations of substances (German J Psychiatry 2008:11: 1-6).

Keywords: Polypharmacy, drug interactions, psychotropic drugs

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Introduction

Current therapeutic guidelines of psychiatric professional societies recommend first implementing monotherapy for nearly all psychiatric disorders. Contrary to the recommendation only to administer one substance in the optimal dosage, clinicians frequently apply combination therapies, which often are substantiated by little or no scientific evidence. Stahl aptly described the discrepancy between the evidence-based recommendations and the actual practice in the treatment of schizophrenic disorders as "the dirty little secret" of psychiatry (Stahl, 1999).

In the treatment of patients with schizophrenic disorders, this discrepancy becomes particularly clear where combination therapy is the rule in clinical practice. Therapy may include combinations of several anti-psychotic drugs as well as the combination of anti-psychotics with psychotropic drugs from other drug classifications (including antidepressants, mood stabilizers, or anxiolytics/hypnotics) (Messer et al., 2006). In this regard, an increase has been observed in the use of combination treatment (Clark et al., 2002; Edlinger et al., 2005). Indeed, among therapy-resistant affective disorders, a growth in polypharmacy has also been noted (Frye et al., 2000). The frequency of polypharmacy increases with the length and severity of the illness (Linden et al., 2004). Despite insufficient scientific evidence, polypharmacy may be advisable once other options for therapy – such as psychotherapy, socioenvironmental therapy and complementary support – have been tried. This is especially true in the presence of comorbidity with an additional men-

tal disorder. On the other hand, problematic combinations, or combinations deemed irrational for theoretical reasons can be avoided based on drug interactions and side effects (Messer et al., 2006).

The present study investigates the frequency and type of polypharmacy in various diagnostic groups among patients at the psychiatric outpatient care unit of the Hanover Medical School (HMS) – a clientele, which has a high risk of polypharmacy due to the severity and chronic nature of their illnesses as well as the frequency of comorbidity.

Methods

The psychiatric outpatient care unit of the HMS provides the care for a region of Hanover, a catchment area of approximately 62,000 residents near the city centre. The team includes 17 staff members from five occupational groups and integrating two different care programmes: Initial contact and short-term crisis intervention take place at the social-psychiatric service of the policlinic. The psychiatric outpatient care unit carries out long-term, continuous, multidiscinplinary treatment programs.

Patients' medical records were used to collect data on the most recently prescribed psychopharmacological medication (antipsychotics, antidepressants, mood stabilizers, tranquilizers/hypnotics, anticholinergics/antiparkinsonian-drugs) in 2005 for all patients of the outpatient care unit (N = 429). Diagnosis were made according ot ICD-10 criteria. We could only take into account those medications prescribed by the psychiatric outpatient care unit. We did not collect data on drugs prescribed by other physicians treating the outpatients. Since the drug dose changed for many patients during the course of the study, we only conducted an assessment of the drug classes in the present study.

The descriptive and statistical analysis was conducted using SPSS 13.0. The independence of two values measured was checked for discrete or nominal characteristics using the Fisher's exact test (exact significance, 2-sided).

Results

In 2005, 429 patients were treated at the outpatient care unit. The average age was 47. The majority of patients were female (54 %). 18 % of the persons investigated lived in a therapeutic home. Patients were most frequently treated for an initial diagnosis of schizophrenic psychosis (ICD-10: F2) (50 %), followed by patients with affective disorders (17 %), personality disorders (14 %) and neurotic, stress, and somatoform disorders (12 %).

Table 1 shows the distribution of patients across the individual categories of the first diagnosis. Patients with a schizophrenic psychosis (ICD-10:F2) and those with affective disorders (ICD-10:F3) together comprised 67 % of the patients. These disorder groups also contained the highest percentage of patients who received a psychotropic drug. 75 % of the patients with a schizophrenic psychosis and 61 % of patients with an affective disorder were prescribed psychotropic drugs. The percentage of patients receiving combination therapies was 49 % in those with an F2 diagnosis and 38 % in patients with an affective disorder. The larger diagnostic groups F2, F3, F4 and F6 differed highly significantly both in terms of frequency of a prescribed psychotropic drug and in terms of combination therapy (Fisher's exact test, $p < 0.001$).

Table 1. Prescription of psychotropic drugs and percentage of combination therapy in the individual diagnostic groups in 2005

ICD-10 Code	Psychotropic drug(s) (%)	Polypharmacy (%)
F0 (n = 15)	4 (27 %)	2 (13 %)
F1 (n = 13)	1 (8 %)	0 (0 %)
F2 (n = 215)	162 (75 %)	106 (49 %)
F3 (n = 72)	44 (61 %)	27 (38 %)
F4 (n = 52)	14 (27 %)	9 (17 %)
F5 (n = 1)	0 (0 %)	0 (0 %)
F6 (n = 59)	18 (31 %)	12 (20 %)
F7 (n = 1)	0 (0 %)	0 (0 %)
F9 (n = 1)	0 (0 %)	0 (0 %)
F0-F9 (n = 429)	243 (57 %)	156 (36 %)

F0: organic, including symptomatic, mental disorders; F1: mental and behavioural disorders due to psychoactive substance use; F2: schizophrenia, schizotypal and delusional disorders; F3: mood (affective) disorders; F4: neurotic, stress-related and somatoform disorders; F5: behavioural syndromes associated with physiological disturbances and physical factors; F6: disorders of adult personality and behavioural; F7: mental retardation; F9: behavioural and emotional disorders with onset usually occurring in childhood and adolescence.

Table 2 shows the frequencies of prescription according to drug classes and Table 3 shows the score of various combination therapies. 57 % of the patients received at least one psychotropic drug. One fifth of the patients underwent monotherapy and 36 % combination therapy. Of those administered combination therapy, 18 % of the patients received two, 11 % three, 6 % four, 1 % five, 1 % six and one female patient 7 psychotropic drugs (including anticholinergics and antiparkinsonian drug treatment). Of the patients receiving psychotropic medication, 36 % were administered monotherapy and 64 % combination therapy. Most frequently, atypical antipsychotic drugs were prescribed (29 %), followed by low-potency antipsychotics (21 %) and anti-depressants (17 %). The medication usually was administered orally. 24 patients (6%) received a high-potency conventional antipsychotic drug and one patient received risperidone depot injections. The most frequent combinations were atypical antipsychotic drugs with low-potency antipsychotics (11 %), conventional high-potency antipsychotics with a low-potency antipsychotic drug (8 %) and an antidepressant with a low-potency antipsychotic drug (7 %). The combination of two medications from the same drug class was rare. 5 % of the patients received two anti-depressants, while 2 % received two atypical antipsychotic drugs and another 2 % two mood stabilizers.

Table 2. Frequency of prescription of psychotropic drugs from various drug classes

Drugs	Mean (n=429)	2005 (n=429)
Psychotropic drugs in total	1.2	57%
AD	0.2	17%
AP total	0.7	47%
AP low-potency	0.2	21%
AP high-potency typical	0.2	16%
AP high-potency typical depot neuroleptic	0.06	6%
AP atypical	0.3	29%
AP atypical – depot neuroleptic	0.002	0.2%
MS	0.2	14%
TQ	0.1	7%
AC	0.1	6%

AD, antidepressant
AP, antipsychotic
MS, mood stabilizer
TQ, tranquilizer/hypnotic
AC, anticholinergic/antiparkinsonian drug

Table 4 shows the scores of drug combinations for antipsychotic drugs, anti-depressants, mood stabilizers and tranquilizers. Tranquilizers and mood stabilizers were administered in over 90% of the cases as part of a combination therapy. The corresponding amount of anti-depressants was 77 % and 69 % for antipsychotics. For all drug classes, physicians preferred to prescribe additionally a (second) antipsychotic drug in the combination therapy.

Due to the large number of patients with schizophrenic psychosis in our sample and the significance of antipsychotic drugs established for combination treatments, we tested, according to the recommendations of Messer et al. (Messer et al., 2006), the extent to which the administered combination therapies involving antipsychotic drugs were appropriate, problematic, or irrational treatments (see Table 5). A combination can be labelled "appropriate" if an additive antipsychotic effect can be achieved or adverse effects can be reduced and the pharmacokinetic and pharmacodynamic interactions are tolerable. Nevertheless, also "appropriate" combinations may associated with drug interactions and can be dangerous in the individual case. Combinations can be labelled "problematic" if there is a potential of dangereous side effects (e. g. agranulocytosis or QT_C prolongation) – or a high risk of pharmacokinetic or pharmacodynamic interactions. Combinations maybe regarded as irrational, when the receptor profile is similar, adverse effects are seen more frequently or when there is no evidence for additional efficacy of the combination.

The majority of combination therapies involving antipsychotic drugs which we investigated were appropriate combinations at least. Merely one problematic combination (clozapine with carbamazepine) was discovered. Carbamazepine induces the liver enzyme CYP450 3A4, for which clozapine is a substrate. Therefore, the clozapine plasma level may decrease, which may result in worsening of psychotic symptoms. The carbamazepine plasma level itself can be increased, thus increasing the risk of side effects. Moreover, the risk of agranulocytosis and neuroleptic malignant syndrome increases.

One case of suspected "irrational combination" turned out to be the cross-tapering phase of moving from amisulpride to ziprasidone.

Table 3. Frequency of combination therapies involving two psychotropic drugs

Drugs	2005 (n=429)
Monotherapy	20%
Polypharmacy	36%
High-potency typical AP and low-potency AP	8%
High-potency typical AP and atypical AP	3%
High-potency typical AP and low-potency typical AP	0.2%
High-potency typical AP and AD	1%
High-potency typical AP and MS	3%
High-potency typical AP and AC	4%
High-potency typical AP and TQ	1%
Atypical AP and low-potency AP	11%
Atypical AP and atypical AP	2%
Atypical AP and AD	6%
Atypical AP and MS	6%
Atypical AP and AC	3%
Atypical AP and TQ	3%
AD and low-potency AP	7%
AD and AD	5%
AD and MS	5%
AD and AC	1%
AD and TQ	4%
Low-potency AP and low-potency AP	0.2%
Low-potency AP and MS	6%
AP low-potency and AC	4%
AP low-potency and TQ	4%
MS and MS	2%
MS and AC	2%
MS and TQ	2%
AC and AC	0.2%
AC and TQ	1%
TQ and TQ	1%

AD, antidepressant
AP, antipsychotic
MS, mood stabilizer
TQ, tranquilizer/hypnotic
AC, anticholinergic/antiparkinsonian drug

Table 4. Score of drug combinations according to drug groups in 2005

Drug Class	n Patients	Drug Combinations	Drugs Used for Coadministration			
			AP	AD	MS	TQ
AP	200	137 (69 %)	36 %	21 %	23 %	11 %
AD	74	57 (77 %)	57 %	27 %	28 %	22 %
MS	58	52 (90 %)	78 %	36 %	14 %	16 %
TQ	30	29 (97 %)	70 %	53 %	30 %	10 %

AP; antipsychotic; AD, antidepressant; MS, mood stabilizer; TQ; tranquilizer/hypnotic

Discussion

Despite unsatisfactory evidence, polypharmacy is common practice in psychiatry. Doubtlessly the possibilities of monotherapy should first be exhausted. A single drug should be administered in sufficient dosage over a sufficiently long period of time, and the patient's compliance should be encouraged and, as necessary, monitored by determining the serum plasma levels. When polypharmacy becomes necessary, it should, whenever possible, be implemented according to evidence-based data or at least rational considerations with regard to pharmacokinetic and pharmacodynamic interactions. The large number of drugs available for treatment can make it difficult for physicians to maintain in-depth knowledge of all drug interactions, therefore they should rely on appropriate medical databases. For adequate pharmacological treatment, it is of utmost importance that the type, dose and length of treatment is documented in correlation to the clinical changes. Even increased awareness of the problem of polypharmacy and corresponding educational programmes can help reduce the practise (Alexander et al., 1983; Patrick et al., 2006; Schroeder et al., 1979).

The frequency of polypharmacy has been investigated both in outpatients (Brunot et al., 2002; Clark et al., 2002; de las Cuevas and Sanz, 2004; Leslie and Rosenheck, 2001; Segal et al., 1992; Tapp et al., 2003) and inpatients (Ereshefsky, 1999; Ito et al., 1999; Kiivet et al., 1995; Rittmannsberger et al., 1999; Schumacher et al., 2003). These studies generally focused on the combination of antipsychotics in patients with schizophrenic disorders. The combination with low-potency antipsychotics and with medications from other drug classes has largely been disregarded. In their review article, Messer et al. find that 40-50 % of schizophrenic patients requiring inpatient treatment and 15 - 25 % of the outpatients receive an antipsychotic combination therapy (Messer et al., 2006).

A study investigated the prescription of antipsychotic drugs and co-medications in an Australian community psychiatric service in the year 1998 bearing a close resemblance in structure to our outpatient care unit (Keks et al., 1999). Of the 859 patients included in the study, 77% received an antipsychotic medication. The percentage of atypical antipsychotic drugs was 53 %. Patients who were administered a conventional antipsychotic drug, received it in 66 % of the cases as a depot antipsychotic. 13 % received a combination therapy of antipsychotics, most frequently including a combination of an atypical with a conventional antipsychotic in 8% of the cases. Investigations into the patterns of drug prescription in psychiatric outpatient care units in the German-speaking world do not exist as far as we know.

A large portion of the patients we treated received psychopharmacological medication. When psychopharmacological drugs were prescribed, they mostly were part of a combination therapy. The frequency of combination therapy differed between the diagnostic groups and most often occurred in patients with a schizophrenic psychosis and those suffering from an affective disorder. In our sample, antipsychotics were preferentially prescribed, which is explained by the distribution of patients across the diagnostic categories. Atypical antipsychotics were prescribed considerably more frequently than conventional antipsychotics – the proportion roughly being 2:1. In comparison with the cited Australian study, where the proportion was approximately 1:1, one must take into consideration changes to the guidelines that took place between 1998 and 2005 and their effect on the patterns of prescribing antipsychotic therapy. Among antipsychotics, administered in depot form, the conventional antipsychotics clearly dominated. This is due to the fact that a large part of the patients receiving the depot drug had been

Table 5. Appropriate, problematic and irrational combination therapies of antipsychotics in the entire sample (N = 429)

Possibly appropriate combinations	Number
Clozapine + amisulpride	7
Clozapine + risperidone	0
Clozapine + aripiprazole	0
Clozapine + lamotrigine	0
Clozapine + ziprasidone	0
Olanzapine + risperidone	1
Olanzapine + aripiprazole	0
Olanzapine + amisulpride	1
Atypical + typical high-potency antipsychotic	11
Atypical antipsychotic+ low-potency antipsychotic	46
Typical antipsychotic + low-potency antipsychotic	32
Problematic combinations	
Clozapine + fluvoxamine	0
Clozapine + carbamazepine	1
Irrational combinations	
Clozapine + olanzapine	0
Clozapine + quetiapine	0
Olanzapine + quetiapine	0
Amisulpride + ziprasidone	1 (cross-tapering phase)

taking it for many years, were well-adjusted to it and tolerated it well.

In drug combinations antipsychotics played a special role. When physicians prescribed an antidepressant, mood stabilizer, tranquilizer/hypnotic or antipsychotic drug, an antipsychotic was the most frequent combination partner. The combination of an atypical antipsychotic with a high-potency conventional antipsychotic or another atypical antipsychotic can be advisable in the presence of therapy resistance in monotherapy or to reduce side effects of a high-dose monotherapy. In these cases, pharmacokinetic and pharmacodynamic interactions must be taken into account (Messer et al., 2006). Among the atypical and conventional antipsychotics and in the antidepressants we frequently found a combination therapy with low-potency antipsychotics that were administered, depending on the diagnostic category, as a co-medication soporific drug or sedative. Anti-depressants can be usefully combined with antipsychotics in the presence of a schizo-affective disorder or comorbidity of a depressive disorder with a schizophrenic psychosis. Furthermore, this combination can become necessary in depressive episodes with psychotic symptoms. The combination of antipsychotics with mood stabilizers usually is prescribed in bipolar affective or schizo-affective disorders and can be advisable in the context of therapy-resistant schizophrenic disorders. Mood stabilizers and tranquilizers were almost always prescribed as co-medication in our sample in combination with an additional psychotropic drug.

If combination of psychotropic drugs is necessary, possible drug interactions and potential adverse effects like induction or inhibition of CYP450 enzymes, CNS depression, risk of heart arrhythmias, anticholinergic effects etc. has to take into account. To check potential drug interactions we refer to helpful data bases in the world wide web.

Besides the above-mentioned dual combinations, 19% of the patients in our sample received three or more psychotropic drugs (including anticholinergics and antiparkinsonian drug treatment). As the number of prescribed psychotropic drugs increases, the pharmacokinetic and dynamic interactions grow more complex and the danger of sometimes hazardous side effects increases as well. Furthermore, the interactions with medications that have been prescribed due to somatic comorbidity must also be taken into account. In addition to rational therapy considerations, other reasons can also lead to polypharmacy. In some instances a combination therapy is maintained when the transition phase from one medication to another shows improvement and this improvement is not clearly attributable to the new medication or the combination thereof. Moreover, initial combination therapies that were necessary due to an exacerbation of a psychological disorder during inpatient care may be continued in outpatient care. To some extent this might be connected to irrational fears on the part of the attending physician and patients concerned that a change in medication could lead to a relapse. The magnitude of polypharmacy in our study can also be explained in part by the fact that the chronically and severely ill patients treated in our outpatient care unit belong to a high-risk population due to therapy resistance and comorbidities, and for whom a polypharmacy of psychotropic substances may be advisable.

Due to the widespread use of polypharmacy in psychiatry, further investigations into drug combinations within the framework of controlled studies are urgently needed in the future.

Conclusion

When polypharmacy becomes necessary, it should only be administered, whenever possible, according to evidence-based data or at least after a good deal of rational considerations given to the pharmacokinetic and dynamic interactions. In order to carry out adequate psychotropic drug therapy, the documentation of the type, dose and duration of the medication in correlation to the clinical changes are of crucial importance. Due to the widespread use of polypharmacy in psychiatric care units, we are in urgent need of controlled studies further investigating combinations of substances.

References

Alexander B, Nasrallah HA, Perry PJ, Liskow BI, Dunner FJ. The impact of psychopharmacology education on prescribing practices. Hosp Community Psychiatry 1983;34:1150-1153

Brunot A, Lachaux B, Sontag H, Casadebaig F, Philippe A, Rouillon F, Clery-Melin P, Hergueta T, Llorca PM, Moreaudefarges T, Guillon P, Lebrun T. [Pharmacoepidemiological study on antipsychotic drug prescription in French Psychiatry: Patient characteristics, antipsychotic treatment, and care management for schizophrenia]. [French]. Encephale 2002;28:129-138

Clark RE, Bartels SJ, Mellmann T.A., Peacock WJ. Recent trends in antipsychotic combination therapy of schizophrenia and schizoaffective disorder: implications for state mental health policy. Schizophr Bull 2002;28:75-84

de las Cuevas C, Sanz EJ. Polypharmacy in psychiatric practice in the Canary Islands. BMC Psychiatry 2004;4:18

Edlinger M, Hausmann A, Kemmler G, Kurz M, Kurzthaler I, Walch T, Walpoth M, Fleischhacker WW. Trends in the pharmacological treatment of patients with schizophrenia over a 12 year observation period. Schizophr Res 2005;77:25-34

Ereshefsky L. Pharmacologic and pharmacokinetic considerations in choosing an antipsychotic. J Clin Psychiatry 1999;60 Suppl 10:20-30

Frye MA, Ketter TA, Leverich GS, Huggins T, Lantz C, Denicoff KD, Post RM. The increasing use of polypharmacotherapy for refractory mood disorders: 22 years of study. J Clin Psychiatry 2000;61:9-15

Ito C, Kubota Y, Sato MA. A prospective survey on drug choice for prescriptions for admitted patients with schizophrenia. Psychiatry Clin Neurosci 1999;53 Suppl:S40

Keks NA, Altson K, Hope J, Krapivensky N, Culhane C, Tanaghow A, Doherty P, Bootle A. Use of antipsychosis and adjunctive medications by an inner urban

community psychiatric service. Aust N Z J Psychiatry 1999;33:896-901

Kiivet RA, Llerena A, Dahl ML, Rootslane L, Sanchez VJ, Eklundh T, Sjoqvist F. Patterns of drug treatment of schizophrenic patients in Estonia, Spain and Sweden. Br J Clin Pharmacology 1995;40:467-476

Leslie DL, Rosenheck RA. Use of pharmacy data to assess quality of pharmacotherapy for schizophrenia in a national health care system: individual and facility predictors. Med Care 2001;39:923-933

Linden M, Scheel T, Xaver EF. Dosage finding and outcome in the treatment of schizophrenic inpatients with amisulpride. Results of a drug utilization observation study. Hum Psychopharmacol 2004;19:119

Messer T, Tiltscher C, Schmauss M. Polypharmacy in the treatment of schizophrenia [German]. Fortschr Neurol Psychiat 2006;74:377-391

Patrick V, Schleifer SJ, Nurenberg JR, Gill KJ. Best practices: An initiative to curtail the use of antipsychotic polypharmacy in a state psychiatric hospital. Psychiatr Serv 2006;57:21-23

Rittmannsberger H, Meise U, Schauflinger K, Horvath E, Donat H, Hinterhuber H. Polypharmacy in psychiatric treatment. Patterns of psychotropic drug use in Austrian psychiatric clinics. Eur Psychiatry 1999;14:33-40

Schroeder NH, Caffey EM, Jr., Lorei TW. Antipsychotic drugs: can education change prescribing practices? J Clin Psychiatry 1979;40:186-189

Schumacher JE, Makela EH, Griffin HR. Multiple antipsychotic medication prescribing patterns. Ann Pharmacother 2003;37:951-955

Segal SP, Cohen D, Marder SR. Neuroleptic medication and prescription practices with sheltered-care residents: a 12-year perspective. Am J Public Health 1992;82:846-852

Stahl SM. Antipsychotic polypharmacy, Part 1: Therapeutic option or dirty little secret? J Clin Psychiatry 1999;60:425-426

Tapp A, Wood AE, Secrest L, Cubberley L, Kilzieh N. Combination antipsychotic therapy in clinical practice. Psychiatr Serv 2003;54:55-59