Concurrent use of more than one major psychotropic drug (polypsychopharmacy) in out-patients—a prescription database study

J.-U. ROSHOLM, J. HALLAS & L. F. GRAM

Department of Clinical Pharmacology, Institute of Medical Biology, Odense University, DK-5000 Odense C, Denmark

- 1 In order to assess the prevalence of concurrent use of more than one major psychotropic drug (polypsychopharmacy) in out-patients, a prescription database study was conducted in the Odense area for a period of 2 years.
- 2 During the index period 5.12% of the inhabitants purchased major psychotropic drugs. Of these, 14% had a period of polypsychopharmacy recorded. The age-specific prevalence of users increased with age, the prevalence for over 90 years of age was 18%. Sixty-seven per cent of the psychotropic drug users were women.
- 3 For neuroleptic and antidepressant users, about 20% were subject to polypsychopharmacy, for lithium 61%. The most prevalent combination was neuroleptics-neuroleptics. In none of the 10 most prevalent combinations were the mean daily doses significantly lower on polypsychopharmacy compared with single drug regimens, in two they were higher.
- 4 Polypsychopharmacy with psychotropic drugs was frequent in out-patients. In polypsychopharmacy daily doses were not lowered in order to limit side effects.

Keywords psychotropic drugs polypsychopharmacy interactions
prescription database

Introduction

Polypsychopharmacy may be defined as the simultaneous use of two or more psychotropic drugs [1].

Polypsychopharmacy may be problematic since the treatment is more complicated to control and side effects and interactions may occur [2–17] (Table 1). In addition, the scientific rationale for polypsychopharmacy is often uncertain. In a review, Hemminki found that in only 3 of 14 studies had there been a better effect of polypsychopharmacy than on a single drug regimen [3]. However, polypsychopharmacy may be used for complicated patients where the aim is better treatment with smaller doses and fewer side effects [3].

A previous Danish study has shown that about 30% of the patients prescribed psychotropic drugs in general practice received two or more psychotropic drugs concomitantly [18]. Similarly, several other studies have shown that polypsychopharmacy is widespread in psychiatric hospitals and in the elderly [2, 3, 19].

The aim of this prescription database study was to

describe polypsychopharmacy outside hospitals, and to compare polypsychopharmacy patients with patients on single drug regimen. The study base was the Odense-area in Denmark (210 000 inhabitants) for a period of 24 months. To our knowledge, no previous polypsychopharmacy survey has covered a study base of similar size.

Methods

The setting for this study has been described in detail elsewhere [20].

Briefly, in Denmark, all out-patient users of antidepressants, lithium, and neuroleptics receive a subsidy from the National Health Insurance System (Sygesikringen). Reports on this subsidy are transferred from the pharmacy to the National Health Insurance by way of a computer system. Since October 1990, these computerized prescription reports from

Table 1 Drug-drug interactions with psychotropic drugs in various references (numbers in brackets)

<i>Psychotropic drugs</i>	<i>Psychotropic drugs</i>			
	<i>Tri- and tetracyclic antidepressants (TCA)</i>	<i>Selective serotonin reuptake inhibitors (SSRI)</i>	<i>MAO-inhibitors (MAOI)</i>	<i>Lithium</i>
Neuroleptics	Neuroleptics inhibit TCA-metabolism (CYP2D6) [4]. Additive cardiotoxicity (overdose) [5]	Possible mutual inhibition of metabolism (CYP2D6) [11]	Blood pressure fall [15], increased parkinsonism [16]	Neurotoxic syndrome [17]
Lithium	Lithium potentiates antidepressant effect [6]	Possible pharmacodynamic or kinetic interactions [12]	?	
MAO-inhibitors (MAOI)	Classical MAOI: toxic CNS and cardiovascular reactions [6]. Moclobemide: possible inhibition of TCA-metabolism (CYP2D6) [7]. 'Serotonin syndrome' [8].	'Serotonin syndrome' [13, 14]		
Selective serotonin reuptake inhibitors (SSRI)	Several SSRI inhibit TCA-metabolism (CYP2D6) [9, 10].			

Odense, (210 000 inhabitants, mainly urban) have been collected in the Odense PharmacoEpidemiologic Database (OPED). From these data, the *individual* drug history of a cohort of patients can be constructed. The single patient's daily dose can be estimated for patients who have presented more than one prescription on the same drug during the index period by the following equation:

$$\text{Dose} = \frac{A}{t} \cdot \frac{N-1}{N}$$

where A = total amount of psychotropic drug purchased; t = time span from first to last prescription; N = number of prescriptions presented.

The indications of the treatment are not transferred by the above described administrative procedures and are thus not recorded in the database.

The data for this study consisted of all recorded major psychotropic drug purchases by citizens in Odense in 1991 and 1992. Major psychotropic drugs are neuroleptics, antidepressants and lithium. Hypnotics and anxiolytics were not recorded since no subsidy is given to these drugs. The drugs were divided into five groups, according to their pharmacological properties: neuroleptics, lithium, monoamineoxidase-inhibitors (MAO-inhibitors), tri/tetracyclic antidepressants, and selective serotonin reuptake inhibitors.

The assumption that a patient was subject to polypsychopharmacy relied on certain criteria of prescription timing. We defined polypharmacy as (Figure 1):

1. Simultaneous purchase of two different drugs, or
2. One drug purchased between two purchase dates of another drug.

If both drugs were purchased more than once, a *period* of polypsychopharmacy could be defined. The purchase dates defined a period of usage for each drug. We defined the polypsychopharmacy period simply as the overlapping interval of these periods of usage.

Figure 1 Definition of polypharmacy and comparison with single drug regimen. Each circle represents a patient.

Only one polypsychopharmacy period was recorded for each patient. In case of more than one polypsychopharmacy period, we chose the one with the largest number of drugs included (1st priority). In case of several periods with an equal number of drugs, we chose the longest (2nd priority).

Statistical method used was Mann-Whitney with a significance level of 0.05. Ninety-five per cent confidence intervals (CI) for prevalences were calculated by using the Poisson distribution, corresponding to the number which the estimate was based on.

Results

A total of 10 738 patients presented prescriptions on psychotropic drugs during the 24 month index period, corresponding to 5.12% (CI:5.02–5.22%) of the total population in the Odense-area. For 1522 patients (14%), a polypsychopharmacy period was recorded (Table 2), corresponding to 0.73% (CI:0.69–0.76%) of the total population. Among these 1030 patients only received the psychotropic drugs in combination whereas 482 patients had other drugs recorded before

Table 2 Number of patients and number of drugs given per patients during the index period of 24 months

Number of drugs	As single drug regimen Number of patients	In polypharmacy-combinations only Number of patients	As polypharmacy	
			In polypharmacy-combination plus single drug regimen before/after polypharmacy Number of patients	Total Number of patients
1	8051			8051
2	930	916		1846
3	194	104	259	557
4	33	10	140	183
5	7	0	52	59
6	0	0	29	29
7	1	0	8	9
8	0	0	2	2
9	0	0	2	2
Total	9216	1030	492	10 738

or after the period of polypharmacy. The largest number of drugs recorded in polypsychopharmacy combination for a single patient was 7 (one patient) and 5 (two patients). Besides the drugs in combination, these patients had used major psychotropic drugs before or after the period of polypharmacy. Sixty-five per cent of all the users took neuroleptics, and 40% tri/tetracyclic antidepressants (Table 3). Of all the patients taking neuroleptics, only 3% used depot.

The female patients constituted 67% of all the users. The age specific period prevalence of psychotropic drug users is shown in Figure 2. Among citizens of 90 years of age or more, 18% were given major psychotropic drugs. The patients on single drug regimen were the same age as polypsychopharmacy patients (median age 58 years (interquartile range 43–72) vs 56 (43–69)).

The most prevalent types of combinations were neuroleptics-neuroleptics (599 patients), neuroleptics-tri/tetracyclic antidepressants (373 patients) and tri/tetracyclic antidepressants-tri/tetracyclic antidepressants (107 patients).

About 20% of all the patients in each drug group were given polypsychopharmacy, except for lithium users, 61% of whom used other major psychotropic drugs (Table 3). Of 599 patients taking a combination of two neuroleptics, 92 patients (15%) were given a high potency plus a low potency neuroleptic.

The 10 most prevalent combinations of specific drugs can be seen in Table 4. The mean daily doses used in two of these combinations (levomepromazine/perphenazine and levomepromazine/zuclopentixol) were significantly higher than the doses given in single drug regimen, and in no case were they lower (Table 4).

Discussion

The indications of the treatment are not recorded in the database, and thus the reasons for prescribing the

drugs studied cannot be evaluated. Nevertheless, a quantitative study like the present may contribute to the identifications of problems for further, more qualitative studies. Purchase of a drug does not unconditionally mean that the drug has been ingested, and non-compliance is widespread in psychiatric patients [21]. However, the observed repeated purchases of drugs by many of the patients in this study, are an indication that the drugs were actually ingested by the patients [20]. As only one polypharmacy or single drug regimen period was recorded for each patient, some data were excluded. Therefore the figures given may underestimate actual drug consumption.

The proportion of the psychotropic drug users on polypsychopharmacy (14%) was substantially lower than found in previous studies [2, 3, 18, 22]. This is most likely a consequence of not recording prescriptions on anxiolytics and hypnotics, which are by far the most used psychotropic drugs in general [23] and

Figure 2 Age-specific prevalence of patients on a single drug regimen (▨) and on polypsychopharmacy (▧) with psychotropic drugs. Twenty-four months index period.

Table 3 Number of patients given psychotropic drugs and polypharmacy in the various drug groups

Psychotropic drug group	All users of the drug Patients	Polypharmacy with drugs from the same group Patients/%*	Polypharmacy with one drug from another drug Patients/%*	Polypharmacy with two or more drugs from other drug groups Patients/%*	All polypharmacy Patients/%*
Neuroleptics	6983	599 8.6	427 6.1	255 3.7	1281 18.3
Lithium	310	0 0	95 30.6	95 30.6	190 61.3
MAO-inhibitors	363	0 0	25 6.9	41 11.3	66 18.2
Tri/tetracyclic antidepressants	4275	107 2.5	462 10.8	303 7.1	872 20.4
Selective serotonin reuptake inhibitors	853	2 0.2	77 9.0	88 10.3	167 19.6

*Percentage of all users of the drug group.

in combination [22, 24]. However it seems likely that the more severe drug-drug interaction problems would relate to the combination of the major psychotropic drugs.

Some psychotropic drug combinations may have a well defined indication [3], but for many polypsychopharmacy combinations, the rationale is probably uncertain. Several reasons for polypsychopharmacy have been suggested: when a new drug is given to the patient, the drug already given is not discontinued [25]; the patient does not understand the limitations of drugs therapy [25], and polypsychopharmacy is a kind of ritual making him or her feel secure [26]. Polypsychopharmacy could also result from therapeutic failure with single drug regimen.

The frequent concurrent use of two neuroleptics is surprising. There may be a rationale for combining low- and high-potency neuroleptics, but only 15% of concurrent users were prescribed such a combination.

Our setting did not allow investigation of the possible occurrence of clinically significant interactions. However, several of the drug combinations that may carry a risk of interaction (Table 1) were recorded. In 93 patients, neuroleptics and lithium were given concomitantly, and in 641 patients neuroleptics and tricyclic antidepressants were combined.

Lithium is more often used in combinations than any of the other drugs in this study. This is in

accordance with its use in long-term maintenance treatment for affective disorders, where the treatment is often combined with other psychotropic drugs either permanently or when the patient has a relapse of the disease [6].

One of the arguments for polypsychopharmacy is that lower doses of the drugs can be given [3]. This was not reflected when the daily doses given in polypsychopharmacy were compared with the daily dose given in single drug regimens. On the contrary, for some combinations, the doses given in polypsychopharmacy were significantly higher, perhaps suggesting that patients on polypsychopharmacy were more seriously ill and treatment-resistant. On the other hand, the two combinations in question both involved a combination of a high- as well as a medium-potency neuroleptic, a combination without any rationale.

In conclusion, we found that combinations of major psychotropic drugs are widespread. The scientific and clinical rationale for the use of these combinations in terms of efficacy and safety is often insufficient, and more cautious use of these drug combinations seems to be desirable.

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Table 4 Estimated median daily dose for the 10 used combinations of psychotropic drugs compared with daily dose where only one drug was given. Doses were only estimated for patients who presented more than one prescription during the index period

<i>Levomepromazine</i>	<i>Polypharmacy</i>		<i>Single drug regimen</i>		<i>P value†</i>
	<i>Median daily dose (mg)</i>	<i>Patients</i>	<i>Median daily dose (mg)</i>	<i>Patients</i>	
Perphenazine	7.8	26	8.7	351	0.850
Nortriptyline	51		62	598	0.697
Lithium*	16	23	18	120	0.411
Nortriptyline	66		62	598	0.057
Levomepromazine	18	22	12	712	0.120
Flupentixol	1.0		0.8	624	0.057
Levomepromazine	39	21	12	712	0.00008
Perphenazine	27.9		8.7	351	0.00012
Levomepromazine	18	20	12	712	0.391
Amitriptyline	64		46	540	0.218
Levomepromazine	21	18	12	712	0.00001
Zuclopentixol	32		4	256	<0.00001
Levomepromazine	30	16	12	712	0.054
Nortriptyline	76		62	598	0.136
Levomepromazine	24	15	12	712	0.068
Clomipramine	40		41	327	0.819
Flupentixol	0.8	10	0.8	624	0.651
Nortriptyline	41		62	598	0.241
Perphenazine	6	10	8.7	351	0.405
Amitriptyline	49		35	540	0.119

*Dose in mmol.

†Mann-Whitney test.

References

- 1 Gardos G, Perenyi A, Cole JO. Polypharmacy revisited. *McLean Hosp J* 1980; **V**: 178–195.
- 2 Laska E, Siegel C, Simpson G. Automated review system for orders of psychotropic drugs. *Arch Gen Psychiatry* 1980; **37**: 824–827.
- 3 Hemminki E. Polypharmacy among psychiatric patients. *Acta psychiat Scand* 1977; **56**: 347–356.
- 4 Brøsen K, Gram LF. Clinical significance of the sparteine/debrisoquine oxidation polymorphism. *Eur J clin Pharmac* 1989; **36**: 537–547.
- 5 Wilens TE, Stern TA, O'Gara PT. Adverse cardiac effects of combined neuroleptic ingestion of tricyclic antidepressant overdose. *J clin Psychopharmac* 1990; **10**: 51–54.
- 6 Baldessarini RJ. Drugs and the treatment of psychiatric disorder. In *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, Eighth Edition, eds Goodman Gilman A, Rall TW, Nies AS, Taylor P. New York: Pergamon Press, 1990.
- 7 Gram LF, Brøsen K. Danish University Antidepressant Group. Moclobemide treatment causes substantial rise in the sparteine metabolic ratio. *Br J clin Pharmac* 1993; **35**: 649–652.
- 8 Spigset O, Mjörndal T, Löveheim O. Serotonin syndrome caused by a moclobamide-clomipramine interaction. *Br med J* 1993; **306**: 248.
- 9 Brøsen K, Hansen JG, Nielsen KK, Sindrup SH, Gram LF. Inhibition by paroxetine of desipramine metabolism in extensive but not in poor metabolizers of sparteine. *Eur J Clin Pharmacol* 1993; **44**: 349–355.
- 10 Vaughan DA. Interaction of fluoxetine with tricyclic antidepressants. *Am J Psychiatry* 1988; **145**: 1478.
- 11 Goff DC, Midha KK, Brotman AW, Waites M, Baldessarini RJ. Elevation of plasma concentrations of haloperidol after the addition of fluoxetine. *Am J Psychiatry* 1991; **148**: 790–792.
- 12 Hadley A, Cason MP. Mania resulting from lithium-fluoxetine combination. *Am J Psychiatry* 1989; **146**: 1637–1638.
- 13 Feighner JP, Boyer WF, Tyler DL, Neborsky RJ. Adverse consequences of fluoxetine-MAOI combination therapy. *J clin Psychiatry* 1990; **51**: 222–225.
- 14 Steiner W, Fontaine R. Toxic reaction following the combined administration of fluoxetine and L-tryptophan: five case reports. *Biol Psychiatry* 1986; **21**: 1067–1071.
- 15 Watsky EJ, Salzman C. Psychotropic drug interactions. *Hospital and Community Psychiatry* 1991; **3**: 247–256.
- 16 Hansten P, John JR. *Drug interactions*. Sixth Edition. Philadelphia, London: Lea & Febiger, 1989; pp 342.
- 17 Goff DC, Baldessarini RJ. Drug interactions with anti-psychotic agents. *J clin Psychopharmac* 1993; **13**: 57–67.
- 18 Holm M, Olesen F. Psykofarmakaordination i almen praksis (Prescribing of psychotropic drugs in general practice). *Ugeskr Læger* 1989; **151**: 2122–2126.
- 19 Tyrer P. Drug treatment of psychiatric patients in general practice. *Br med J* 1978; **2**: 1008–1010.
- 20 Rosholm JU, Hallas J, Gram LF. Outpatient utilization of antidepressants—a prescription database analysis. *J affective Disorders* 1993; **27**: 21–28.
- 21 Haynes RB. Determinants of compliance: the disease and the mechanics of treatment. In *Compliance in health care* eds, Haynes RB, Taylor DW, Sackett DL. Baltimore & London: Johns Hopkins University Press, 1979.
- 22 Bergman U, Dahlström M, Gunnarson C, Westerholm B. Why are psychotropic drugs prescribed to outpatients? *Eur J clin Pharmac* 1979; **15**: 249–256.
- 23 Dansk Lægemiddelstatistik. Lægemiddelforbruget i Danmark 1991 (The consumption of drugs in Denmark 1991). København, 1991.
- 24 Salzman C. Psychotropic drug use and polypharmacy in a general hospital. *General Hospital Psychiatry* 1981; **3**: 1–9.
- 25 Rapp MS, Kaplan A. Polypharmacy revisited. *Can J Psychiatry* 1981; **26**: 569–573.
- 26 Sturges S, Brown M. Polypharmacy. *Bull-Meninge-Clin*. 1975; **39**: 274–279.

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