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Patterns of drug treatment of schizophrenic patients in Estonia, Spain and Sweden

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1 Patterns of drug treatment and the use of polypharmacy in schizophrenic in-patients were compared and evaluated in the University Teaching Hospitals of Psychiatry in Badajoz, Spain, Huddinge, Sweden, and Tartu, Estonia.

2 The medical records of up to 100 consecutively admitted patients were retrospectively reviewed using a standardized data form.

3 The male patients were significantly younger than females in all study locations, but there were no age differences between the locations. The length of stay was equal for the two series in the same hospital, but considerably longer in Tartu than in Badajoz and Huddinge.

4 The neuroleptic drugs used most commonly in Badajoz and Tartu were similar in prescription frequency and in the doses prescribed, but different from those used in Huddinge. Haloperidol was the most frequently prescribed neuroleptic in Badajoz and Tartu, accounting for one third of all neuroleptic prescriptions. In Huddinge the choice of neuroleptics was more evenly spread over several compounds. Intramuscular injections other than depot preparations were commonly used in Tartu and Badajoz, but not in Huddinge.

5 At least two neuroleptics were prescribed simultaneously on 73% of treatment days in Badajoz and 46% in both Huddinge and Tartu. The average cumulative daily doses of concomitant multiple neuroleptic treatment, expressed in chlorpromazine equivalents, were lower in Huddinge than in the other study locations and higher for male patients in Badajoz and Tartu.

6 Anticholinergics were used together with neuroleptics in 42% of treatment days in Badajoz and 30% in Huddinge as compared with 75% in Tartu. The use of anticholinergics increased in parallel to the increase in the number and the cumulative dose of concomitant neuroleptics in all study locations.

7 About 15% of patients in Badajoz and Tartu, but only 1% in Huddinge, received concomitant treatment with antidepressant drugs. The simultaneous use of antidepressants and benzodiazepines was inversely related to the number and the cumulative dose of neuroleptics in Badajoz and Tartu. In contrast, the cumulative dose and number of neuroleptics were greater, when additional benzodiazepines were prescribed in Huddinge.

8 The study in schizophrenic in-patients revealed that polypharmacy with concomitant multiple neuroleptics, additional anticholinergics and other psychotropics is an international phenomenon.

Keywords drug utilization schizophrenia in-patients neuroleptics

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Introduction

Growing concern about the excessive use of psychotropic drugs has stimulated studies revealing polypharmacy and irrational prescribing both in general practice [1] and in psychiatric hospitals [2–5]. Most of these studies have included psychiatric patients independent of diagnosis and provide little information on prevailing treatment strategies of specific psychiatric disorders. Among studies in more homogenous patient groups, the patterns of drug treatment of schizophrenia have been reviewed in several papers [3, 6–9]. Widespread and unsystematic polypharmacy as well as the use of megadoses of neuroleptics have been reported [10, 11].

We have previously observed threefold international differences in the use of antipsychotic and antidepressant drugs between Estonia, Spain and the Nordic countries [12, 13]. These studies were based on national sales data and the defined daily doses methodology [14], and thus the results may be influenced by differences in the doses actually used in psychotic and depressed patients, and/or by the use of psychotropic drugs on other indications. This investigation was aimed to provide a qualitative and quantitative description of the use of neuroleptic drugs in schizophrenic patients in three psychiatric university clinics, in Estonia, Spain and Sweden. Schizophrenia was chosen for diagnosis, because the incidence of schizophrenia has been found to be similar across different cultures and countries with different socioeconomic backgrounds [15, 16]. Special emphasis was paid to estimate the cumulative prescribed daily doses of antipsychotics, the variation in the doses used, and the extent of polypharmacy.

Methods

The data were collected from the psychiatric units of in-patient care, serving a defined population in the corresponding catchment area: the Psychiatry Departments of the University Hospitals of Extremadura (Badajoz and Merida, Spain), the Department of Psychiatry I, Huddinge University Hospital (Huddinge, Sweden), and the Tartu University Psychiatry Clinic (Tartu, Estonia). The study received prior approval from the local University Ethics Committees.

Study population and data collection from medical records

The medical records of 50 male and 50 female consecutive (by admission date) schizophrenic patients were selected retrospectively at each centre. Basic demographic information, clinical and drug treatment data were retrieved from the records for subsequent analysis.

The patients were selected according to the following inclusion criteria:
(a) age 18–69 years;
(b) admission to hospital after February 1, 1992, and discharge from hospital before December 31, 1992;
(c) diagnosis of schizophrenia upon discharge (based on the 9th version of the International Classification of Diseases, ICD-9);
(d) the length of stay of at least 7 days, but less than 4 months (120 days).

The medical records were excluded from analysis, if:
(a) the demographic, medical or drug treatment data were incomplete;
(b) the patient had some concurrent serious somatic disease (hepatic or renal, epilepsy) or the patient had received electro-convulsive therapy, which could affect the choice of drug and/or dosage;
(c) the patient was treated as in-patient one month (30 days) before or after the first eligible admission;
(d) the patient was sent to another in-patient institution upon discharge from the psychiatric unit.

The rationale for these criteria was to study patients, in whom the hospital treatment (including drug therapy) could be judged to be effective, as the patients were able to live in a community for at least 1 month before and after discharge, and at the same time, to exclude most patients, who were repeatedly hospitalized for social reasons.

Calculation of prescribed daily doses

The prescribed daily dose (PDD) for a drug was defined as the daily dose of a drug formulation (oral, i.m. injection, or depot injection), calculated separately for each treatment day of an individual patient, who was treated with this particular drug formulation for at least three consecutive days (irrespective of the dose). Different formulations of the same drug were separated, because of lower bioavailability of neuroleptics after oral administration. The PDD of a depot formulation was calculated by dividing the given dose by the number of days until the next depot injection, or by 30, in the case that depot injection was no more prescribed. The first 3 days after the first depot injection were omitted from the calculations, as was the whole depot injection, if it was performed in 3 days prior to discharge. The average PDD for a study location was calculated, if a drug formulation was prescribed to more than six patients.

Polypharmacy

For each treatment day, all psychotropic drugs prescribed to every patient were counted, independent of the dose and separating different formulations of the same substance. Thus a number, expressing the sum of concomitant prescriptions (including concomitant neuroleptics) for each treatment day was obtained. Subsequently, all treatment days for all study patients were divided into subgroups according to the number and combination of different prescriptions of psychotropic drugs, and analysed for differences in prevalence among the three study locations. The prevalence of polypharmacy was expressed as the percentage of the total number of treatment days, during which one or more neuroleptics (or different formulations of one drug)

were used at the same time in the same patient. In this study, simultaneous treatment of one neuroleptic together with an antidepressant, an anticholinergic drug, a benzodiazepine or another neuroleptic was defined to be present, if it occurred on at least 3 consecutive treatment days.

Cumulative daily doses of neuroleptics

The prescribed daily doses of neuroleptics were converted to an estimated equivalent amount of chlorpromazine on the basis of potency ratios, suggested by previous reviewers based on controlled clinical studies [17, 18], and enlisted in Table 4. It has been shown [17], that the criteria used for estimation of chlorpromazine equivalents approximate closely the doses prescribed blindly by investigators in many clinical trials.

Statistical analysis

Data were analysed using Student's *t*-test, two-way ANOVA, and Spearman rank correlation. A value of $P<0.05$ was taken to be statistically significant.

Results

Characteristics of the study locations and schizophrenic patients

The characteristics of the study locations and study populations are presented in Table 1. Male patients were significantly younger than female patients in all study locations. No differences were observed in the ages of the male or female patients between the three centres. The average hospitalization time was significantly longer in Tartu as compared with Badajoz and Huddinge both for males and females. Diagnostic subtypes of schizophrenia according to the ICD-9 were different in all three study centres. Additional somatic medication was prescribed to 16 patients in Badajoz, 12 in Huddinge and 9 patients in Tartu.

Due to the relatively smaller catchment area in Huddinge, the number of schizophrenia bed-days was also less, and we could only include 87 consecutive patients in the study (instead of 100). Nevertheless, from among the total number of schizophrenia bed-days during the study period, the treatment time of the patients included into the study account for 58% in Huddinge, 30% in Badajoz, and 36% in Tartu, respectively, thus describing a representative sample from the study locations (Table 1).

Drug treatment of schizophrenic patients

The most often prescribed neuroleptic drugs are presented in Table 2. The patients received altogether 275 prescriptions of different neuroleptics or their formulations in Badajoz (100 patients), 180 in Huddinge (87 patients), and 214 in Tartu (100 patients). Thus, on average, during his or her stay, each patient received 2.8 different neuroleptics in Badajoz and 2.1 in Huddinge and Tartu. Haloperidol was the most commonly used neuroleptic in Badajoz and Tartu, and thioridazine in Huddinge. Oral formulations of neuroleptics were dominant in all study locations (Table 3), but depot injections were used almost twice as often in Huddinge and Tartu as compared with Badajoz (21%, 21% and 13% of all prescriptions, respectively). Intramuscular injections were routinely used for maintenance treatment in Badajoz and Tartu (21% and 23% of treatment days), but rarely given in Huddinge, where only 27 single injections were given to the 87 patients during the total of 2631 treatment days.

The average prescribed daily doses (PDD) of the different formulations of neuroleptic drugs to the schizophrenic patients are presented in Table 4. Eleven different formulations of neuroleptics were used in more than six patients in at least two study locations. Among these, eight formulations were common in Badajoz and Tartu. The PDDs were significantly different only for one drug—chlorpromazine as parenteral formulation. In contrast, the PDDs in Huddinge were different from those of the other two locations for five drugs out of six. Thus, the choice and dosage of neuroleptics were similar in Badajoz and Tartu, but somewhat different from those in Huddinge.

The variation between the lowest and highest PDD was more than tenfold for all neuroleptics in all three clinics. Among the most commonly prescribed neuroleptics, the median doses of chlorpromazine and thioridazine were twice as high in Huddinge, while the dose of haloperidol was half of that prescribed in Badajoz and Tartu (Figure 1). For the two former drugs the variability in dosage between patients was more pronounced in Huddinge compared with Badajoz and Tartu.

We also analysed the data for relationships between the dose of neuroleptics (in chlorpromazine equivalents) and the sex, age and hospitalization time of the patients. The only statistically significant results were: (a) the average doses of neuroleptics were higher in women, who stayed in the hospital longer in Badajoz ($r=0.29$; $P=0.043$); (b) male patients stayed in the hospital longer if they were older in Badajoz ($r=0.34$; $P=0.017$); but (c) older patients in Huddinge stayed shorter ($r=0.27$; $P=0.022$); and (d) the cumulative dose of neuroleptics was lower in older women in Tartu ($r=0.40$; $P=0.004$). Thus, it can be concluded, that increasing the doses of neuroleptics had no influence on the length of stay of patients in this study.

Polypharmacy

Concomitant treatment with at least two neuroleptics (or two different formulations of the same substance) occurred in 76% of patients in Badajoz, as compared with 59% in Huddinge and 56% in Tartu (Table 5), which corresponds to 73%, 46%, and 46% of the total number of treatment days, respectively. There were

Table 1 Main medical and demographic characteristics of the schizophrenic patients included in the study. Where appropriate, the mean and standard deviation are given

	Badajoz (Spain)	*Huddinge (Sweden)*	*Tartu (Estonia)*
Study locations			
Catchment area	676 900	105 000	305 000
Number of beds	722	128	280
Number of psychiatrists	16	18	18
Total number of schizophrenia bed-days in the study location during the study period	8592	4521	12 513
Total number of bed-days of all schizophrenic patients included in the study	2621	2631	4501
Schizophrenic patients			
Males/females	50/50	47/40	50/50
Age (males)	34.2±10.0	35.1±9.7	36.2±12.2
Age (females)	41.3±13.6*	39.5±10.2*	41.4±12.4*
Hospitalization time, days (males)	25.0±14.8	30.3±25.1	45.4±25.2†
Hospitalization time, days (females)	27.5±23.5	30.2±21.8	44.7±27.8†
Number of cases, based on ICD-9			
295.0 (simple)	1	0	9
295.1 (hebephrenia)	16	3	6
295.2 (catatonia)	1	1	13
295.3 (paranoid)	36	21	65
295.4 (acute)	3	3	1
295.6 (residual)	21	3	0
295.7 (affective)	10	8	5
295.8 (other specified)	1	2	1
295.9 (not specified)	10	46	0

* $P<0.05$ as compared with the corresponding male group in the same location (t-test)
† $P<0.005$ as compared with both Badajoz and Huddinge patients (ANOVA)

Table 2 Ranking of the top five neuroleptics in study groups expressed as percentage of the total number of neuroleptic prescriptions

Badajoz (Spain)		*Huddinge (Sweden)*		*Tartu (Estonia)*	
1 Haloperidol	36%	1 Thioridazine	19%	1 Haloperidol	35%
2 Levomepromazine	27%	2 Zuclopenthixol	17%	2 Chlorpromazine	15%
3 Chlorpromazine	10%	3 Levomepromazine	14%	3 Thioridazine	14%
4 Thioridazine	8%	4 Perphenazine	13%	4 Trifluoperazine	11%
5 Fluphenazine	7%	5 Haloperidol	11%	5 Fluphenazine	7%
First five in total					
88%		74%		82%	
Average number of neuroleptic prescriptions per one study patient					
2.8		2.1		2.1	

more treatment days without any neuroleptic prescription in Huddinge (11%) than in Badajoz (3%) and Tartu (5%).

The average cumulative daily doses of neuroleptic drugs (Table 6), expressed in chlorpromazine equivalents, were similar in Badajoz (505 mg) and Tartu (515 mg), but significantly lower in Huddinge (399 mg). Lower doses were used in females than in males. The cumulative dose of neuroleptics increased, when several neuroleptics were prescribed on the same day. In Tartu and Badajoz this increase was not linear, suggesting that additional neuroleptics were prescribed in lower doses than when they were used as single drugs. In Huddinge, however, a higher than proportional increase was observed when more than two neuroleptics were prescribed.

Anticholinergic drugs were prescribed most frequently in Tartu (75% of all treatment days) and least frequently in Huddinge (30%). Only one, but different anticholinergic drug was used in each centre: biperiden in Badajoz, orphenadrine in Huddinge and trihexyphenidyl in Tartu. The frequency of concomitant treatment with

Table 3 Main characteristics of psychotropic drug treatment in terms of percentage of the sum of total treatment days of all schizophrenic patients. Where appropriate, the percentage of patients are given in brackets

	Badajoz	*Huddinge*	*Tartu*
Sum of total treatment days	2621	2631	4501
% of days with prescription of			
No neuroleptics	3 (4)	11 (5)	5 (3)
1 neuroleptic	24 (20)	43 (36)	49 (40)
2 neuroleptics	51 (50)	37 (42)	35 (41)
3 or more neuroleptics	22 (26)	9 (17)	11 (15)
Route of administration of neuroleptics			
Oral	66	79	56
Injection	21	n.a.	23
Depot injection	13	21	21
Use of study drugs			
Neuroleptics	97 (96)	89 (95)	95 (97)
Anticholinergics	42 (51)	30 (31)	75 (76)
Antidepressants	8 (15)	0.3 (1)	14 (16)
Benzodiazepines	26 (33)	40 (39)	30 (41)

n.a., not applicable as not used for maintenance treatment

anticholinergics increased parallel to the number of neuroleptics in Huddinge and Tartu, but not in Badajoz (Table 5).

In addition to neuroleptics, antidepressants were prescribed to the same proportion of patients in Badajoz and Tartu (15–16%, Table 3). In Tartu antidepressants (mainly amitriptyline) were used for longer periods, in lower doses, and mainly in the evenings as single injections (data not shown). Only one patient received an antidepressant in Huddinge. Benzodiazepines were used to the same extent in all locations. As a rule, the use of antidepressants and benzodiazepines decreased, as the number of concomitant neuroleptic drugs increased. In Huddinge, however, the use of benzodiazepines increased in parallel with the number and dosage of neuroleptic drugs used (Table 5).

There was an association between concomitant therapy with antidepressants, benzodiazepines and anticholinergic drugs, and the dose of neuroleptics (Table 6). During treatment days with anticholinergic drugs, the average cumulative dose of neuroleptics was higher than during days without anticholinergics. The cumulative dose of neuroleptics was lower, if additional antidepressants or benzodiazepines were prescribed in Badajoz and Tartu.

Discussion

In this study we found both differences and similarities among the three European university clinics in the patterns of choice and dosage of neuroleptic drugs, and in the prevalence of polypharmacy in schizophrenic in-patients. Different concepts about diagnosis and treatment among psychiatrists in different countries are well known [19]. Schizophrenia was chosen as a study diagnosis, because it is generally regarded as having similar incidence between different cultures and times [15, 16]. Effort was made to include similar patient populations in the three study locations. The inclusion and exclusion criteria were chosen with the aim to include patients with acute exacerbations of psychotic symptoms requiring hospitalization, but who were able to live outside in-patient institutions for at least one month before and after hospitalization. The diagnostic subtypes of schizophrenia, however, differed markedly between the three study locations. The clinical significance of this finding is unclear.

Drug treatment preferences of schizophrenia

Six out of the eight most commonly prescribed neuroleptics to the schizophrenics in Badajoz were the same as those in Tartu, although differing somewhat in rank order. Haloperidol was the most frequently prescribed neuroleptic, accounting for one-third of the prescriptions of neuroleptics both in Badajoz and Tartu. In addition to similarities among usage rates of specific drugs in the two samples, there were strong parallels in the relative doses of products that differ widely in milligram potencies. Only parenteral chlorpromazine was prescribed in significantly lower mean doses in Badajoz compared to Tartu.

In Huddinge, the choice of drug was spread more evenly over several neuroleptic compounds (Table 2). The high-dose neuroleptics chlorpromazine and thioridazine were used in higher PDDs in Huddinge as compared with both Badajoz and Tartu (Figure 1). In contrast, the mean PDDs of haloperidol, perphenazine and zuclopenthixol in Huddinge were half of those in the other locations (Table 4). Haloperidol and thioridazine were found among the most frequently prescribed neuroleptics in all three locations. The high use of thioridazine, particularly in Huddinge, is somewhat surprising, as this drug has recently been associated with sudden death in Finland [20].

The reasons for the observed differences in the PDDs of some of the drugs between Huddinge and the other two centres cannot be elucidated by the present study. The low doses of chlorpromazine and thioridazine used in Badajoz and Tartu might reflect their use primarily as sedatives added to the basic treatment. Similarly, in Huddinge, levomepromazine was frequently used in a low dose as a sedative in the evenings. It is noteworthy, that therapeutic drug monitoring, which is not available in Badajoz or Tartu, is performed for several neuroleptics including haloperidol, perphenazine and zuclopenthixol in Huddinge Hospital following recommendations by the Swedish health authorities [21]. This may have had an impact on the dosage schedules used.

The interindividual differences between the PDDs were almost tenfold in all study locations and in case of all neuroleptics. The data for chlorpromazine, thioridazine and haloperidol are given in Figure 1. At the same time, the 95% confidence intervals of PDDs differed less than twofold (Table 4). This observation probably

Table 4 The Prescribed Daily Doses (PDD) of neuroleptics and their formulations, if used at least in six patients in at least two of the study locations. The mean PDD in milligrams is shown and the 95% confidence intervals of the mean are given in brackets

		Badajoz			*Huddinge*			*Tartu*			
Drug	*Formulation*	*PDD*		*Number of patients*	*PDD*		*Number of patients*	*PDD*		*Number of patients*	*Chlorpromazine equivalent factor*
Chlorpromazine	Oral	163	(116...210)	15	334*	(250...418)	12	118	(72...164)	14	1
Haloperidol	Oral	10.7	(9.2...12.2)	73	5.6*	(4.3...6.9)	15	11	(9.6...12.4)	39	45
Thioridazine	Oral	166	(138...194)	22	317*	(265...369)	34	153	(98...208)	29	1
Levomepromazine	Oral	97	(77...117)	57	92	(67...117)	26	n.a.		1	1
Chlorpromazine	Injection	55†	(41...69)	10	n.a.		0	127	(93...161)	18	2
Clozapine	Oral	230	(163...297)	8	n.a.		4	167	(73...261)	6	1
Fluphenazine	Depot	2.2	(1.5...2.9)	18	n.a.		1	2.1	(1.4...2.8)	16	100
Haloperidol	Injection	13	(9.9...16.1)	27	n.a.		4	15	(12...18)	17	45
Trifluoperazine	Oral	13	(8.8...17.2)	12	n.a.		0	12	(7.4...16.6)	14	25
Perphenazine	Oral	n.a.		2	17†	(10...24)	13	40	(21...59)	7	12
Zuclopenthixol	Depot	n.a.		0	13†	(10...16)	16	23	(18...28)	10	25

* $P<0.05$ as compared with both Badajoz and Tartu patients (ANOVA)

† $P<0.05$ as compared with Tartu patients (t-test)

n.a. – not applicable

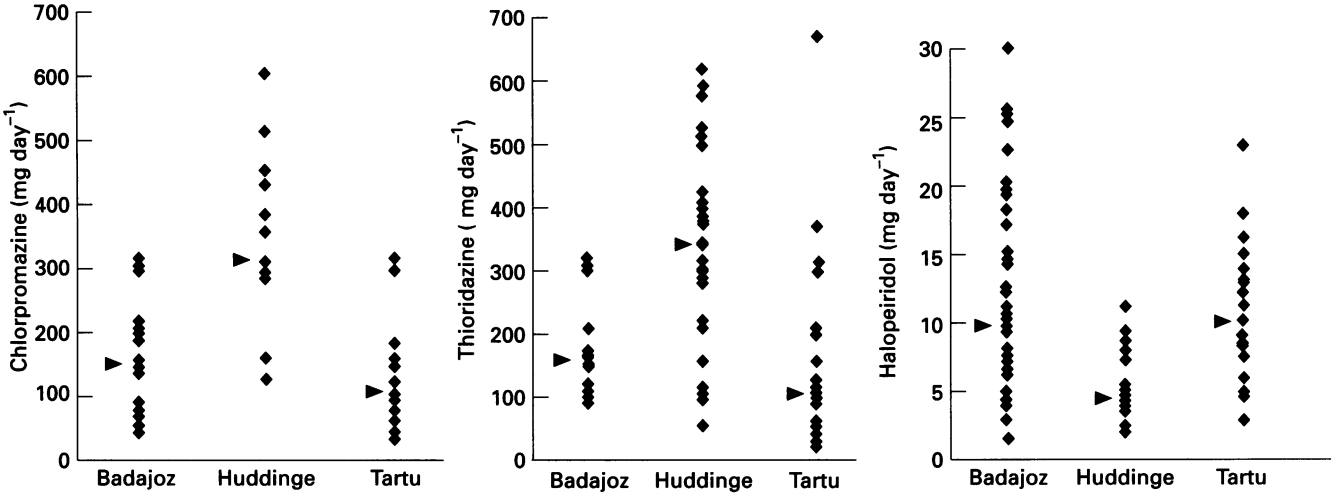

Figure 1 Variation in the prescribed daily doses of neuroleptics in different study locations. The corresponding median daily dose is indicated by the arrow.

Table 5 The use of antidepressants (AD), benzodiazepines (BD) and anticholinergic drugs (ACh) in combination with neuroleptics (NL). The concomitant use is expressed in terms of percentage of treatment days with one or more neuroleptics, or no neuroleptic, respectively

	No NL	*1 NL*	*2 NL*	*3 NL*	*4–6 NL*	*Total*
Badajoz						
Number of treatment-days	70	643	1338	514	56	2621
+Ach	16%	24%	57%	32%	7%	1091
+AD	80%	21%	3%	–	–	213
+BD	97%	56%	16%	7%	31%	687
Huddinge						
Number of treatment-days	291	1122	982	211	25	2631
+Ach	31%	25%	24%	75%	40%	779
+AD	–	0.6%	–	–	–	3
+BD	43%	37%	39%	50%	60%	1047
Tartu						
Number of treatment-days	206	2223	1563	509	–	4501
+Ach	32%	67%	87%	92%	–	3387
+AD	20%	17%	10%	7%	–	626
+BD	65%	40%	15%	15%	–	1343

reflects the need to use very low or high doses in the treatment of selected patients. The scientific basis of this clinical tradition in psychiatry—interindividual genetic differences in the metabolism of neuroleptics—have been revealed in recent pharmacogenetic studies [22–24].

There is increasing evidence, that moderate doses of neuroleptics are as effective as, and presumably safer than high doses [11, 25, 26]. Similarly, no difference in the relapse rate and in the outcome of treatment with neuroleptics was revealed in long-term studies with various neuroleptics in doses between the equivalent of 100 and 2500 mg of chlorpromazine, or at doses above versus below 310 mg day^{-1} [10]. The average cumulative daily doses of neuroleptics, expressed in equivalent doses of chlorpromazine, observed in this study, are similar to those reported in the treatment of schizophrenics by some authors [3, 6] and half of those, reported by others [8, 9]. Thus, the dosing of neuroleptics in all study locations was in the lower range, according to the available literature. However, the validity of the criteria for converting doses of neuroleptics to chlorpromazine equivalent units is not firmly established, and this may affect the accuracy of our findings. Comparisons have been made mainly by averaging typical doses of various agents found to be effective in placebo-controlled clinical trials [17, 18].

Polypharmacy

Our results clearly suggest a tendency towards polypharmacy in schizophrenic in-patients. This tendency is evident by the concomitant use of multiple neuroleptics and by the use of neuroleptics together with anticholinergics and benzodiazepines. In half of the treatment days in Huddinge and Tartu and 73% of those in Badajoz, the patients received at least two neuroleptics (or different formulations of one neuroleptic compound). This finding is not unexpected, but difficult to explain

Table 6 The cumulative daily doses of neuroleptics (NL), separated by sex and according to the number of neuroleptics and concomitant treatment with antidepressants (AD), anticholinergic drugs (Ach) and benzodiazepines (BD). The mean dose of the corresponding treatment days in milligrams, expressed as chlorpromazine equivalents, and the 95% confidence intervals of the mean are given in the brackets. The % values are the mean dose expressed as a percentage of the corresponding mean dose with only one neuroleptic compound or without the additional drugs (set at 100% as indicated)

	Badajoz		%	*Huddinge*		%	*Tartu*		%
All patients	505	(438...572)		399*	(337...461)		515	(454...576)	
Males	594	(492...696)		432	(327...537)		577	(488...666)	
Females	416‡	(336...496)		360	(300...420)		450‡	(369...531)	
Neuroleptic treatment									
1 NL	339	(245...433)	100	242	(209...275)	100	399	(346...452)	100
2 NL	584	(509...659)	172	499	(418...580)	206	634	(561...707)	159
3 NL	872	(730...1014)	257	956	(705...1207)	395	1132	(1011...1253)	284
4 or more NL	848	(629...1067)	250	1220	(978...1462)	504	–		
Treatment-days with neuroleptics									
Without Ach	430	(334...526)	100	347	(299...395)	100	292	(208...376)	100
NL+Ach	599†	(511...687)	139	543†	(369...717)	156	595†	(529...661)	204
Without AD	555	(482...628)	100	–			541	(474...608)	100
NL+AD	341†	(209...473)	61	–			438	(292...584)	81
Without BD	584	(497...671)	100	360	(303...417)	100	564	(493...635)	100
NL+AD	408†	(317...499)	70	476†	(345...607)	132	486	(385...587)	86

* $P<0.05$ as compared with both Badajoz and Tartu (ANOVA)

† $P<0.05$ as compared with days without corresponding additional psychotropics in the same study location (*t*-test)

‡ $P<0.05$ as compared with male patients in the same location (*t*-test)

on scientific grounds, as there is no evidence of greater efficacy of two neuroleptic drugs over one. In fact, controlled randomized studies of the effects of combination treatment with neuroleptics are lacking. Nevertheless, the combination strategy of multiple neuroleptics is often used, both with the aim to spread side-effects and to accomplish as little sedation as possible in day-time, but sedation at night. The suggestion, that there may be a relationship between increasing doses of neuroleptics and decreasing length of stay in the hospital [8] was not supported by our study as differences in stay were not related to cumulative dose of neuroleptics in any of the study locations.

Similar to our findings, more than half of the patients were receiving antiparkinsonian medication in studies performed in chronic schizophrenics in one hospital [6, 9] and multinationally [7]. These drugs are still widely prescribed, despite the suggestions, that only 10 to 33% of patients require these drugs once antipsychotic maintenance medication had been established [3, 4]. It is tempting to speculate that the anticholinergic drugs were prescribed for prophylactic reasons, despite the fact that they are not effective in preventing extrapyramidal side effects [27, 28]. Similarly, when a patient's symptoms were well controlled and parkinsonian side-effects became apparent, an anticholinergic may have been started instead of decreasing the dosage of the antipsychotic medication, but this hypothesis must be addressed in a separate study.

The use of benzodiazepines in the treatment of schizophrenia (26–30% of all treatment days in our study) is difficult to explain, especially as the anxiety in schizophrenia remains untouched by these agents [6, 18]. The risks of dependence should also be taken into consideration, but our findings suggest, that this may not be well recognized in the study locations, especially in Tartu, where benzodiazepines were prescribed for prolonged periods (13 days on average). There is some evidence [21], that the combined use of neuroleptics and benzodiazepines in the treatment of acute psychoses may reduce the required dose of neuroleptics. However, in the Huddinge sample the use of benzodiazepines increased in parallel to the dose and number of multiple neuroleptics, while the number and doses of neuroleptics were smaller in Badajoz and Tartu, when concomitant benzodiazepines (and antidepressants) were prescribed. It is noteworthy that the increase in the dose of neuroleptics in parallel with the use of benzodiazepines occurred in Huddinge, the centre with the lowest cumulative daily dose of neuroletics (Table 6). In fact, despite the increase, the cumulative daily dose of neuroleptics remained, lower than that in the other centres without benzodiazepines. The observed pattern in Huddinge may reflect an attempt to potentiate the treatment in relatively treatment-resistant patients or, possibly, treatment of akathisia with benzodiazepines. There is very little information in the literature to support the use of antidepressants in schizophrenic patients, and the prescribing of antidepressants in Badajoz and Tartu must thus be regarded as a therapeutic trial.

One of the arguments for polypharmacy is that lower doses of the different drugs can be given. This was not reflected in any of the study locations, when the doses of neuroleptics given together with anticholinergic drugs were compared with the doses given as a single drug regimen. Additionally to this, the dictum that polypharmacy leads to more polypharmacy [27] seems to apply

in the Huddinge sample, as in contrary to the other study locations, if more than two neuroleptics were prescribed, the doses were higher as compared with single prescriptions. These data, however, derive from only 17% of patients (9% of all treatment days) in Huddinge, and thus need to be interpreted with caution. In fact, the treatment of schizophrenic patients with polypharmacy with varying doses resembles the pattern of treatment of epilepsia some two decades ago. Today, with the guidance of therapeutic drug monitoring, most epileptic patients can be managed with monotherapy.

The potential harmful effects of polypharmacy in psychiatry should also be recognized in the context of contemporary pharmacogenetic knowledge. Most neuroleptics and antidepressants (e.g. haloperidol, perphenazine, zuclopethixol, nortriptyline, amitriptyline) are metabolized by the same isoenzyme of the cytochrome P450 (CYP) family, CYP2D6, and are also potent inhibitors of this enzyme [23, 24]. Due to inhibition of CYP2D6, the phenotype of efficient metabolizers may be transformed to 'poor metabolizers' [22], and higher than anticipated plasma concentrations of either one or both of the drugs may occur during concomitant therapy with neuroleptics and/or antidepressants. Thus, polypharmacy exposes patients to risks of concentration-dependent adverse effects.

Our findings of different prescription practices in Estonia, Spain and Sweden to schizophrenic in-patients are in line with the major international differences, that have been revealed in the treatment of somatic diseases, such as, diabetes [29] and hypertension [30]. In order to improve clinical practice and on economic grounds, further effort should be made to rationalize prescribing behaviour. This survey may be of interest to those wishing to improve hospital prescribing habits by continuing education in psychopharmacology.

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