Eur Arch Psychiatry Clin Neurosci (2003) 253 : 175 – 184 DOI 10.1007/s00406-003-0422-9

ORIGINAL PAPER

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Atypical and typical neuroleptics in acute schizophrenia and related delusional disorders

Drug choice, switching and outcome under naturalistic treatment conditions

Received: 16 October 2002 / Accepted: 17 April 2003

Abstract Atypical neuroleptics have improved drug treatment in schizophrenia. However, their use varies greatly between countries and continents. Recent meta-analyses have deemphasized the range and magnitude of their superiority compared to typical neuroleptics. Aims of the present study were to contribute effectiveness data to this discussion. In 725 inpatients with ICD-10 diagnoses F20, 22–25 from four German psychiatric inpatient units acute neuroleptic treatment and outcome were analyzed under naturalistic conditions. Treatment strategies were stratified post hoc to answer the question, which proportion – and which kind – of patients are primarily given atypicals or typicals, for how long, at which rate and when the atypical/typical drugs are switched to typical/atypical drugs, and what the respective outcomes are. As the results demonstrate, atypicals were administered one time during inpatient treatment in nearly 48 % of the patients, however as first choice drugs in only 15 % of this population. Treatment change occurred in 28 % after 5–6 weeks irrespective of the first drug choice. Outcome differences were, if at all, only modest and not systematically biased towards a single strategy. In conclusion, frequency of inpatient treatment with atypical neuroleptics corresponds to pharmaco-epidemiological data in Europe, but is still lower than in the US. Contrary to contemporary guideline recommendations atypical neuroleptics under routine inpatient treatment conditions were scarcely administered as first choice treatment, and acute clinical outcome is comparable to that under treatment with typical neuroleptics. Reasons and implications of these findings considering the methodological limitations are discussed.

Key words schizophrenia · acute drug treatment · treatment guidelines · typical and atypical neuroleptics · drug switching

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Introduction

Drug treatment of schizophrenia has improved with the introduction of new, atypical, second generation antipsychotics. Advantages which have been claimed are a better effect/side effect profile, i. e. comparable antipsychotic efficacy with less or no incidence of EPS, better effect on negative symptoms, efficacy in nonresponders, effect on cognitive dysfunction, lower relapse rate (possibly due to better compliance), and improved quality of life. The exact mechanisms, however, that make these drugs 'atypical' are still debated (Kapur and Remington 2001). Treatment guidelines were reserved in their recommendation of atypicals at first (American Psychiatric Association 1997; DGPPN 1998; Lehman and Steinwachs 1998), but have recently become much more positive (McEvoy et al. 1999; NICE 2002), although some authors still claim conventional neuroleptics as the first choice treatment (Steel and Johnstone 2000). Hence, their market share has increased over the years, but there is still a significant gap between the US (about 40 to 70 % for out-

patient and inpatient treatment, respectively (Tapp et al. 2003; Clark et al. 2002) and Europe (Schwabe and Paffrath, 2003, report 23 % atypical neuroleptics of all administered neuroleptics in outpatient health care in Germany; Frangou & Lewis, 2000, found that 26 % of the patients with schizophrenia were treated with atypicals in a British sample of psychiatric outpatient services; Brunot et al., 2002, report that 56 % of schizophrenic patients in a 2/3 inpatient and 1/3 outpatient mixed French sample received atypical neuroleptics). Cost has been claimed a major impediment to their more widespread use (Martin et al. 2001; Campbell et al. 1999), although cost-effectiveness analyses show slightly lower (or, at worst, no different) total costs to the health care system in long-term treatment (Tilden et al. 2002; Knapp 2000; Galvin et al. 1999; Revicki 1999; Tunis et al. 1999). Consequently, professionals and consumers have joined in public activities to fight for their broader availability. However, some recent meta-analyses come to the conclusion that besides their lower induction of EPS atypicals have not proven superior to conventional neuroleptics, particularly, if the latter are administered in low doses (Geddes et al. 2000; Leucht et al. 1999). Moreover, recent reports on their side effects profile including weight gain and metabolic effects, i. e. induction of type II diabetes and increased levels of lipids, all of them independent risk factors for cardiovascular disease, have begun to overshadow the positive opinions on atypicals. In fact, a need for new and different treatment strategies for schizophrenia, especially in cases of treatment resistance, has been claimed (Chakos et al. 2001).

Effectiveness studies are important to evaluate treatment decisions, guideline adherence and drug effects under naturalistic conditions in unselected populations. How many – and which kind of – patients are primarily given atypicals or typicals, for how long, what are the respective response rates, at which proportion and when is the atypical/typical drug switched to a typical/atypical principle, what are the respective outcomes including illness severity, psychopathological profile, side effects, social functioning, treatment satisfaction, and length of stay – these are some of the questions to be answered to better understand the position of atypical neuroleptics within the armamentarium of acute drug treatment in schizophrenia. The present analysis from our quality management study on acute inpatient treatment in a large sample of schizophrenic patients from four German psychiatric hospitals (Gaebel et al. 2000; Janssen et al. 2000) aims to answer some of these questions.

Methods

Sample

Centers involved in the recruitment and treatment of patients were the departments of psychiatry at the Universities of Düsseldorf and Aachen, and the psychiatric hospitals in Bonn and Gummersbach.

Schizophrenia and schizophrenia related disorders were diagnosed according to the 10th revision of the International Classification of Diseases [ICD-10] (World Health Organization 1978), including ICD-10 F20 (schizophrenia), F22 (persistent illusional disorder), F23 (acute and transient psychotic disorders), F24 (induced delusional disorder) and F25 (schizoaffective disorder). Out of 1048 suspect cases screened, 983 patients fulfilling the diagnostic requirements were included. Patients were excluded in case of diagnostic change to categories other than F2x during the inpatient treatment, no availability of informed consent or an age less than 18 years.

For the present analysis patients with a minimum stay of 15 days were selected. This left a number of 742 cases, of which 17 patients where unaccounted for because of not receiving neuroleptic treatment during inpatient stay, resulting in 725 patients for analysis.

Drug treatment strategies

According to the naturalistic study design, the kind, dose, application and timing of neuroleptic drugs used were totally left to the clinicians' discretion. For reasons of post-hoc data stratification three treatment groups were defined. Depending on the drug group first given (for a minimum of 3 days), patients were assigned to either an 'initially typical' or an 'initially atypical' group. If both typical and atypical NL were initially given together, patients were assigned to the group 'combined typical and atypical treatment'. For the definition of 'typical' and 'atypical' neuroleptics see Table 2.

In a second step, cases with maintained treatment of their first drug principle (typical or atypical neuroleptic) and those with a later change to the other principle (atypical or typical neuroleptic) were considered for comparison.

Instruments of measurement

Information on different target areas was collected at admission and discharge. In addition, information on drug treatment was documented continuously by the clinician throughout inpatient treatment. For details see Janssen et al. (2000).

As a prognostic measure the prognosis scale developed by Strauss et al. (1977) was used. Psychopathological symptoms were measured by means of the Brief Psychiatric Rating Scale [BPRS] (CIPS 1981), illness severity, treatment-related clinical change and side-effects by means of the Clinical Global Impression scale [CGI] (CIPS 1981). Psychosocial functioning was assessed using the Social and Occupational Functioning Assessment Scale [SOFAS] (American Psychiatric Association (APA) 1994). Subjective treatment satisfaction was measured by means of the ZUF 8 (Spiessl et al. 1995). Interrater reliability checks of the BPRS, CGI and SOFAS reached acceptable results of intra-class correlations about 0.70.

Data analysis

Differences among the (post hoc classified) groups in several (dependent) variables were examined using chi-square measures for nominal variables and ANOVA or t-test procedures for continuous (numeric) variables. Furthermore multivariate analysis was performed to select relevant predictors for the groups using logistic regression analysis. More details are given in the respective results sections.

Results

Recruitment of patients

Recruitment took place between 1997 and 1998. During the recruitment phase, a total number of n = 1048 schizophrenia suspect cases had been screened, of which n = 65 cases (6.2 %) were excluded during the initial recruitment phase.

The most frequent reasons (multiple occurrence) for

exclusion were change of diagnosis (92.3 %) and no available informed consent (9.2 %). Accordingly, from the resulting n = 983 cases, 725 with a minimum length of stay of 15 days were included in the present analysis.

Basic sample and treatment data

Table 1 gives basic data for the total sample (n = 725). The various neuroleptic drugs administered during the present inpatient stay are listed in Table 2.

Drug treatment strategies

Fig. 1 gives the prevalence rates of the three treatment groups defined above. Characteristics of treatment change are listed in Table 3. In those 184 patients in whom treatment was changed, the first drug principle (typical or atypical) was maintained for 57.4 days on average. In comparison, the mean duration of drug administration in those 459 patients, in whom the initially administered drug principle was maintained, was 50.9 days. In case of drug switching the second drug was initiated after 32.6 days and maintained for another 48.8 days. Obviously, drug exchange was carried out in an overlapping manner. There was no significant difference in the length of first choice drug treatment in case of change (56.8 vs. 60.2 days), whereas in case of maintained treatment atypical drugs were administered for longer (61.9 days) than typical drugs (48.5 days; p = 0.02).

Comparison among treatment strategies

In the following section results of comparisons among treatment strategies concerning patient, illness and outcome characteristics are reported.

Table 1 Sample characteristics (n = 725)

		Rate	Mean (SD)	Differences between hospitals
Sex:	male:	49.4 %		n. s.
Age at study entry:		41.6 (13.5)		(p = 0.06)
ICD 10 diagnosis (F2x)	F20: F25: F22, F23, F24:	80.7 % 14.3 % 5.0 %		n. s.
First episode cases:		14.1 %		p < 0.001
Duration of illness (years):			11.7 (9.1)	p = 0.003
Frequency of previous inpatient treatment:			3.8 (2.8)	p = 0.02
Length of present inpatient stay (days):			63.6 (48.1)	p < 0.001

Table 2 Neuroleptic drugs administered during present inpatient treatment (the 3 most often applied typical neuroleptics are indicated)

	Frequency of different drugs	Frequency of patients[1]	% of all 725 patients[1]	Differences between hospitals
Total		**725**	**100.0**	
Typical neuroleptics	**26**	**644**	**88.8**	**n. s.**
• *High potency neuroleptics*	*10*	*527*	*72.7*	*n. s.*
– Haloperidol		294	40.6	
– Flupentixol		117	16.1	
– Fluphenazine		84	11.6	
• *Medium potency neuroleptics*	*3*	*135*	*18.6*	*p = 0.003*
– Perazine		102	14.1	
– Thioridazine		21	2.9	
– Sulpirid		19	2.6	
• *Low potency neuroleptics*	*13*	*352*	*48.6*	*p < 0.001*
– Promethazine		126	17.4	
– Chlorprothixen		101	13.9	
– Levomepromazine		77	10.6	
Atypical neuroleptics	**5**	**347**	**47.9**	**p < 0.001**
– Olanzapine (16.5; 6.9)[2]		149	20.6	
– Clozapine (395.1; 174.7)		125	17.2	
– Risperidone (5.3; 1.8)		87	12.0	
– Zotepine (179.0; 95.1)		40	5.5	
– Sertindole (17.3; 4.8)		15	2.1	

[1] Given at least one time during hospital stay; [2] Dose of atypical neuroleptics in mg/d (mean; standard deviation)

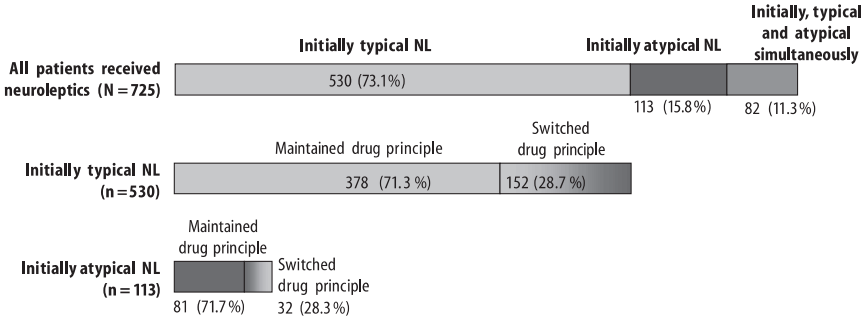

Fig. 1 Prevalence of drug treatment strategies (n = 725)

Table 3 Drug treatment strategies – duration of drug administration

	Mean	SD
All patients, in whom treatment was changed (n = 184)		
Time (days) of administration of first NL	57.4	53.6
Time-span (days) from beginning of first to beginning of second NL	32.6	39.0
Time (days) of administration of second NL	48.8	45.8
All patients *without* treatment change (n = 459)		
Time (days) of administration of first NL	50.9	36.8
'Initially typical NL' and *no* treatment change (n = 378)		
Time (days) of administration of (first) typical NL	48.5	34.1
'Initially typical NL' and treatment change (n = 152)		
Time (days) of administration of first (typical) NL	56.8	49.8
Time-span (days) from beginning of first to beginning of second (atypical) NL	31.9	30.4
Time (days) of administration of second (atypical) NL	51.3	46.0
'Initially atypical NL' and *no* treatment change (n = 81)		
Time (days) of administration of (first) atypical NL	61.9	46.1
'Initially atypical NL' and treatment change (n = 32)		
Time (days) of administration of first (atypical) NL	60.2	70.0
Time-span (days) from beginning of first to beginning of second (typical) NL	35.8	66.9
Time (days) of administration of second (typical) NL	36.8	43.2

First choice treatment

Table 4 gives results of comparisons among first choice treatment strategies. A significant hospital effect indicates differences among the 4 hospitals regarding treatment strategies. Significant differences in patient and illness characteristics are age (post hoc tests do not reach the 5% significance level), illness duration, rate of first episode schizophrenia and illness course (comparably more episodic remitting, but also incomplete remission courses in the 'initially atypical' group). No significant differences between patients with ICD-10 diagnosis F20 compared to patients with diagnosis F25 occurred.

At admission, significant differences were observed for the BPRS subscale 'schizophrenia' and for 'anxiety/depression'. Concerning length of stay patients in the 'initially atypical' group stayed significantly longer than patients in the 'combined' group. Furthermore only slight differences between the groups occurred at discharge (BPRS subscale 'anxiety/depression': higher scores for the 'combined' compared to the 'initially typical' group; CGI Scale 'treatment effect': post hoc tests did not reach the 5% significance level), and change scores adjusted for the admission score did not show any significant differences.

In order to identify predictors for the clinical allocation to any of the three treatment strategies, multivariate logistic regression analysis was performed considering the following variables: age, first episode, illness duration, illness course, Strauss-Carpenter Prognosis Score, several rating scale scores at admission (BPRS, CGI, SOFAS), and hospital.

As significant predictors were identified: age (patients in the 'combined' group were significantly younger than patients with 'initially typical' neuroleptics; $p = 0.008$), BPRS subscores 'schizophrenia' (lower scores for the 'initially atypical' and 'combined' group; $p = 0.01$) and 'anxiety/depression' (higher scores for the 'initially atypical' compared to the 'initially typical' group; $p = 0.02$). Hospital did not continue to be a predictor. Because of the high positive correlation between age and illness duration, another model was computed without age. However, illness duration as a potential predictor again missed the 5% level of significance.

Maintained drug treatment vs. change in drug principle

Table 5 gives results of comparisons between patients maintained on either typical or atypical neuroleptics and those changed to the other drug principle. In

Table 4 Comparison of first choice drug treatment strategies

	initially …	… atypical NL		… typical NL		… typical and atypical NL simultaneously		p
		%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	
	Total	**15.6**		**73.1**		**11.3**		
PATIENT	Age		39.6 (12.6)		42.4 (14.0)		39.0 (10.4)	**0.03**
PATIENT	Sex							n. s.
PATIENT	– Male	16.3		70.2		13.5		
PATIENT	– Female	15.1		75.9		9.0		
	Hospital							**0.04**
	– A	17.4		71.7		10.9		
	– B	15.9		74.9		9.2		
	– C	19.0		71.1		10.0		
	– D	8.0		74.5		17.5		
ILLNESS	First episode	8.9		84.2		6.9		**0.03**
ILLNESS	Multiple episode	16.6		71.3		12.1		
ILLNESS	Illness duration (years)		9.6 (7.2)		12.1 (9.5)		12.4 (8.4)	**0.04**
ILLNESS	Illness course							**0.02**
ILLNESS	– Continuous	16.7		66.7		16.7		
ILLNESS	– Episodic with progressive deficit	12.6		70.6		16.8		
ILLNESS	– Episodic with stable deficit	15.6		74.5		9.9		
ILLNESS	– Episodic remittent	19.6		71.5		8.9		
ILLNESS	– Incomplete remission	28.6		55.1		16.3		
ILLNESS	Strauss-Carpenter prognosis score		45.5 (12.4)		45.9 (12.7)		42.3 (11.9)	(0.07)
ADMISSION	BPRS							
ADMISSION	– Total		52.7 (14.5)		55.7 (13.8)		54.6 (13.4)	n. s.
ADMISSION	– Schizophrenia		28.8 (12.4)		33.5 (12.3)		30.9 (10.2)	**< 0.001**
ADMISSION	– Anergia		11.4 (4.4)		10.7 (4.5)		10.7 (4.2)	n. s.
ADMISSION	– Anxiety/Depression		12.6 (5.0)		11.4 (5.1)		13.0 (5.5)	**0.006**
ADMISSION	CGI: Severity		5.2 (0.9)		5.3 (0.9)		5.3 (0.9)	n. s.
ADMISSION	SOFAS		42.1 (16.8)		40.8 (15.2)		41.0 (12.9)	n. s.
DISCHARGE	BPRS							
DISCHARGE	– Total		33.7 (11.9)		33.7 (11.6)		36.1 (11.9)	n. s.
DISCHARGE	– Schizophrenia		17.3 (8.2)		17.6 (7.7)		19.0 (8.0)	n. s.
DISCHARGE	– Anergia		8.3 (3.3)		8.5 (3.5)		8.5 (3.5)	n. s.
DISCHARGE	– Anxiety/Depression		8.0 (3.7)		7.5 (3.3)		8.6 (3.8)	**0.02**
DISCHARGE	Change admission to discharge (adjusted for admission scores)							
DISCHARGE	BPRS (decrease)							
DISCHARGE	– Total		20.5 (10.5)		21.5 (10.9)		18.8 (10.6)	n. s.
DISCHARGE	– Schizophrenia		14.2 (7.2)		14.9 (7.4)		13.1 (7.1)	n. s.
DISCHARGE	– Anergia		2.6 (2.9)		2.3 (3.0)		2.2 (3.1)	n. s.
DISCHARGE	– Anxiety/Depression		4.0 (3.0)		4.1 (2.9)		3.7 (3.3)	n. s.
DISCHARGE	CGI							
DISCHARGE	– Severity		4.0 (1.3)		4.0 (1.2)		4.2 (1.1)	n. s.
DISCHARGE	– Change		2.1 (0.9)		2.0 (0.9)		2.2 (0.8)	(0.08)
DISCHARGE	– Therapeutic efficacy		1.9 (0.9)		1.8 (0.8)		2.0 (0.9)	**0.04**
DISCHARGE	– Side effects		1.5 (0.7)		1.5 (0.7)		1.5 (0.7)	n. s.
DISCHARGE	Patients' satisfaction		20.4 (1.3)		20.3 (1.5)		20.5 (1.0)	n. s.
DISCHARGE	SOFAS		55.5 (16.4)		54.3 (15.3)		52.0 (15.3)	n. s.
DISCHARGE	Length of stay (days)		73.9 (56.3)		62.8 (46.9)		55.1 (41.6)	**0.02**

slightly more than one third the neuroleptic drug principle was changed. Again, there were significant differences among the hospitals. Regarding patient characteristics, the two groups differed significantly in age, illness duration and rate of first episode schizophrenia. Again, no significant differences with regard to ICD-10 diagnosis (F20 vs. F25) was observable.

In addition, patients with change in drug principle exhibited a higher score in CGI 'severity' at admission and a higher score in CGI 'side-effects' at discharge.

Table 5 Comparison of groups with maintained drug principle and with change in drug principle

		Maintained drug principle		Change in drug principle		p
		%	Mean (SD)	%	Mean (SD)	
	Total	**63.3**		**36.7**		
PATIENT	Age		43.1 (13.9)		38.9 (12.3)	**< 0.001**
PATIENT	Sex					n. s.
PATIENT	– Male	61.2		38.8		
PATIENT	– Female	65.5		34.5		
	Hospital					**0.001**
	– A	50.7		49.3		
	– B	64.4		35.6		
	– C	63.5		36.5		
	– D	73.7		26.3		
ILLNESS	First episode	51.5		48.5		**0.008**
ILLNESS	Multiple episode	65.3		34.8		
ILLNESS	Illness duration (years)		12.6 (9.5)		10.2 (8.1)	**0.002**
ILLNESS	Illness course					n. s.
ILLNESS	– Continuous	55.1		44.9		
ILLNESS	– Episodic with progressive deficit	65.0		35.0		
ILLNESS	– Episodic with stable deficit	70.2		29.8		
ILLNESS	– Episodic remittent	63.1		36.9		
ILLNESS	Strauss-Carpenter prognosis score		44.9 (12.4)		46.3 (12.8)	n. s.
ADMISSION	BPRS					
ADMISSION	– Total		54.9 (13.9)		55.4 (14.0)	n. s.
ADMISSION	– Schizophrenia		32.4 (12.4)		32.6 (12.0)	n. s.
ADMISSION	– Anergia		11.0 (4.3)		10.6 (4.7)	n. s.
ADMISSION	– Anxiety/Depression		11.5 (5.1)		12.2 (5.2)	n. s.
ADMISSION	CGI: Severity		5.2 (0.8)		5.4 (0.9)	**0.024**
ADMISSION	SOFAS		41.7 (15.6)		39.9 (14.5)	n. s.
DISCHARGE	BPRS					
DISCHARGE	– Total		33.9 (11.5)		34.0 (12.2)	n. s.
DISCHARGE	– Schizophrenia		17.9 (7.8)		17.4 (7.9)	n. s.
DISCHARGE	– Anergia		8.4 (3.4)		8.6 (3.6)	n. s.
DISCHARGE	– Anxiety/Depression		7.6 (3.3)		8.0 (3.6)	n. s.
DISCHARGE	Change admission to discharge (adjusted for admission scores)					
DISCHARGE	BPRS (decrease)					
DISCHARGE	– Total		21.0 (10.6)		21.1 (11.3)	n. s.
DISCHARGE	– Schizophrenia		14.4 (7.2)		14.9 (7.7)	n. s.
DISCHARGE	– Anergia		2.5 (2.9)		2.1 (3.2)	n. s.
DISCHARGE	– Anxiety/Depression		4.1 (2.9)		4.0 (3.2)	n. s.
DISCHARGE	CGI					
DISCHARGE	– Severity		4.0 (1.2)		4.0 (1.2)	n. s.
DISCHARGE	– Change		2.1 (0.9)		2.0 (0.9)	n. s.
DISCHARGE	– Therapeutic efficacy		1.8 (0.8)		1.8 (0.8)	n. s.
DISCHARGE	– Side effects		1.4 (0.6)		1.5 (0.7)	**0.03**
DISCHARGE	Patient satisfaction		20.3 (1.5)		20.4 (1.2)	n. s.
DISCHARGE	SOFAS		54.1 (15.6)		54.5 (15.3)	n. s.
DISCHARGE	Length of stay (days)		53.8 (38.0)		80.7 (58.1)	**< 0.001**

Again, change scores adjusted for the admission score did not show any significant differences. However, patients whose drug principle was changed, stayed much longer in hospital.

Identification of potential predictors by means of logistic regression analysis resulted in significant contributions for age (patients with drug change are younger; $p < 0.001$), rate of first episodes (more first episode patients had a change in drug-principle; $p = 0.01$), hospital ($p = 0.02$), and the BPRS subscale 'anxiety/depression' at admission (higher scores for patients with change; $p = 0.03$). Computed without age, illness duration became a significant predictor (shorter illness duration in patients with change; $p = 0.03$).

Maintained typical vs change to atypical treatment

In 28.7 % of 530 patients, who first received typical neuroleptics, treatment was changed to atypical drugs. Significant differences between the no-change and the change group were found for hospital ($p = 0.001$), age (patients with change were younger; $p < 0.001$), illness duration (shorter illness duration for patients with change; $p < 0.001$), rate of first episodes (more first-episode patients were changed from typical to atypical; $p = 0.001$), illness course (drug treatment was more often changed in patients with a continuous course, whereas typical neuroleptics were more often maintained in patients with an episodic course with stable deficits; $p = 0.049$), and the Strauss-Carpenter Prognosis Score (better prognosis in patients whose drug treatment was changed; $p = 0.001$).

In addition, patients with neuroleptic change showed higher CGI 'severity' at admission ($p = 0.013$) and lower scores for the BPRS subscale 'schizophrenia' at discharge ($p = 0.02$). Again, patients whose drug principle was changed stayed much longer in the hospital ($p < 0.001$).

Regarding change scores adjusted for the admission score, patients with drug change showed a stronger decline in the BPRS subscore 'schizophrenia' ($p = 0.0013$) and a greater improvement in the SOFAS score ($p = 0.006$).

Results of the logistic regression analysis are similar to those obtained for change in drug principle in general. Significant predictors were age ($p = 0.003$; or illness duration: $p = 0.05$), first episode ($p = 0.02$), hospital ($p = 0.001$), and the Strauss-Carpenter Prognosis Score ($p = 0.01$).

Maintained atypical vs change to typical treatment

In 28.3 % of 113 patients, who first received atypical neuroleptics, treatment was changed to typical drugs. There are no significant differences concerning hospital and patient characteristics between the two groups. Again, change scores adjusted for the admission score did not show any significant differences. Only the CGI score 'side-effects' at discharge reached significance level (more side-effects in patients with drug change; $p = 0.017$). Patients with drug change again stayed much longer in the hospital ($p = 0.005$).

Corresponding to these univariate results, no significant predictors for drug-change vs. no change could be identified by logistic regression analysis.

Maintained typical vs maintained atypical treatment

A comparison of the 378 patients maintained on typical treatment with the 81 patients maintained on atypical neuroleptics led to the following results: patients on typical neuroleptics are older ($p = 0.02$), have a longer illness duration ($p = 0.009$), have higher BPRS total ($p = 0.05$) and schizophrenia scores ($p = 0.004$) at admission and a shorter length of hospital stay (51.4 vs. 64.7 days; $p = 0.004$). Apart from this, no other outcome differences occurred.

Discussion

Typical and atypical neuroleptics as first choice treatment

The total amount of patients receiving atypical neuroleptics during their hospital stay one time or another is about 48 %. However, the rate of patients who initially received atypical neuroleptics was rather low: 15.6 % compared to 73.1 %, who initially received typical neuroleptics, and 11.3 %, who received a combination of both.

Hence, during the observation phase 1997–1998 the *primary use* of atypical neuroleptics in four German psychiatric hospitals was rather low. The reason for this is not quite clear. Whereas for outpatient treatment economic barriers (budgeting) – recently removed – have been accused, this does not hold for inpatient services. Despite the development and broader dissemination of treatment guidelines for schizophrenia, some of which recommend the utilization of atypical neuroleptics in almost all treatment instances (e. g. McEvoy et al. 1999), guideline adherence can be observed in only 50 % of schizophrenia cases (Lehman and Steinwachs 1998). Besides economic reasons a low rate of utilization of second generation antipsychotics (as first choice treatment) may be possibly due to ignorance or rejection of claimed effects, clinical conservatism, reluctance based on satisfaction with conventional neuroleptics, or desire not to disrupt stable treatment regimens (World Psychiatric Association 2000). In the light of recent meta-analyses on the effects and side-effects of new atypical neuroleptics (Geddes et al. 2000; Leucht et al. 1999), our findings underscore the need for evidence-based guidelines on neuroleptic drug treatment and their more systematic implementation.

Switching between typical and atypical neuroleptics

The switch rate was identical for both typical (28.7 %) and atypical drugs (28.3 %). If one rules out other reasons such as intolerable side-effects this may be understood in terms of an identical response rate for first choice drug treatment. Voruganti et al. (2002) similarly report on an effectiveness rate of 75 % in a cohort of patients under maintenance treatment switched from conventional to novel antipsychotics.

Concerning the question when to switch, mean treatment duration until change was quite similar for both drug principles (about 5–6 weeks) in accordance with guideline recommendations.

Predictors of drug choice and drug switching

Younger patients were more often started on combined treatment, perhaps because atypicals alone were not expected to work sufficiently or were temporarily combined with parenteral application of typical neuroleptics. Atypical neuroleptics, contrary to their proven equal *efficacy*, were more often given in patients with lower schizophrenia admission-scores. This may point to experienced differences in *effectiveness*. Under naturalistic conditions typical neuroleptics still seem to be first choice in patients with more pronounced illness severity. This may in part relate to their availability for parenteral application. On the other hand, preference of atypicals in patients with higher anxiety/depression-scores may be due to their proven efficacy in affective symptoms and their lower potential to aggravate these symptoms via EPS.

Drug change – irrespective of first drug choice – occurred more often in younger patients with shorter illness duration or first episode schizophrenia, and in those with a higher anxiety/depression-score at admission. A similar predictor pattern – adding a better prognosis according to the Strauss-Carpenter Prognosis Scale – was found in particular for those patients switched from typical to atypical neuroleptics. This could point to a subgroup with candidates to be primarily put on atypical neuroleptics, because they do not respond well to typical neuroleptics. Accordingly, this predictor pattern did not apply for drug-change in patients primarily given atypical neuroleptics. For this group no significant predictors at all could be identified – leaving the question unanswered, why about 28 % of these patients also could not be maintained on atypical neuroleptics.

Outcome of different treatment strategies

According to current general opinion one should expect patients primarily put on atypical drugs to have a better outcome, especially concerning negative symptoms, side-effects and social adjustment (e. g. Kasper et al. 1999; Möller 1996). However, concerning clinical and social measures there were only marginal differences between patients at the end of treatment under either atypical or typical neuroleptics. Irrespective of first drug choice and response to first or second drug principle, outcome was almost similar. The primary 'non-response' rates, i. e. switch-rates (see above), were identical for those started on typical or atypical neuroleptics. Global side-effect ratings at discharge seemed to be slightly more pronounced for those patients switched to typical neuroleptics, but no difference in treatment satisfaction could be obtained. Voruganti et al. (2000) from a naturalistic cross-sectional study also reported no superiority of atypical neuroleptics in clinician rated (objective) measures of psychosocial functioning, but found a better subjective tolerability, side-effect profile and self-rated quality of life.

Concerning length of stay, patients in the 'initially atypical' group stayed significantly longer than patients in the 'combined' group. Patients maintained on atypical neuroleptics also stayed longer (64.7 days) than those maintained on typical neuroleptics (51.4 days), although there was no difference in treatment outcome. In general, however, all patients whose drug principle had to be switched, stayed much longer in hospital compared to their counterparts maintained on their first choice drug principle. It could be argued that in these patients the response per time trajectory is less steep and takes more time until remission. Whether the kind of first drug choice or the switching to another drug principle can accelerate this process could only be answered from randomized controlled research. Contrary to clinical folklore, studies have shown that in case of non-response switching from one class of typical neuroleptics to another is not very effective (Kinon et al. 1993), whereas change to an atypical drug may be effective, at least in the case of clozapine (Kane et al. 1988) and perhaps also in some of the other second generation neuroleptics (Chakos et al. 2001). According to our results, change to an atypical drug at least seems to correlate with a stronger decline in psychopathology and a greater improvement in social functioning. However, under naturalistic conditions there seem to be 'many roads to Rome', i. e. different strategies are leading to quite similar results.

Methodological limitations

Since treatment was left to the clinicians' discretion, various treatment patterns occurred which for the purpose of data analysis have been stratified. This stratification is an arbitrary approach to treatment reality. According to the naturalistic study design, results of comparison between treatment strategies and drug principles must be considered cautiously. Furthermore, since clinical documentation took place only at admission and discharge, treatment course could not be exactly monitored and reasons for treatment decisions, e. g. drug switching, could only be inferred indirectly. Hence, hospital differences in treatment decisions, although in part due to differences in patient selection, could not be fully explained. Finally, detailed data on treatment side-effects were also not available for this project, since only the CGI was used for overall side-effect ratings. This limitation in particular renders comparison between typical and atypical neuroleptics difficult.

Conclusion

This naturalistic study has demonstrated that, comparable to other European countries, about 50 % of patients with schizophrenia or related delusional disorders were treated with atypical neuroleptics at one time or another during their hospital stay; however these second gener-

ation antipsychotics are still rarely administered as first choice treatment. Contrary to clinical guidelines, first episode patients seem not yet to be sufficiently considered primary candidates for atypical neuroleptics. The preferential use of typical drugs in cases of higher illness severity may result from the clinicians' belief of their superior efficacy under routine conditions with a population different from phase III research. This, however, should be substantiated by future research on treatment attitudes.

Irrespective of first drug choice, response rates under routine conditions may not be higher than 70 %, and outcome differences between drugs under routine treatment conditions may only be marginal. However, this statement should be taken cautiously since this was a non-randomized naturalistic study and more sophisticated side-effect ratings were not available. Primary nonresponders to whatever kind of drug treatment, on average seem to have a 27 days longer inpatient stay. As to the health political implications of these findings, the pre-treatment identification of nonresponders and the development of special treatment options for them seems a challenging task for the future.

Acknowledgment The study was supported by a grant from the German Ministry of Health (GMQK01184297).

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