Implementation of a Schizophrenia Practice Guideline: Clinical Results

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Background: In mental health care, a range of guidelines with sound methodology is available; however, implementation studies in routine care are scarce.

Method: In a controlled before-and-after study design, the pharmacologic part of the German evidence-based schizophrenia guideline was implemented using a quality-circle–based intensive implementation program. 151 adult inpatients with a diagnosis of schizophrenia or schizoaffective disorder (according to ICD-10 criteria) were assessed in 4 psychiatric wards before (N = 77) and after (N = 74) guideline implementation. Treatment process and patient outcome were assessed at admission and discharge using the Positive and Negative Syndrome Scale (PANSS) and predefined process measures. A propensity score model adjusted for baseline psychopathology and sociodemographic variables was used. Data were collected from April to September of 2005 and from January to May of 2006 for the preintervention and postintervention periods, respectively.

Results: After guideline implementation, the rate of antipsychotic monotherapy at discharge increased from 39.5% to 67.6% (p = .021) and the incidence of significant neurologic side effects decreased from 26.3% to 7.0% (p = .038). Antipsychotic dosage and prescriptions of other psychotropic drugs did not change. Although patients in the postintervention group were more severely disturbed at baseline, the reduction in PANSS total score was significantly greater among this group than among the preintervention group (p = .048).

Conclusion: After guideline implementation, we observed significantly more antipsychotic monotherapy and a decrease in adverse drug effects. Changing physician behavior and improving process and outcome measures requires intense efforts.

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In the last 2 decades, guideline development and evaluation methods have been significantly improved, resulting in a considerable number of evidence-based mental health guidelines in many countries across the world. Evidence-based practice guidelines in psychiatry are viewed as an essential asset if appropriately developed and applied.[1]

However, there has been little research on the influence of specific psychiatric guidelines on physician behavior, treatment process, and patient outcome. Both in general medicine and in psychiatry, there is insufficient evidence to support specific guideline implementation methods.[2,3]

Evaluation of the influence of guidelines on the care process poses some methodological challenges, as guidelines, unlike specific drug or psychosocial interventions, are complex sets of recommendations. It may take substantial effort to identify the "active ingredients" required for successful implementation projects. Furthermore, it may be difficult to measure the degree to which patients are exposed to the treatment procedures recommended by practice guidelines, and interventions target therapists rather than patients.

In view of the current discussion on the comparative effectiveness of second-generation antipsychotics (SGAs) versus first-generation antipsychotics (FGAs),[4] guideline implementation programs should not primarily intend to increase the prescription rate of specific substances but

should aim to decrease the variability of prescriptions, especially with respect to antipsychotic polypharmacy and excessive dosing, which are prevalent despite guideline recommendations to the contrary.[5,6] Apart from promoting a structured approach toward pharmacotherapy in schizophrenia treatment, our study aimed at increasing the transparency of the treatment, promoting patient involvement in the choice of medication, and reducing possible harm to patients[7] by diminishing antipsychotic and psychotropic polypharmacy.

The principal aim of the present study was to evaluate whether systematic implementation of an evidence-based schizophrenia guideline driven by quality circles improves guideline adherence and patient outcome. A special focus of the study was on reducing antipsychotic polypharmacy. We hypothesized that after guideline implementation, the rate of antipsychotic monotherapy and clinical improvement at hospital discharge would be significantly increased.

METHOD

Study Design and Patient Selection

This study was conducted as a controlled before-and-after study that compared treatment process and patient outcome data before (preintervention period) and after (postintervention period) the structured implementation of the German evidence-based schizophrenia guideline.[8] Data were collected in 2005 and 2006 in 4 general psychiatric wards, 2 of which were closed and 2 of which were open, within a southern German psychiatric hospital. The preintervention recruitment period lasted from April until September 2005, and the postintervention recruitment period lasted from January to May 2006. All female or male patients admitted with a diagnosis of schizophrenia or schizoaffective disorder according to the *International Classification of Diseases, 10th Revision* (ICD-10) and aged between 18 and 65 years were asked to participate and give informed consent. Patients were assessed at admission and were followed up at weekly intervals during the inpatient stay and at the time of discharge. Exclusion criteria were minimal in order to recruit a true representative sample of the guideline target population. The psychotic disorder must have been the primary reason for admission. Individuals must have had minimum German language proficiency in order to give informed consent. Patients with an obvious drug-induced psychosis were excluded. However, patients with a comorbid substance disorder or serious physical illness were not excluded. There was no symptom severity threshold required for participation.

Randomization of patients at the physician or ward level was regarded as not feasible because of the expected "spillover" or contamination effects due to medical and other staff talking about guideline recommendations with effects on control group practice. The period for the guideline intervention was chosen at the time the printed version of the guideline was published so that physicians in the preintervention period did not know the guideline recommendations. During the whole study, physicians from the 4 psychiatric wards had access to the same medications and the same nonpharmaceutical treatment options. Physicians were not forced to follow any of the guideline recommendations.

The study was conducted in accordance with international guidelines for good clinical practice and was approved by the institutional ethics committee of the University of Ulm.

Schizophrenia Guideline and Implementation Intervention

The schizophrenia practice guideline of the German Society for Psychiatry, Psychotherapy, and Nervous Diseases was revised between 2004 and 2005 and published in November 2005 as a systematically developed evidence-based guideline.[1] The guideline comprises (1) a detailed text with key recommendations, short reports on the underlying evidence, and background information (long version); (2) a short version with key recommendations only; (3) algorithms; and (4) a methods section. The guideline consists of 4 parts: (a) pharmacologic and other biological treatments, (b) psychotherapeutic interventions, (c) psychosocial interventions and mental health care delivery systems, and (d) treatment under special circumstances such as agitation, suicidal behavior, treatment resistance, pregnancy, old age, or prodromal stage.

The guideline presents separate recommendations and algorithms for first-episode and multiple-episode psychosis. For each medication step, critical decision points were defined with clear recommendations for medication choice and dosage ranges. Algorithms for treatment resistance and for agitated and severely disturbed patients, as well as for treatment of psychiatric comorbidity, were also used in this study. There were no further patient or family education programs implemented specifically within the study. However, psychoeducation programs and family education sessions were important recommendations of the guideline.

The guideline implementation intervention was performed between the preintervention and the postintervention periods. It took place from October 2005 until May 2006 and consisted of several modules:

1. Dissemination of the book version of the guideline to all psychiatrists, psychologists, and psychiatric nurses involved in the care of patients.
2. Two slide presentations of 90 minutes each on the project and key guideline recommendations for all clinical staff.

Table 1. Process Measures Used as Guideline Adherence Criteria

Guideline Recommendation/Management Principle	Adherence Measure Operationalization
1. Antipsychotic monotherapy at admission	Patients should receive no more than 1 antipsychotic
2. Antipsychotic monotherapy at discharge	Patients should receive no more than 1 antipsychotic
3. SGA monotherapy at discharge	Patients should receive monotherapy with a SGA
4. Adequate dosage of antipsychotics in total at admission	Patients should not receive dosages of more than 1000 mg chlorpromazine equivalent
5. Adequate dosage of antipsychotics in total at discharge	Patients should not receive dosages of more than 1000 mg chlorpromazine equivalent
6. Adequate treatment of significant depressive symptoms	Patients with PANSS score ratings for a minimum of 2 weeks of at least severe for the "depression" item or moderately severe for the "depression" item plus the "guilty ideas," "anxiety," or "concern about physical health" item should receive an antidepressant medication or a change of SGA medication within 2 weeks
7. Adequate treatment of persistent psychotic symptoms	Patients with PANSS score ratings for a minimum duration of 3 weeks of at least severe for the "hallucinations" or "suspiciousness" item, at least moderately severe for the "unusual thought content" or "conceptual disorganization" item, or PANSS total score ratings higher than 90 and the positive subscale score exceeding the negative subscale score should have a significant change of medication dosage not above 1000 mg chlorpromazine equivalent, a change of antipsychotic medication to a monotherapy trial with a different antipsychotic drug class within 3 weeks, a change from antipsychotic polypharmacy to monopharmacy, a switch to clozapine after 2 adequate previous antipsychotic trials during the present episode, or clozapine augmentation with amisulpride in patients already receiving clozapine
8. Adequate treatment of neurological side effects	In case of akathisia, rigor, or dystonia with at least medium intensity or tardive dyskinesia for at least 2 subsequent weeks, antipsychotic dose should be reduced, a different antipsychotic SGA monotherapy should be used within 2 weeks, the patient should be offered treatment with clozapine, or the anti–side effects medication should be changed

Abbreviations: PANSS = Positive and Negative Syndrome Scale, SGA = second-generation antipsychotic.

3. A scheme of 17 biweekly *quality circles* on key issues covered by the guideline. Quality circles were organized as 90 minute meetings involving all physicians on the wards, key nursing staff, and psychologists. Quality circles followed a uniform scheme. During each session, one of a predefined set of themes was chosen by the members, guideline recommendations on the issue were extracted and discussed, treatment as usual was reviewed, a specific aim was set with regard to improving guideline adherence, specific implementation barriers were clarified, and actions were taken. In some sessions, treatment as usual was described using feedback slides based on the preintervention database. Quality circles were moderated by an experienced physician not involved in patient care. The themes were as follows: initial antipsychotic medication in multiple-episode and first-episode patients, pharmacologic and nonpharmacologic treatment of behaviorally disturbed patients, sedation and avoidance of constraint, treatment nonresponse, treatment of patients with suicidal behavior, and psychoeducation.
4. At the end of the intervention period, some typical case reports were discussed in each ward, and solutions for common clinical problems were sought on the basis of specific guideline recommendations.

Research Assessments and Measures of Adherence

Demographic and clinical variables were obtained from patients by an independent rater at the time of admission. Detailed diagnostic and therapeutic processes, the Positive and Negative Syndrome Scale (PANSS),[9] and a social functioning scale (Global Assessment of Functioning [GAF][10]) were recorded. Trained research workers assessed treatment process variables, including medication, using a standardized protocol and patient charts at weekly intervals and at hospital discharge. Further items from a minimum routine data set collected by the treating psychiatrist for all psychiatric inpatients were used. In addition, patient medication adherence was assessed by clinicians using a 4-point Likert scale (active cooperation, passive acceptance, reluctance, and denial) both during the first week after admission and at discharge. PANSS positive and negative subscores and thought disturbance, depression/anxiety, and schizophrenia subscores, including the thought disturbance cluster, activation cluster, and paranoid/belligerence cluster, were calculated according to Kay (1991).[9]

Guideline adherence was measured using 8 criteria (Table 1). Benperidol, flupenthixol, fluphenazine, haloperidol, perazine, perphenazine, pimozide, and zuclopenthixol were classified as medium-potency or high-potency FGA drugs irrespective of their mode of administration. Chlorprothixene, levomepromazine, melperone, and pipamperone were classified as low-potency FGAs. Amisulpride, aripiprazole, clozapine, olanzapine, quetia-

pine, risperidone, ziprasidone, and zotepine were classified as SGAs.

Statistical Methods

Descriptive statistical tests of sociodemographic variables, type of admission (voluntary or involuntary), and illness and clinical baseline variables were performed. To compare these baseline values between preintervention and postintervention groups, we used t tests for continuous variables and χ^2 tests for proportions. An analysis of variance model was applied. Data were analyzed using 2-tailed tests of significance with 95% confidence intervals (CIs). A PANSS response was defined as PANSS improvement of at least 20%. Additionally, a response criterion based on at least 30% PANSS improvement was used in a sensitivity analysis. A p value of .05 or less indicates a significant difference between groups.

Hypotheses were tested hierarchically. The primary study hypothesis was that guideline implementation would lead to a 20% increase in total PANSS reduction. According to an explorative study in the same clinical setting, people with schizophrenia, at admission, had a mean PANSS total score of 87, which declined to a mean of about 60 at discharge. Assuming a standard deviation of 25, we calculated a minimum participant number of 132 to show a 20% increase in PANSS improvement with 80% power, a 5% significance level, and an expected drop out rate of 20%. Secondary hypotheses concerned an increase in the guideline adherence measures (see Table 1) of at least 20%.

To evaluate the influence of guideline implementation on treatment processes controlling for baseline psychopathology, we used a propensity score matching model, as randomization was not possible. This model, used to adjust for preexisting group differences, involves a weighting scheme being formed as the inverse of the predicted conditioned probability that a patient belongs to the preintervention or postintervention group. We calculated the propensity of being treated in the preintervention versus the postintervention group using multivariable logistic regression to model a dichotomous outcome for every observation. A range of confounding variables (covariates) was considered in the propensity score model. The final model included 9 covariates that had a significant association with PANSS total score outcome: baseline PANSS total score, age, sex, assisted living, number of previous psychiatric hospitalizations, illness duration, involuntary admission, age at illness onset, and baseline social functioning (GAF). The propensity score was used as independent variable in a logistic regression model to test differences between the intervention groups in the guideline adherence measures. For PANSS outcomes, a linear regression model was used. All calculations were performed with SPSS, version 12.0 (SPSS Inc., Chicago, Ill.).

RESULTS

Patient Characteristics

A total of 359 patients (177 in the preintervention and 182 in the postintervention period) with an admission diagnosis of schizophrenia or schizoaffective disorder were initially screened for participation. Finally, 151 patients (42.1%) were included in our study, 77 patients before (preintervention) and 74 patients during and after (postintervention) guideline implementation. Reasons for noninclusion in the study (N = 208) were no written informed consent (N = 98; 47.1%), not fulfilling diagnostic inclusion criteria according to ICD-10 (N = 45; 21.6%), less than 3 days' inpatient treatment (N = 29; 13.9%), transfer to other psychiatric units not participating in the study (N = 27; 13.0%), no sufficient German language proficiency (N = 6; 2.9%), and other reasons (N = 5; 2.4%).

With the exception of illness duration, the preintervention and postintervention groups were similar at baseline in terms of sociodemographic characteristics and illness history (Table 2). One in 4 patients was admitted involuntarily. Most patients had a diagnosis of schizophrenia, whereas 7.8% (preintervention group) and 9.5% (postintervention group) were diagnosed with schizoaffective disorder. Mean length of stay did not differ between the 2 groups (49.2 days vs. 48.4 days).

Baseline symptoms according to PANSS differed between the 2 groups (see Table 4). Patients in the preintervention group, at admission, had lower total PANSS scores and lower negative symptom and schizophrenia subscores. The PANSS general psychopathology subscore was significantly lower in the preintervention group (38.5 ± 10.3 vs. 46.7 ± 13.5, p = .001). However, the level of social functioning did not differ between groups (see Table 2).

Guideline Adherence: Pharmacologic Therapy

76 patients in the preintervention group and 71 patients in the postintervention group with sufficient medication data contributed to the evaluation. Most patients in the preintervention group (N = 38; 50.0%), during the first 3 days after admission, were treated with a combination of antipsychotics, primarily combinations of SGA and low-potency FGA. A proportion of 27.6% (N = 21) were treated initially with only 1 SGA, 14.5% (N = 11) were prescribed 2 or more FGAs. In the postintervention group, most patients initially received SGA monotherapy (N = 38; 53.5%) with less than 1 in 3 (N = 22; 31.0%) being prescribed SGA/FGA polypharmacy. Only 4.2% (N = 3) were prescribed more than 1 FGA. The overall difference in the type of initial antipsychotic medication was statistically significant (p = .003, analysis of variance without baseline adjustment of PANSS score).

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Table 2. Baseline Characteristics of Schizophrenia Patients by Treatment Group: Before (pre) and After (post) Guideline Implementation[a]

Characteristic	Pre (N = 77)	Post (N = 74)	Statistic[b]	p Value
Age, mean ± SD, y	41.2 ± 11.0	37.9 ± 11.3	F = 3.3	.07
Gender, female	46.8	44.6	χ^2 = 0.071	.79
Living alone	55.8	48.6	χ^2 = 0.780	.24
Assisted living or living in institution	23.4	16.4	χ^2 = 1.13	.12
High school education	27.8	37.5	χ^2 = 1.46	.15
Receiving financial assistance	76.6	61.6	χ^2 = 3.96	.53
More than 6 previous admissions	18.4	25.0	χ^2 = 0.710	.70
Illness duration, mean ± SD, y	13.4 ± 10.8	8.3 ± 9.1	F = 7.58	< .01
Involuntary admission	22.1	24.6	χ^2 = 0.370	.83
Age at first psychiatric treatment, mean ± SD, y	27.2 ± 9.8	25.7 ± 8.0	F = 0.732	.39
Schizoaffective disorder	7.8	9.5	χ^2 = 0.112	.74
GAF score, mean ± SD	33.0 ± 12.4	35.4 ± 11.5	F = 1.41	.24
Length of stay, mean ± SD, d	49.2 ± 31.0	48.4 ± 31.0	F = 0.021	.89

[a]Values are expressed as percent unless otherwise noted.
[b]For χ^2 values, df = 2.
Abbreviation: GAF = Global Assessment of Functioning.

Table 3. Guideline Adherence by Treatment Group: Before (pre) and After (post) Guideline Implementation, N (%)

Guideline Recommendation/Management Principle	Pre (N = 76)	Post (N = 71)	Exp (B)[a]	p Value[b]
Antipsychotic monotherapy in the first week after admission	27 (35.5)	46 (64.8)	0.289	.029
Antipsychotic monotherapy at discharge	30 (39.5)	48 (67.6)	0.266	.021
Atypical antipsychotic monotherapy at discharge	25 (32.9)	39 (54.9)	0.416	.117
Antipsychotic dosage not above recommendation in the first week after admission	57 (75.0)	58 (81.7)	0.780	.718
Antipsychotic dosage not above recommendation at discharge	59 (77.6)	61 (85.9)	0.451	.341
Antipsychotic dosage within recommended range at discharge	46 (60.5)	52 (73.2)	0.591	.357
Adequate therapy of significant depressive symptoms	5 (35.7)[c]	7 (46.7)[d]	0.594	.667
Adequate therapy of significant persistent psychotic symptoms	8 (44.4)[e]	7 (46.7)[f]	0.814	.795
Significant neurological side effects of more than 1 week duration	20 (26.3)	5 (7.0)	0.368	.038
Adequate therapy of significant neurological side effects	11 (55.0)	4 (80.0)	0.547	.313

[a]Exp (B) represents the regression coefficient in the propensity score model equaling the odds ratio of being in the preintervention versus postintervention group.
[b]The p value is given for the propensity score model with baseline total Positive and Negative Syndrome Scale score as covariate.
[c]N = 14 patients with significant depressive symptoms.
[d]N = 15 patients with significant depressive symptoms.
[e]N = 18 patients with significant persistent psychotic symptoms.
[f]N = 15 patients with significant persistent psychotic symptoms.

There was no change in the discharge prescription rates of benzodiazepines (13.0% preintervention vs. 20.3% postintervention, p = .162), tricyclic or tetracyclic antidepressants (5.2% preintervention vs. 6.8% postintervention, p = .475), selective serotonin reuptake inhibitors and other modern antidepressants (10.4% preintervention vs. 12.2% postintervention, p = .472), and lithium (7.8% preintervention vs. 12.2% postintervention, p = .266). However, carbamazepine was prescribed less frequently in the postintervention group (18.2% preintervention vs. 5.4% postintervention, p = .014), whereas valproate was prescribed more often (1.3% preintervention vs. 9.5% postintervention, p = .028).

The preintervention and postintervention groups differed in guideline adherence rates (Table 3). Following the intervention there was almost a 2-fold increase in the percentage of patients receiving antipsychotic monotherapy in the first week after admission and at discharge.

In contrast, antipsychotic dosages changed only slightly. There was approximately a 10% increase between the preintervention and the postintervention groups in the percentage of patients without excessive dosages at discharge. We found a 12.7% increase in the percentage of patients receiving antipsychotic dosages within the recommended range at discharge; however, these results were not statistically significant. After guideline implementation, there was only a small nonsignificant change in the frequency of adequate treatment of depressive symptoms. Similarly, psychotic symptoms that were persistent and unchanged for more than 3 weeks were treated according to the guideline in less than 50% of cases in both the preintervention and the postintervention groups. There was a significant decrease of patients with neurologic side effects of a minimum of 2 weeks' duration during the hospital stay, but we failed to find significant differences in guideline adherence concerning management of side effects.

On the whole, in 3 of 8 predefined process measures used as quality indicators, there was a significant increase in guideline adherence rates (Table 3). The frequency of involuntary medication, restraint or seclusion, and nonpharmacologic treatment did not change. In contrast, the

Table 4. Outcomes for Patients With Schizophrenia or Schizoaffective Disorder in Preintervention and Postintervention Groups[a]

Outcome	Pre (N = 76)	Post (N = 71)	Statistic	p Value[b]
PANSS total score				
Baseline	77.7 ± 20.8	92.1 ± 26.7	F = 11.717	.001
Discharge	61.1 ± 20.8	68.4 ± 22.2	F = 2.147	.148
Reduction: baseline to discharge	–16.6 ± 16.6	–24.3 ± 19.2	F = 4.147	.048
PANSS positive subscore				
Baseline	21.8 ± 6.8	23.6 ± 7.8	F = 2.730	.101
Discharge	14.7 ± 6.6	14.3 ± 5.2	F = 5.368	.024
Reduction: baseline to discharge	–7.1 ± 6.1	–9.3 ± 6.9	F = 0.084	.775
PANSS negative subscore				
Baseline	16.0 ± 8.4	20.8 ± 8.9	F = 5.665	.019
Discharge	14.2 ± 7.6	17.6 ± 7.0	F = 0.122	.728
Reduction: baseline to discharge	–1.8 ± 6.7	–3.2 ± 5.8	F = 0.195	.661
PANSS schizophrenia subscore				
Baseline	28.8 ± 7.7	30.7 ± 9.9	F = 8.556	.004
Discharge	20.6 ± 8.3	21.0 ± 8.0	F = 3.813	.055
Reduction: baseline to discharge	–6.2 ± 6.2	–9.7 ± 8.0	F = 4.010	.049
PANSS thought disorder subscore				
Baseline	13.0 ± 4.3	13.2 ± 4.9	F = 1.149	.286
Discharge	8.7 ± 4.1	8.2 ± 3.1	F = 7.016	.010
Reduction: baseline to discharge	–4.3 ± 3.3	–5.0 ± 4.1	F = 0.079	.780
PANSS anxiety/depression subscore				
Baseline	9.0 ± 4.5	10.8 ± 4.5	F = 3.806	.053
Discharge	7.4 ± 2.9	7.9 ± 3.2	F = 3.107	.083
Reduction: baseline to discharge	–1.6 ± 3.8	–2.9 ± 3.8	F = 2.798	.099
PANSS response ≥ 20%[c]	57.5	74.5	Exp (B) = 3.996[d]	.050
PANSS response ≥ 30%[e]	34.7	37.7	Exp (B) = 0.331[d]	.222

[a]Values are expressed as mean ± SD unless otherwise noted.
[b]The p value is given for the propensity score model with baseline total PANSS score as covariate.
[c]Percent of patients with at least 20% total PANSS improvement.
[d]Exp (B) represents the regression coefficient in the propensity score model equaling the odds ratio of being in the preintervention versus postintervention group.
[e]Percent of patients with at least 30% total PANSS improvement.
Abbreviation: PANSS = Positive and Negative Syndrome Scale.

degree of cooperation in taking medication changed significantly between the preintervention and postintervention groups. At discharge, only 29.2% in the preintervention group cooperated actively in taking their medication, whereas 61.1% passively accepted medication, and 9.6% were skeptical and needed heavy persuasion. In the postintervention group, 67.2% cooperated actively and 29.3% passively accepted medication. Only 1.7% refused all kinds of medication, and 1.7% were skeptical and needed heavy persuasion. This difference was statistically significant (p = .029, F = 5.027).

Patient Outcome

Using propensity score analysis, the PANSS total score and most PANSS subscores, except for the positive and thought disorder subscores, did not differ significantly at discharge between the preintervention and the postintervention groups (Table 4). However, with patients in the preintervention group having lower baseline mean total PANSS scores and lower PANSS subscores at admission, PANSS total score and schizophrenia subscore reductions in absolute terms during the hospital stay were significantly greater in the postintervention versus preintervention groups. We observed a 46% increase in PANSS reduction in the postintervention group. There were significantly more PANSS responders in the postintervention group, when PANSS response was defined as a minimum of 20% improvement in the total PANSS score (p = .050) from baseline to discharge, but not when PANSS response was defined as an improvement of at least 30% on total PANSS score (p = .222).

DISCUSSION

This controlled before-and-after study demonstrated significant change in the prescription of antipsychotic drugs following guideline implementation, with a 2-fold increase of patients receiving antipsychotic monotherapy at admission and discharge. Apart from reduced polypharmacy and increased SGA medication, there was no further significant change in medication regimes, although there was a nonsignificant increase in the proportion of patients treated within the recommended dose range of antipsychotics. An increase in rates of active medication compliance was observed in the course of the study. The latter finding may be due to the shared decision-making approach endorsed by the guideline, which could have led to more positive attitudes toward medical treatment.[11] This result may be of relevance, especially with regard to the high discontinuation rate of antipsychotic treatment found

in a recent landmark study.[12] Furthermore, the guideline adapted a structured approach to agitation and behavioral disturbance with the aim of reducing restraint and seclusion. In addition, the higher proportion of antipsychotic monotherapy may have facilitated medication compliance by simplifying the medication regimen or reducing neurologic side effects.[13]

Apart from improving clinical outcomes, harm reduction is one of the aims in implementing a clinical guideline. With this short-term study, we were unable to evaluate long-term medication continuation, long-term side effects, or long-term compliance. However, as antipsychotic polypharmacy is often continued after discharge,[14] and because atypical antipsychotic polypharmacy may compromise the reduction in extrapyramidal side effects in patients on SGA treatment,[15] a reduction in polypharmacy as shown in this study may be a goal in its own right. Although most guidelines advocate the use of 1 antipsychotic with the exception of the short period while medications are being switched,[16,17] it is not clear if the preference of monotherapy is always justified. It is argued that polypharmacy, in psychiatric disorders, is often used to increase the likelihood of remission. Thus in depression therapy, some authors claim that monotherapy lacks ecological validity.[18] It may be impossible to exactly describe situations in which polypharmacy may lead to improved outcome, taking into account the scarcity of studies showing any superiority of antipsychotic polypharmacy. In fact, evidence is accumulating that most patients remain stable or improve after switching medication to a single antipsychotic.[19] The same may be true for high antipsychotic doses.[20] Given our finding on monotherapy, we failed to find any deterioration in outcome in the postintervention group compared to treatment as usual, but could demonstrate an increase in the total PANSS response rate, albeit only when response was defined as improvement in the PANSS score of at least 20%, and not 30%.

Further questions concerning guideline algorithms are the critical decision points, when to switch from one algorithm step to another, and the choice between sequential monotherapy versus combination therapy with other psychotropic substances or additional nonpharmacologic therapy. Currently, as there is an enormous variability in antipsychotic response and vulnerability to side effects,[21] antipsychotic switching recommendations are not truly evidence-based and reflect indirect study evidence. In fact, we believe that one of the main factors leading to improved patient outcomes in schizophrenia treatment may be the structured approach itself toward patient care, the commitment toward evidence-based care, and the therapists' forthrightness to question their own decision base.

There is a continuing debate as to how guideline adherence can be measured quantitatively in mental health practice.[22] Although in recent years researchers have claimed that studies are under way to develop and validate process measures for care assessment and improvement in schizophrenia patients,[23] there are very few measures available that can be used in guideline validation studies. Our adherence measures used as process indicators resemble those used in the Texas Medication Algorithm Project (TMAP) study.[24] As in our study, these authors evaluated the performance of indicators chosen a priori. However, the choice of measures always remains somewhat arbitrary. We did not use composite adherence scores integrating all adherence domains as in Dennehy et al.[24] because we regarded the domains as not being equivalent. Thus, we could not relate patient characteristics to guideline adherence.

Our study has certain limitations. First, the design implies difficulties in attributing causality.[25] There was no contemporary control group, thus leaving a certain risk that confounders may have contributed to our findings. The study period lasted more than 1 year. Within that period, there was a further increase in the market share of SGAs. However, our design avoided possible contamination effects that cannot be excluded when a clinical guideline is introduced only in certain wards of a hospital, and when physicians and therapists are in constant contact with each other. In addition, contamination was also avoided by the fact that the guideline intervention began just at the moment when the guideline was publicly accessible. A randomized controlled trial was not considered feasible. The design chosen, however, is superior to uncontrolled designs.

Although there was a good comparability of the sociodemographic variables in both cohorts, the baseline mental state scores differed, especially in the PANSS negative subscore and the schizophrenia subscore. In contrast to this, social functioning was comparable at admission. Patients in the postintervention cohort were rated more severely ill at admission than those in the preintervention cohort. This may reflect a change in the admission policy of the hospital, with fewer patients with mild symptoms being admitted, leading to an increase in the average symptom score. A rater effect with systematically higher ratings in the postintervention group would be an alternative explanation. However, with more severely disturbed patients in the postintervention group, a bias in the conservative direction would be introduced because we would have expected more antipsychotic polypharmacy in this group due to more severe symptoms requiring more medication. With a propensity score analysis, we controlled for differences in baseline mental state and found that the differences in process and outcome effects remained significant.

We used the propensity score model to adjust for baseline differences in psychopathology and sociodemographic variables. This model rests on the "strong ignorability assumption," which means that we had to

assume that in this before-and-after study, patients were sorted into the groups as if randomly assigned, and that there were no unmeasured patient characteristics that might confound the results.[26] This assumption is rather strong. Time differences in clinical or sociodemographic variables may not fully be accounted for. A further problem is the regression toward the mean tendency in repetitive measuring, a finding valid independent of the impact of confounders.[27] Patients with extreme PANSS scores at baseline will, for purely statistical reasons, have less extreme scores when measured again. This tendency may have led to a bias in favor of the more severely disturbed postintervention group.

It is noteworthy that treatment processes changed only in those subject areas that were intensely debated within the quality circles. Change of physician behavior needs strong and continuous efforts and specifically tailored interventions. Without implementation programs, practice guidelines may not exert substantial effects on process and outcomes. Taking into account how little evidence there is on this topic and bearing in mind limitations, this study adds to our knowledge on complex quality-circle driven guideline implementation and how it can affect prescription practice.

In conclusion, our study showed medication changes in some areas after guideline implementation. There was a significant increase in antipsychotic monotherapy and an increase in the proportion of patients with active medication compliance. We found some evidence of outcome improvement, albeit this result depended on the outcome definition and needs to be seen against the background of study limitations. Pragmatic standards in guideline implementation and validation studies would be helpful in comparing the effects of specific guidelines on patient outcome and treatment process and would facilitate the refinement of research on specific implementation tools.

Drug names: aripiprazole (Abilify), carbamazepine (Carbatrol, Equetro, and others), clozapine (FazaClo, Clozaril, and others), haloperidol (Haldol and others), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), pimozide (Orap), quetiapine (Seroquel), risperidone (Risperdal), valproate (Depacon and others), ziprasidone (Geodon).

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