Polypharmacy in Patients With Schizophrenia

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Background: Polypharmacy in patients with schizophrenia is a common practice with little basis in well-controlled studies. The objective of this report is to describe the changes in prescription practices with psychotropic medications for patients diagnosed with schizophrenia in 1995 and 2000.

Method: The medical records of patients who were discharged from our facility in 1995 and 2000 with the diagnosis of schizophrenia (DSM-IV criteria) were reviewed. The psychotropic medications at discharge were compared. The incidence of adverse drug reactions and indicators of patient outcome were also compared.

Results: 459 records were reviewed for 1995 and 584 were reviewed for 2000. Patients discharged in 2000 were significantly more likely to receive antidepressants, mood stabilizers, anxiolytics, and multiple antipsychotics than patients discharged in 1995 ($p < .0001$). Patients discharged in 2000 were given significantly fewer anticholinergics ($p < .0001$). There was a large increase in the use of divalproex. No patients were discharged on treatment with more than 1 antipsychotic in 1995, whereas in 2000, 15.9% of patients were. The most common antipsychotic combination was haloperidol and olanzapine. Paralleling the increased use of polypharmacy, there were significantly fewer adverse drug reactions in 2000 than in 1995 ($p = .002$). In addition, patients with schizophrenia who were discharged in 2000 had significantly shorter lengths of stay ($p < .0001$) and were significantly more likely to be discharged to the community than to a state hospital ($p = .0001$).

Conclusion: This study found that acutely ill hospitalized patients with schizophrenia are being treated with more psychotropic medications, including more than 1 antipsychotic. These changes are coincidental with a decrease in adverse drug reactions and an improvement in indicators of patient outcome.

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While the standard of treatment for schizophrenia is the use of 1 antipsychotic medication,[1,2] polypharmacy is not rare. A 1985 survey[3] found that over 60% of patients in multiple countries with chronic schizophrenia were on treatment with 2 or more antipsychotics, while in Japan, half of hospitalized patients receive 3 or more.[4] Procyshyn et al.[5] recently reported that 27.5% of patients with schizophrenia were discharged from a tertiary care psychiatric institution on treatment with multiple antipsychotics. Other surveys of antipsychotic prescribing practices for the outpatient treatment of schizophrenia have found polypharmacy used in 11% to 25% of patients.[6–8]

Case reports[9–15] have suggested that combining antipsychotics can be advantageous. However, a report by Waddington et al.[16] found an association between excess mortality in schizophrenia and the number of antipsychotics given concurrently. A recent review of the literature[17] on antipsychotic polypharmacy found insufficient data from which to draw conclusions about either efficacy or safety.

In this study, we compare pharmacologic treatment of patients with schizophrenia who were hospitalized at our facility in 1995 and those hospitalized in 2000. Atypical antipsychotics were infrequently used in 1995; by 2000, they had been added to the hospital's formulary. An objective of this report is to describe changes in prescription practices with respect to antipsychotic polypharmacy and overall psychotropic polypharmacy, as well as changes in the incidence of adverse drug reactions that may have occurred. Another objective is to review the possible association that a change in prescribing practices may have had with treatment outcome. This will be done by comparing changes in both the length of stay of acute hospitalization and the proportion of patients who could be discharged to the community as opposed to requiring intermediate hospital care.

METHOD

Study Design

This retrospective study looks at the psychotropic medication treatment for patients with the diagnosis of schizophrenia (DSM-IV criteria) who had been hospitalized at the inpatient psychiatry service in the years 1995 and 2000. Patients were included who were discharged to the community or to a state facility for intermediate care.

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Table 1. Characteristics and Discharge Medication of Patients With Schizophrenia[a]

Variable	1995 (N = 459)[b]	2000 (N = 584)[b]	Comparison
Age, mean ± SD, y	37.6 ± 10.5	39.2 ± 12.0	t = 2.24, df = 1041, p = .02
Sex			χ^2 = 0.04, df = 1, p = .84
Male	303 (66.0)	382 (65.4)	
Female	156 (34.0)	202 (34.6)	
Race/ethnicity			χ^2 = 1.75, df = 3, p = .625
African American	315 (68.6)	409 (70.0)	
Hispanic	112 (24.4)	139 (23.8)	
White	29 (6.3)	29 (5.0)	
Asian	3 (0.7)	7 (1.2)	
Discharge medication			
Antipsychotic	454 (98.9)	583 (99.8)	χ^2 = 3.79, df = 1, p = .05
Two antipsychotics	0 (0.0)	93 (15.9)	χ^2 = 80.25, df = 1, p < .0001
Antidepressant	16 (3.5)	83 (14.2)	χ^2 = 34.42, df = 1, p < .0001
Mood stabilizer	30 (6.5)	112 (19.2)	χ^2 = 34.92, df = 1, p < .0001
Anxiolytic	60 (13.1)	145 (24.8)	χ^2 = 22.49, df = 1, p < .0001
Anticholinergic	298 (64.9)	284 (48.6)	χ^2 = 27.66, df = 1, p < .0001

[a]Values shown as N (%) unless otherwise noted.
[b]Some patients received more than 1 discharge. A total of 371 unique patients in 1995 and 490 unique patients in 2000 were discharged.

The years 1995 and 2000 were chosen for comparison since the availability of psychotropic medication, particularly atypical antipsychotics, on the hospital's formulary had been expanded in this interval. In 1995, the only antipsychotics available were conventional ones, with the exception of clozapine and the addition of risperidone late in the year. By 2000, olanzapine, quetiapine, and other psychotropic drugs had been added to the formulary. There was no change in the hospital's policy to either encourage or discourage the use of polypharmacy during the period of study.

The variables used for comparison were the number of psychotropic medications that a patient was prescribed at the time of discharge and the rates of use of antipsychotics, antidepressants, mood stabilizers, anxiolytics, and anticholinergics. Individual medications in these classes were also examined. The medications at time of discharge were used for comparison since these were taken to be the psychiatrist's best effort at treatment before the patient was transferred to another level of care. Other variables compared were the length of stay at the acute service, the proportion of patients who required transfer to a state facility for intermediate care because of inadequate response, and the incidence of adverse drug reactions.

Data Collection

The medical records of patients who were discharged with the diagnosis of schizophrenia in 1995 and 2000 were reviewed. Patient demographics, medications prescribed, and disposition at discharge were obtained from these records.

Adverse drug reactions were reported to the hospital's pharmacy that provided the data on them for this report. The validity of these reactions was regularly assessed by chart reviews that were reported to the hospital's Pharmacy and Therapeutics Committee. Most of the adverse drug reactions were extrapyramidal effects of antipsychotic medication that required a physician's intervention.

Hospital and Patient Characteristics

The 135-bed psychiatric inpatient service is part of a 413-bed general hospital that serves an impoverished urban population that has not changed appreciably between 1995 and 2000. The community has been designated medically underserved by both federal and state agencies. The inpatient service consists of 6 locked coed units that treat acutely ill adult patients. Approximately 70% of admissions are involuntary. There are over 2000 discharges per year. In 1995, medical records on 459 discharges were reviewed, for which 371 were unique patients. In 2000, 584 medical records were reviewed representing 490 unique patients. Table 1 shows the patient characteristics for these 2 years. Patients from both years were comparable with respect to sex and race/ethnicity. Patients discharged in 2000 were statistically significantly older than patients discharged in 1995.

Treatment Providers

Patients with schizophrenic disorders discharged during 1995 were treated by one of 20 attending psychiatrists. In 2000, 27 attending psychiatrists were involved in the inpatient treatment. With the exception of 4, the attending psychiatrists were different in 1995 and 2000.

Data Analysis

Unpaired, 2-tailed t tests and analyses of covariance were used to compare continuous variables between the 2 years. The chi-square test was used to compare categorical variables. A statistical level of significance was set at .05.

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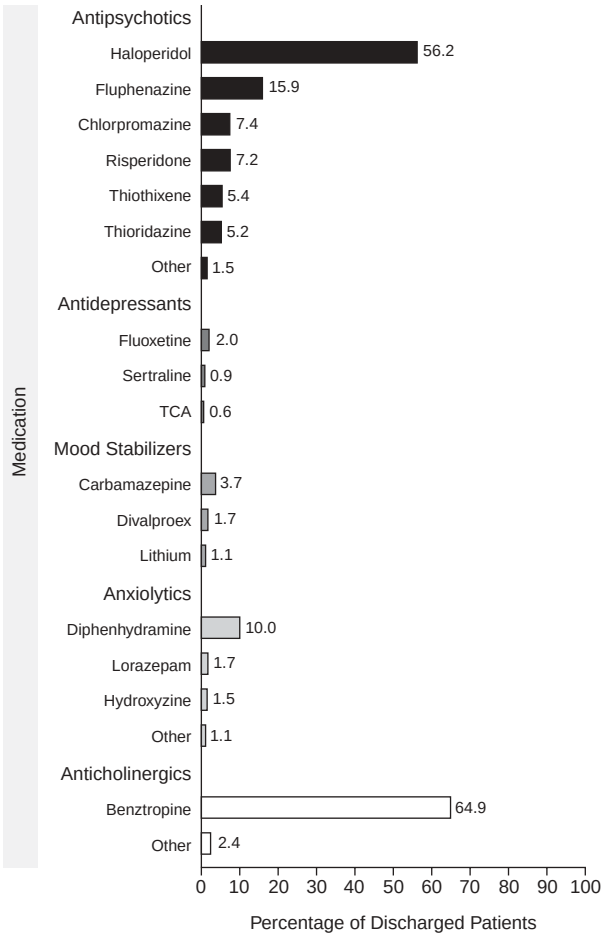
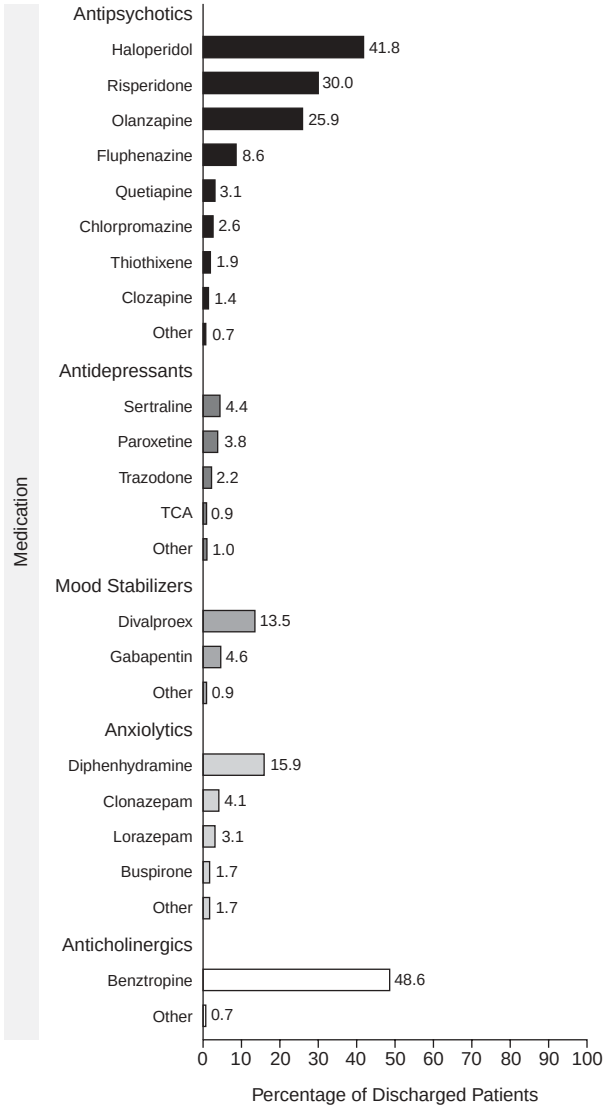
Figure 1. Psychotropic Medication at Discharge in 1995 (N = 459)[a]



[a]Some patients received more than 1 discharge. A total of 371 unique patients were discharged in 1995.
Abbreviation: TCA = tricyclic antidepressant.

Figure 2. Psychotropic Medication at Discharge in 2000 (N = 584)[a]



[a]Some patients received more than 1 discharge. A total of 490 unique patients were discharged in 2000.
Abbreviation: TCA = tricyclic antidepressant.

RESULTS

Psychotropic Use

Patients discharged in 2000 were given a significantly greater number of psychotropic medications than patients discharged in 1995 (mean ± SD: 2.25 ± 0.94 vs. 1.89 ± 0.70; $t = 6.93$, $df = 1041$, $p < .0001$). Table 1 shows the number of patients who received the various classes of psychotropic medication. A significantly greater proportion of patients discharged in 2000 were given multiple antipsychotics, antidepressants, mood stabilizers, and anxiolytics. However, significantly fewer patients in 2000 were given anticholinergics at discharge than patients in 1995. A greater percentage of patients were discharged on treatment with an antipsychotic in 2000 than in 1995; in 1995, 5 patients were not given an antipsychotic and in 2000, 1 was not. In 1995, no patients were discharged on treatment with more than one antipsychotic; in 2000, 93 patients (15.9%) were discharged on treatment with 2 antipsychotics. This difference was statistically significant ($\chi^2 = 80.25$, $df = 1$, $p < .0001$). No patients were discharged on treatment with more than 2 antipsychotics during either year.

Figure 1 shows the use of psychotropic medication for discharged patients with schizophrenia in 1995. The most commonly prescribed medications were haloperidol and benztropine. Figure 2 shows the use of psychotropic medication for discharged patients in 2000. The most commonly prescribed medications were haloperidol, ris-

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Table 2. Polypharmacy in Patients Discharged on Treatment With Antipsychotics in 2000

Medication	Patients (N = 583)[a] N	%
Agents used as cotreatments		
Haloperidol	65	11.1
Olanzapine	56	9.6
Risperidone	35	6.0
Fluphenazine	15	2.6
Chlorpromazine	6	1.0
Quetiapine	6	1.0
Thioridazine	2	0.3
Clozapine	1	0.2
Medication combinations		
Haloperidol + olanzapine	38	6.5
Haloperidol + risperidone	21	3.6
Fluphenazine + olanzapine	8	1.4
Fluphenazine + risperidone	6	1.0
Olanzapine + risperidone	5	0.9
Haloperidol + quetiapine	3	0.5
Chlorpromazine + risperidone	2	0.3
Chlorpromazine + olanzapine	2	0.3
Other	8	1.4

[a]Some patients received more than 1 discharge. A total of 490 unique patients were discharged in 2000. Of the 584 patients discharged in 2000, 1 was not receiving an antipsychotic.

peridone, olanzapine, divalproex sodium, diphenhydramine, and benztropine.

Antipsychotic Polypharmacy

Table 2 shows the frequency with which antipsychotics were used as a cotreatment for those patients who were discharged on treatment with at least 1 antipsychotic in 2000. The antipsychotics most commonly used in combination were haloperidol, olanzapine, risperidone, and fluphenazine. Table 2 shows the frequency of antipsychotic combinations. The most common combination was haloperidol plus olanzapine.

Adverse Drug Reactions

There were statistically significantly fewer adverse drug reactions in patients discharged in 2000 with schizophrenia than in patients discharged in 1995 (1995: 18 [3.9%]; 2000: 6 [1.0%]; $\chi^2 = 9.58$, df = 1, p = .002). In 1995, 16 of these adverse reactions were extrapyramidal reactions from antipsychotics; in 2000, all 6 were extrapyramidal reactions.

Treatment Outcome

A smaller proportion of patients were transferred to a state hospital in 2000 for intermediate care than in 1995: 94 (16.1%) vs. 123 (26.8%). This difference was statistically significant ($\chi^2 = 17.86$, df = 1, p < .0001). Therefore, a greater proportion of patients in 2000 could be discharged to the community. The acute length of stay was also shorter in 2000 than in 1995 (mean ± SD: 25.1 ± 17.8 vs. 28.9 ± 13.2 days). This difference was also statistically significant (t = 3.86, df = 1041, p = .0001). The length of stay remained significantly shorter in 2000 than in 1995 after controlling for the total number of psychotropic medications using analysis of covariance (F = 19.38, df = 1,1039; p < .0001). However, controlling for the number of antipsychotics eliminated the statistical significance in length of stay between the 2 years (F = 1.40, df = 1,1039; p = .24).

Data Subset

The prescribing practices of the 4 psychiatrists who were involved in discharging patients in both 1995 and 2000 were reviewed separately. This was done to control for the variability between 1995 and 2000 that may have been due to different psychiatrists. There remained a statistically significantly larger number of psychotropics (t = 4.23, df = 253, p < .0001) prescribed and significantly more patients being prescribed multiple antipsychotics ($\chi^2 = 15.41$, df = 1, p < .0001), antidepressants ($\chi^2 = 11.94$, df = 1, p = .005), mood stabilizers ($\chi^2 = 14.94$, df = 1, p = .0001), and anxiolytics ($\chi^2 = 4.36$, df = 1, p = .04) at discharge in 2000 than in 1995. However, the use of anticholinergics did not differ significantly ($\chi^2 = 2.07$, df = 1, p = .15).

DISCUSSION

The results of this study show that there have been significant changes in the pharmacologic treatment of schizophrenia at our institution between 1995 and 2000. These changes are marked by an increase in the use of all psychotropic medications (except for anticholinergics) and an increase in the use of multiple antipsychotics. These changes have paralleled fewer adverse drug reactions, a shorter length of stay, and a greater proportion of patients discharged to the community rather than to a state hospital. These changes have also occurred during a period when the hospital's formulary was expanded to include atypical antipsychotics as well as additional psychotropic medications from other classes (e.g., paroxetine, mirtazapine, gabapentin, buspirone).

There are certainly multiple factors contributing to the changes in prescribing practices. One possibility is that the availability of a greater number of psychotropic drugs has led to a greater number being prescribed. These newer drugs are heavily promoted and usually touted as being safer. Considering the significant morbidity from schizophrenia and the frequently modest responses to antipsychotic monotherapy, physicians may have chosen to try many medications from the wide selection of available psychotropics in the hopes that some would be beneficial.

The use of more than 1 antipsychotic was usually the combination of an atypical (most commonly olanzapine) and a conventional antipsychotic (most commonly haloperidol). A possible conclusion from this is that atypical antipsychotics, despite their reported advantages, often

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seem inadequate by themselves in managing the acute symptoms of schizophrenia. In the 1999 consensus treatment guidelines for schizophrenia,[2] the combination of an atypical and a conventional antipsychotic was a second-line choice for those patients who had significant positive symptoms after a trial of an atypical.

The greater use of antidepressants, mood stabilizers, and anxiolytics in 2000 is interesting. This greater use may reflect more attention being paid by the clinician to the mood symptoms of schizophrenia, or the decreased use of conventional antipsychotics has resulted in less blunting of affect. The dramatic increase in the use of divalproex warrants attention. It is likely that it is being used as much to manage aggression and violence as to control more classically manic symptoms. This use is sanctioned by treatment guidelines.[1,2] The reduced use of anticholinergics in 2000 is very likely due to the increased use of atypical antipsychotics, which are associated with a lower risk of extrapyramidal side effects. This hypothesis is borne out by the decreased incidence of adverse drug reactions in 2000, which is attributable to fewer extrapyramidal effects. Although the use of multiple medications increases the potential for adverse effects and drug interactions,[18] this finding was not apparent with these data. Adverse drug reactions reported were only those severe enough to warrant a physician's active intervention. The presence of side effects that did not meet this threshold was not investigated.

The increase in the use of polypharmacy for schizophrenia is associated with indicators of better patient outcome (lower length of stay, fewer transfers to state hospitals). Many factors may account for this finding, but changes in prescribing practices may be one of them. Of note is that when the effect of the number of antipsychotics prescribed on length of stay was factored out, the difference in length of stay lost statistical significance. This finding suggests that the use of more than 1 antipsychotic had a significant impact on length of stay; on the other hand, the total number of psychotropic drugs does not appear to have had such an effect. As the use of polypharmacy for bipolar disorder is now an acceptable approach,[19] the use of multiple medications to treat the varying manifestations of schizophrenia may prove to be equally optimal. Kapur and Remington[20] have proposed a theoretical basis for this strategy.

There are many limitations to this study, its retrospective nature being one of them. In addition, the generalizability of these results from our facility to other practice locations is unknown. The dose of medications used, the explicit rationale for choosing a drug and drug combinations, and the validity of the diagnosis of schizophrenia were not investigated. As for the latter, the focus of the study was on the prescribing practices by psychiatrists for patients that they believed had schizophrenia; the validity of this diagnosis was of secondary concern. Additionally, over the past decade the hospital's administration has pushed for reducing the length of stay. This has probably contributed to the lower length of stay independent of any changes in prescribing practices. However, the administrative pressure to decrease length of stay was present in 1995 as well as 2000, and non–managed care Medicaid remained the primary insurer in both periods. Patients in 2000 were also statistically significantly older than those in 1995. However, the mean difference is less than 2 years of age, and it is unlikely that this had a clinically significant impact on the results.

In summary, our study found that acutely ill hospitalized patients with schizophrenia are being treated with more psychotropic medications, including more than 1 antipsychotic. These changes are coincidental with a decrease in adverse drug reactions and an improvement in indicators of patient outcome. Of great practical importance would be testing the efficacy of the psychotropic combinations. However, this remains a challenge because of the proprietary concerns of the pharmaceutical companies for their newer products as well as the difficult methodology involved[17,21] with such studies.

Drug names: benztropine (Cogentin and others), buspirone (BuSpar), carbamazepine (Carbatrol, Tegretol, and others), chlorpromazine (Thorazine, Sonazine, and others), clonazepam (Klonopin and others), clozapine (Clozaril and others), diphenhydramine (Benadryl and others), divalproex sodium (Depakote), fluoxetine (Prozac and others), fluphenazine (Prolixin, Permitil, and others), gabapentin (Neurontin), haloperidol (Haldol and others), hydroxyzine (Vistaril and others), lorazepam (Ativan and others), mirtazapine (Remeron), olanzapine (Zyprexa), paroxetine (Paxil), quetiapine (Seroquel), risperidone (Risperdal), sertraline (Zoloft), thiothixene (Navane and others), trazodone (Desyrel and others).

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