Risperidone Use at a State Hospital: A Clinical Audit 2 Years After the First Wave of Risperidone Prescriptions

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Background: In spite of some inherent limitations, naturalistic data can provide information on populations that have greater heterogeneity than can controlled clinical trials and on functional outcomes that may be especially important in clinical practice. In the present retrospective naturalistic study, we evaluated key clinical outcomes among the first wave of risperidone-treated patients at a state psychiatric hospital.

Method: Outcome data were extracted from the charts of 142 patients 2 years after initiation of treatment with risperidone. Their diagnoses included DSM-III-R schizophrenia (57%), schizoaffective disorder (22%), dementia and other organic conditions (7%), bipolar disorder (5%), and other psychiatric disorders (9%).

Results: During the 2-year period, 92 of 142 patients were discharged from the hospital: 61 (43%) were discharged on risperidone treatment and 31 (22%) were discharged on treatment with other drugs. At the time of the study, 50 of 142 patients were still in the hospital: of these, 18 (13%) were still receiving risperidone. The modal maximum daily dose of risperidone was 4.1 mg in patients discharged on risperidone treatment and 7.5 mg in patients still in the hospital. All groups were granted more ward privileges after starting risperidone, the most being granted to patients discharged from the hospital on risperidone treatment ($p < .05$ versus patients discharged on treatment with other drugs) and those still receiving risperidone in the hospital. Significantly fewer patients discharged on risperidone treatment than on treatment with other drugs were readmitted to the hospital within 2 years after discharge ($p < .01$).

Conclusion: Improved privilege levels and a reduced readmission rate indicate that risperidone was an effective antipsychotic agent among a heterogeneous patient population in a state hospital. These factors may be especially important to justify use of this agent in the current fiscal climate.

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Double-blind, placebo-controlled clinical trials provide important preapproval data on the efficacy, safety, and tolerability of a new drug. Because of rigid criteria mandated by regulatory agencies, however, these trials cannot investigate the diversity of patients or therapeutic situations commonly encountered in clinical practice. Naturalistic outcome studies have the advantage of providing data on heterogeneous patient populations in realistic settings. Data obtained from naturalistic studies are often more useful to practicing clinicians than information reported from the controlled trials. Naturalistic studies may modify the use of a drug in day-to-day clinical application.

As investigators at a participant site in the North American clinical trial of risperidone,[1,2] we were particularly interested in the postmarketing use of the drug. In that double-blind, placebo-controlled clinical trial, 8 weeks of risperidone treatment resulted in significant reductions in symptoms of psychosis in hospitalized patients diagnosed with chronic schizophrenia.[1,2] In 1994, 142 hospitalized psychiatric patients at Mayview State Hospital, Bridgeville, Pennsylvania, received risperidone over a 14-week period soon after the drug was marketed. The goal of the present chart review study was to evaluate clinical improvement and key clinical outcomes in these patients over the 2-year period after initial treatment.

METHOD

After study approval by the Hospital Review Board and the Office of Mental Health of the Commonwealth of Pennsylvania, the medical records of 142 patients who received risperidone at Mayview State Hospital from March 1 to June 15, 1994, were reviewed 2 years later in June 1996. The monthly census revealed that these 142 patients represented 21% of the Mayview patient population at that time. Attending psychiatrists initiated patients on risperidone therapy for treatment of psychoses. This action was consistent with Mayview Hospital and Mayview Department of Psychiatry guidelines for risperidone use. Except for patients admitted for forensic psychiatric evaluations, there are no direct admissions to Mayview State Hospital. Patients are admitted only after failing to respond to inpatient psychiatric treatment in various area community hospitals.

Relevant clinical information, including demographic data, DSM-III-R diagnoses, age at onset (first hospitalization for psychoses), number and dates of admission and discharge, start and stop dates of risperidone treatment, titration speed (either rapid 3-day titration as initially suggested by the manufacturer or a slower titration), and the modal maximum daily dose of risperidone, was extracted from the medical charts. Reasons for risperidone discontinuation were noted.

Clinical Outcome

Clinical outcomes were classified by group as follows: (1) patients discharged from the hospital on risperidone treatment (group 1); (2) patients discontinued from risperidone and discharged on treatment with other antipsychotic drugs (group 2); (3) patients who remained in the hospital 2 years later, still receiving risperidone (group 3); and (4) patients who remained in the hospital 2 years later, receiving other antipsychotic drugs after discontinuing risperidone (group 4).

Data on ward privileges granted to the patients during the year before and year after initiation of risperidone were used to assess clinical improvement. These data are reasonably good indices of clinical functioning in this and similar settings.[3] The following ward privileges were evaluated and reviewed: (1) a "ground card" that allowed patients to walk unescorted on the grounds of the hospital with access to a drop-in center and a coffee and snack bar; (2) self-signed passes that permitted patients to leave the hospital when they were not involved in therapy and return of their own accord at specified times; (3) day or overnight passes to leave the hospital with family members; (4) participation in at least 50% of vocational or occupational therapy programming, which included preparing food-service kits, working in the greenhouse, making cardboard cartons, and labeling clothes; and (5) participation in at least 50% of recreational activities, which included bowling, dancing, playing softball or basketball within the hospital grounds, and visiting movie theaters, shopping malls, and sporting events outside the hospital with peers and staff.

Ward privileges were determined by the attending psychiatrist with significant input from the treatment team (based on the clinical status of the patient) and were applied uniformly throughout the hospital. These privileges were generally determined by the following criteria: compliance with medication regimens; the presence or absence of dangerousness; the severity of patient psychopathology and its impact on impulse control and judgment; the need (or absence of need) for restrictive measures, including the use of concomitant antipsychotic or antiparkinsonian medications, exclusion, seclusion, or restraint; and the need to control excessive water and fluid intake. Each of the 5 privileges were scored categorically as follows: 1 if granted or 0 if not granted for a maximum score of 5.

After information had been extracted from patients' medical charts, accuracy of these data were verified against separate hospital record files containing physician's orders, progress notes by attending psychiatrists justifying each order, and monthly staff summaries of vocational, occupational, and recreational therapy goals.

Six patients who were switched from clozapine to risperidone (when it was first available) were analyzed separately because of clinical concern about their status.

Data Analyses

Statistical analyses were performed using a paired t test for within-group comparisons of continuous variables; analysis of variance (ANOVA) was used for between-group comparisons. The Bonferroni correction was applied for multiple post hoc comparisons. Chi-square analyses were used for categorical data. Comparisons of duration of hospital stay were analyzed using the Fisher exact test, 2-tailed.

RESULTS

The 142 patients included 74 women and 68 men, with a mean age of 49 years. Diagnoses (DSM-III-R) were schizophrenia in 57%, schizoaffective disorder in 22%, dementia and other organic conditions in 7%, bipolar disorder in 5%, and other psychiatric disorders in 9%. Thirty-eight patients (27%) had an additional diagnosis of alcohol or substance abuse (mainly marijuana or cocaine). The mean age at onset of psychoses was 32 years, and the patients had been hospitalized a mean of 4.5 times previously. Duration of current hospitalization ranged from less than 1 year (in 50%) to more than 10 years (in 11%). Patient demographics and clinical characteristics are presented in Table 1.

Two years after the patients had started treatment with risperidone, 92 had been discharged from the hospital; 61 of these (group 1; 43% of the total) had been discharged on risperidone treatment and 31 (group 2; 22%) had been dis-

Table 1. Patient Characteristics

Variable	Value
Total N	142
Women/men, N	74/68
Race, N (%)	
White	104 (73)
Black	37 (26)
Other	1 (1)
Age, y, mean ± SD	49 ± 16
Previous hospitalizations, mean ± SD	4.5 ± 4.7
Diagnoses (DSM-III-R), N (%)	
Schizophrenia	81 (57)
Paranoid, N	49
Undifferentiated, N	25
Disorganized/residual, N	7
Schizoaffective	31 (22)
Dementia, organic conditions	10 (7)
Bipolar	7 (5)
Major depression, dysthymia	3 (2)
Other	10 (7)
Alcohol/substance abuse, N (%)	38 (27)
Age at onset, y, mean ± SD	32 ± 15

charged on treatment with other antipsychotic agents after risperidone discontinuation. Of the 50 patients still in the hospital, 18 (group 3, 13% of the total) were still receiving risperidone and 32 (group 4; 22%) were receiving antipsychotics other than risperidone. The reasons for risperidone discontinuation were, in group 2, lack of efficacy in 16 patients, adverse events in 8, patient refusal in 6, and unclear reasons in 1; and in group 4, lack of efficacy in 18 patients, adverse events in 10, patient refusal in 3, and unclear reasons in 1. Diagnoses at hospital discharge were similar in groups 1 and 2: schizophrenia in 56% of group 1 and 55% of group 2, schizoaffective or bipolar disorder in 30% and 36%, respectively, and other disorders in 14% and 9%, respectively.

The average length of risperidone treatment, the modal maximum daily dose, and the titration schedule for the 4 groups are shown in Table 2. The risperidone dose was lowest—4.1 mg/day—in groups 1 (discharged on risperidone treatment) and 2 (discharged on treatment with other antipsychotic drugs after a trial of risperidone) and highest in the hospitalized patients still receiving risperidone (group 3, 7.5 mg/day). Similar proportions of patients in groups 1, 2, and 3 had received either the fast 3-day titration or a slower titration of risperidone, whereas almost all of the patients in group 4—those still in hospital but no longer receiving risperidone (94%)—had received the fast titration ($p < .001$).

Ward Privileges

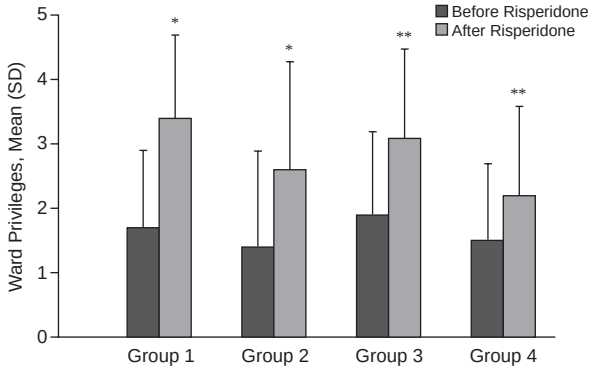
Ward privilege levels at baseline were not significantly different among the 4 groups. Patients in all 4 groups were granted increased ward privileges a maximum of 1 year before to a maximum of 1 year after starting risperidone (Figure 1). The most privileges were granted to patients who continued taking risperidone (groups 1 and 3). Post hoc comparisons between the discharged patients

Table 2. Duration of Risperidone Treatment, Modal Maximum Dose of Risperidone, and Percentages of Patients Switched to Risperidone According to a Fast or Gradual Titration[a]

Group (N)	Treatment Duration, d (mean ± SD)	Daily Dose, mg (modal maximum ± SD)	Titration, % Fast/% Slow
Group 1 (61)	163 ± 135	4.1 ± 2.1	57/43
Group 2 (31)	76 ± 120	4.1 ± 2.4	50/50
Group 3 (18)	…[b]	7.5 ± 3.0	60/40
Group 4 (32)	155 ± 135	6.5 ± 1.5	94/6[c]

[a]Groups defined as follows: group 1 = patients discharged from hospital on risperidone treatment, group 2 = patients discharged on treatment with other antipsychotics after risperidone discontinuation, group 3 = patients still hospitalized receiving risperidone, group 4 = patients still hospitalized taking other antipsychotics.
[b]Patients still receiving risperidone when data extracted.
[c]$\chi^2 = 16.6$, $p < .001$.

Figure 1. Numbers of Ward Privileges Granted to the Patients in the 4 Groups a Maximum of 1 Year Before and a Maximum of 1 Year After Initiation of Risperidone Treatment



*p < .001.
**p < .01.

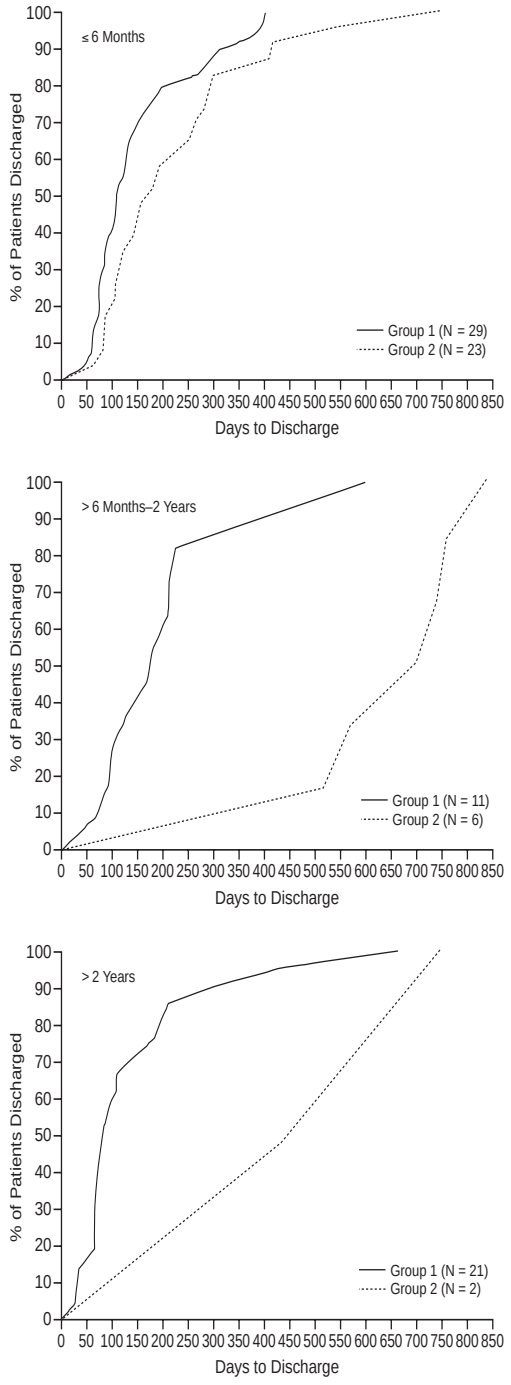
(groups 1 and 2) indicated a significantly higher ($p < .05$) privilege level among patients discharged on risperidone treatment (group 1) than patients discharged on treatment with other drugs (group 2). Among patients who remained in the hospital 2 years later (groups 3 and 4), post hoc analyses revealed a higher ($p < .03$) privilege level among patients still taking risperidone.

Duration of Hospital Stay and Readmissions

Duration of hospitalization was much longer in group 1 patients (1369 ± 3546 days) than group 2 patients (194 ± 366 days) before receiving risperidone. In contrast, duration of hospitalization after initiation of risperidone treatment for group 1, i.e., discharged on risperidone treatment (163 ± 135 days), was one half that for group 2, i.e., those discontinued from risperidone and discharged on treatment with other drugs (340 ± 248 days).

For the comparisons in Figure 2, hospital stay before initiation of risperidone was categorized as ≤ 6 months (29 patients in group 1 and 23 patients in group 2), > 6 months to 2 years (11 patients in group 1 and 6 patients in

Figure 2. Days to Discharge From the Hospital in Patients Hospitalized ≤ 6 Months, 6 Months to 2 Years, and > 2 Years Before Initiation of Risperidone Treatment



group 2), and > 2 years (21 patients in group 1 and 2 patients in group 2). The discharge rate was similar among patients in the 2 groups who had been in the hospital ≤ 6 months before receiving risperidone. However, among longer-stay patients, those who responded to risperidone (group 1) were discharged much sooner than patients not responding to risperidone (group 2; see Figure 2). Six of the group 1 patients had been continuously hospitalized for 10 years or longer.

Table 3. Mean ± SD Numbers of Psychotropic Agents Taken Before and After Initiation of Risperidone

	Antianxiety[a]		Antipsychotic[b]	
Group (N)	Before	After	Before	After
Group 1 (61)	4.4 ± 11.4	2.5 ± 6.5	0.7 ± 3.5	0.4 ± 0.3
Group 2 (31)	9.4 ± 16.4	1.3 ± 2.7	0.8 ± 2.7	0.5 ± 1.5
Group 3 (18)	5.9 ± 19.7	0.9 ± 1.7	0.6 ± 2.7	0
Group 4 (32)	4.4 ± 14.7	0.8 ± 4.0	0	0

[a]Oral or intramuscular lorazepam.
[b]Intramuscular droperidol or haloperidol.

During the 2 post-risperidone years, significantly fewer patients discharged on risperidone treatment (group 1,10%) than those discharged on treatment with other antipsychotic agents (group 2, 34%) were readmitted to the hospital ($p < .01$).

Concomitant Psychotropic and Antiparkinsonian Medications

Ninety-nine patients were receiving concomitant and as-needed psychotropic medications at baseline. Reductions in the use of psychotropic medications were noted in all 4 groups after initiation of risperidone (Table 3). Antiparkinsonian medications were taken regularly and daily by 21% of group 1 (discharged on risperidone treatment). Ten subjects in this group received benztropine (range, 2 to 6 mg/day), 2 subjects received trihexyphenidyl (10 mg/day), and 1 subject received diphenhydramine (50 mg/day). These 13 subjects in group 1 received risperidone at a mean dose of 5.9 mg/day (range, 2 to 9 mg/day). Twenty-five percent of group 2 (discharged on treatment with other drugs) received antiparkinsonian agents. Five subjects in this group received benztropine (range, 3 to 6 mg/day), 1 subject received trihexyphenidyl (15 mg/day), and 2 subjects received diphenhydramine (100 and 150 mg/day). Forty-four percent of group 3 (receiving risperidone and still in the hospital) received antiparkinsonian medications. Five subjects received benztropine (range, 3 to 6 mg/day), 2 received trihexyphenidyl (range, 10 to 15 mg/day), and 1 subject received diphenhydramine at a dose of 150 mg/day. The mean dose of risperidone among these 8 subjects in group 3 was 9.6 mg/day (range, 6 to 14 mg/day). Twenty-eight percent of group 4 (those still in hospital having discontinued risperidone, and receiving other neuroleptic or antipsychotic drugs) received antiparkinsonian agents. Seven patients in this group received benztropine (range, 3 to 6 mg/day), and 2 subjects received 150 mg/day of diphenhydramine.

Clozapine and Risperidone

Six patients (4 with schizophrenia, 1 with schizoaffective disorder, and 1 with bipolar mania) were gradually

transferred from clozapine to risperidone over periods ranging from 3 to 6 weeks. They had received clozapine (mean dosage = 475 mg/day) for 8 months to 3 years. One of the 6 (a patient with paranoid schizophrenia who had been on clozapine treatment for 3 years and was rated a partial responder) improved significantly on risperidone treatment and was discharged from the hospital 4 months later. Three patients experienced severe worsening of psychoses and agitation during the change to risperidone, were switched back to clozapine after 4 to 7 weeks, and were discharged after a further 3 to 10 months. Risperidone was discontinued in 2 patients because of lack of efficacy; they were then switched to conventional neuroleptics and remained in the hospital 2 years later.

Six of the patients who discontinued risperidone subsequently received clozapine. Three of these improved significantly and were discharged on clozapine treatment 4 to 24 months later (group 2), and 3 were partial responders and remained in the hospital 2 years later, still on clozapine treatment (group 4). The 3 patients in group 2 received risperidone at an average dose of 4.8 mg/day for 6 to 20 weeks before being discontinued for lack of efficacy and adverse events (sexual dysfunction in 1 patient). The 3 patients in group 4 received risperidone for 6 weeks to 5 months at an average dose of 6.2 mg/day and were discontinued because of lack of efficacy and adverse events (severe extrapyramidal symptoms in 1 patient).

DISCUSSION

The findings of this naturalistic study suggest that risperidone was an effective antipsychotic agent for a heterogeneous population of psychiatric patients in a state hospital that included a subgroup who had been hospitalized for 2 years or longer. The low average dose of risperidone (4 mg/day) for those discharged on treatment with this medication reflects the national trend and may reflect a broader patient population than patients chosen for controlled clinical trials. Not surprisingly, among patients who were not discharged, the dose of risperidone was higher, reflecting the practice of some physicians to try higher doses in less responsive patients.

Controlled clinical trials provide valuable efficacy and safety data and are important from a regulatory perspective. These studies provide the pivotal information prior to the approval of a drug. However, naturalistic studies are often "real world," cost less to do, often have minimal or absent investigator bias, and often produce readily accessible data. Also, naturalistic data may modify the use of a drug in day-to-day clinical application. These data may also suggest undiscovered uses or concerns in patient populations excluded from controlled clinical trials (for example, elderly, pediatric, or medically compromised patients). Finally, data from naturalistic studies may contribute essential functional outcome information to assist the clinician in long-term, comparative treatment evaluations.

However, there are limitations as well to naturalistic data. For instance, disease characteristics and prognostic factors may not be randomly distributed in the patient population; patients may be preselected for characteristics such as treatment responsiveness or treatment-refractoriness. The conditions under which patients are treated may not be the same; for instance, differences may exist in prescription patterns between physicians and in management practices between wards. These factors may affect outcome considerably depending on the variable(s) being evaluated. It also may not be possible (or practical) to validate the data from some naturalistic studies. Nonetheless, naturalistic data provide clues that may be hard to obtain in controlled trials, and in so doing may lead to further clinical research.

The use of discharge rates and ward privileges rather than standardized rating scales to measure functional improvement among state hospital patients seemed appropriate. Negron et al.[3] reported that Clinical Global Impressions scale scores and ward privilege levels were significantly correlated among patients treated with risperidone in a similar state hospital setting. Patients who were either discharged or continued on risperidone treatment appeared to gain the most ward privileges. These improved functional outcomes may partly explain why some patients continued to receive risperidone 2 years after initiation of treatment even though they remained hospitalized.

The number of concomitant psychotropic agents taken by patients was reduced after initiation of risperidone (the differences, however, were not statistically significant). Among those who were discharged while taking risperidone or other drugs, between 21% and 25% received antiparkinsonian agents. This rate is similar to that reported by Negron et al.[3] Among patients who remained in the hospital, an even higher percentage received antiparkinsonian agents, which may not be surprising given that they received higher daily doses of risperidone. Most of the patients who received antiparkinsonian agents were being treated with doses of risperidone exceeding 6 mg/day.

Significantly fewer patients who were discharged on treatment with risperidone than with other drugs were readmitted to the state hospital in the 2 years after initial treatment, despite the longer period out of the hospital in the risperidone group and their much longer duration of hospitalization before risperidone was started. Moreover, among those who had been hospitalized for 6 months or longer, patients who responded to risperidone were discharged from the hospital much sooner than patients not responding to risperidone (see Figure 2).

In the current fiscal climate, it is both significant and instructive that readmission rates in this study were lower among patients discharged on risperidone treatment. Reductions in the utilization of health care resources and sav-

ings in overall treatment expenses have also been reported in other studies with risperidone.[4–6] Finally, from a broader health care perspective, the expense of newer antipsychotic agents, like risperidone, is justified by the lower overall expense of treatment for patients with chronic disease.

Drug names: benztropine (Cogentin and others), clozapine (Clozaril), diphenhydramine (Benadryl and others), droperidol (Inapsine), haloperidol (Haldol and others), lorazepam (Ativan and others), risperidone (Risperdal), trihexyphenidyl (Artane and others).

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