Neurologic side effects in neuroleptic-naive patients treated with haloperidol or risperidone

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Article abstract—*Objective:* To compare the side effect profile of risperidone with that of oral haloperidol in patients with no previous exposure to antipsychotic drugs (APDs). *Background:* Early studies suggested that the APD risperidone may have a side effect profile comparable with that of placebo. These early studies involved patients with chronic schizophrenia and a long history of APD use. Very little information is available regarding the neurologic side effects of risperidone in patients without previous APD exposure. *Methods:* The authors prospectively studied 350 consecutive neuroleptic-naive patients admitted to their acute-care psychiatry service; 34 of these were treated with risperidone (mean dose, 3.2 mg/d) and 212 were treated with low-dose haloperidol (mean dose 3.7 mg/d). All patients were assessed on admission and twice weekly thereafter using rating scales for dystonia, parkinsonism, akathisia, and dyskinesia. *Results:* The incidence and severity of dystonic reactions, akathisia, parkinsonism, and dyskinesia were comparable in the risperidone- and haloperidol-treated groups. *Conclusions:* The neurologic side effect profile of low-dose risperidone is comparable with that of haloperidol in patients receiving APDs for the first time. Risperidone may not be a useful alternative to typical APDs for patients with PD and psychosis.

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Neuroleptic medications constitute the primary pharmacologic treatment for a wide variety of psychiatric disorders. It has long been recognized, however, that these drugs are associated with neurologic side effects, including dystonia, parkinsonism, akathisia, and tardive dyskinesia. In an effort to match the therapeutic efficacy of neuroleptics without incurring the neurologic side effects, a host of so-called atypical neuroleptics have recently been introduced. One of these, risperidone, has been reported in several multicenter trials to have a side effect profile comparable with that of placebo and significantly less than that of haloperidol when used in doses of 6 mg/d or less.[1-5] This has raised hope among neurologists that risperidone might be a useful agent for the treatment of patients with PD and psychosis. The early multicenter studies, however, involved hospitalized patients with chronic schizophrenia, all of whom had a history of long-term neuroleptic use. Very little information is available regarding the neurologic side effects of risperidone in patients with no previous exposure to neuroleptics.

We have compared the side effect profile of risperidone with that of oral haloperidol in patients with no prior exposure to antipsychotic drugs (APDs).

Methods. *Patients.* Over the past 9 years, we have prospectively studied the neurologic side effect profile of 350 consecutive neuroleptic-naive patients admitted to our acute-care psychiatric inpatient service who were subsequently treated with APDs. Our 28-bed unit is one of three university-affiliated facilities in the region to which patients are admitted from a central emergency service, serving a catchment area of approximately 500,000 people. The particular unit to which patients are admitted from the emergency service is determined by bed availability.

The only exclusion criterion for entry into the study was a history of APD exposure, as confirmed by 1) interviews with the patient and relatives; 2) review of hospital records; and 3) contact with the family physician. All patients signed an informed consent to be prospectively examined for medication side effects. The choice of APD, dosage, and use of concurrent medications were determined by one of three treating psychiatrists. Prophylactic medications such as benztropine were not used on a routine basis. Of the 350 patients, 34 were treated with risperidone and 241 with haloperidol. For the purposes of comparison with risperidone, we included only those patients treated with oral haloperidol (n = 212), excluding anyone who had received intramuscular injections in the emergency ward or at any time during hospitalization. The larger number of haloperidol-treated patients in the study to date reflects the later introduction of risperidone for routine clinical use in Canada.

Assessments. Before treatment, patients were examined by a psychiatrist (P.R.), a neurologist (M.M.), and a research nurse, and assessed for dystonia, parkinsonism,

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Table 1 Clinical and pharmacologic characteristics of neuroleptic-naive patients treated with either risperidone or haloperidol during hospitalization

	Risperidone, n = 34	Haloperidol, n = 212	Analysis*
Age, y, mean (SD)	37.1 (18.56)	41.63 (20.6)	NS
Sex, M/F	19/16	112/100	NS
Pretreatment BPRS, mean (SD)	50.24 (12.88)	47.28 (11.52)	NS
BPRS at discharge, mean (SD)	23.5 (4.56)	24.77 (8.16)	NS
Duration of APD treatment, d, mean (SD)	27.9 (15.41)	27.52 (15.96)	NS
Daily APD dosage, mg, mean (SD)	3.2 (1.38)	3.7 (2.24)	NS
Length of admission, d, mean (SD)	31.68 (16.05)	33.93 (19.58)	NS
Diagnosis, n (%)			
Affective disorder	13 (38)	98 (46)	NS
Schizophrenia/schizoaffective disorder	10 (29)	39 (18)	NS
Other	11 (32)	75 (35)	NS
Concurrent medication use, n (%)			
Benzodiazepines	26 (77)	187 (88)	NS
Antidepressants (TCAs, SSRIs)	9 (26)	64 (30)	NS
SSRIs alone	8 (24)	20 (9)	Chi-square = 5.77, $p = 0.025$
Lithium	9 (26)	74 (35)	NS
Benztropine	14 (41)	127 (60)	NS

* Statistical analyses were performed using chi-square for categorical variables or the two-tailed Student's *t*-test for continuous variables.

BPRS = Brief Psychiatric Rating Scale; APD = antipsychotic drugs; TCA = tricyclic antidepressants; SSRI = selective serotonin reuptake inhibitors; NS = nonsignificant.

akathisia, and dyskinesia. A number of psychopathology scales, including the Brief Psychiatric Rating Scale (BPRS), which we report here, were also completed for the purposes of the study. Patients were then reassessed twice weekly during their acute hospitalization by the research nurse, who remained blinded to the medication regimen. Mean daily dosages of the APDs and any other psychotropic medications used during treatment, including lorazepam, lithium, antidepressants, and benztropine, were calculated after the patient's discharge.

Acute dystonia was diagnosed if the patient manifested a sustained muscle contraction sufficiently severe to require immediate treatment with intramuscular benztropine.

Akathisia was rated using the Barnes Akathisia Scale (BAS).[6] The BAS includes four items: two reflect subjective restlessness and discomfort, one measures objective restlessness, and one is a global impression of severity. The latter item is scored from 0 to 5 (0 = absent, 1 = questionable, 2 = mild, 3 = moderate, 4 = marked, and 5 = severe). A patient was considered to have akathisia if a global impression score of 2 or more was assigned on at least one occasion during hospitalization.

Our parkinsonism scale was adapted from the motor examination subsection of the United Parkinson's Disease Rating Scale, and included the following items: facial and vocal expression; tremor; an alternate motion rate task; rigidity; posture, gait, and armswing; and writing. The degree of impairment for all items except those relating to the face and voice is rated on a scale from 0 to 4 as 0 = normal, 1 = minimal, 2 = mild, 3 = moderate, and 4 = severe. Face and voice are rated from 0 to 3: 0 = normal, 1 = mildly affected, 2 = moderately affected, and 3 = severely affected. Patients are also assigned a global clinical impression score in which 0 = absent, 1 = minimal, 2 = mild, 3 = moderate, and 4 = severe impairment. Parkinsonism was considered to be present when a patient obtained a global score of 2 or more on at least one occasion.

Dyskinetic movements were assessed using the Abnormal Involuntary Movement Scale (AIMS).[7] A score of moderate severity (AIMS = 3) in one body part or of mild severity (AIMS = 2) involving two or more body parts constituted the minimal threshold for a diagnosis of dyskinesia in accordance with the established research definition.[8]

Analysis of interrater reliability among the investigators (P.R., M.M., and research nurse) for these scales demonstrated the following intraclass correlations: 0.85 and 0.91 for the subjective and objective items, respectively, of the BAS; 0.90 for the Parkinson's scale; 0.80 for the AIMS; and 0.90 for the BPRS.

Statistical analyses. Categorical variables were analyzed using the chi-square test and continuous variables were analyzed using the two-tailed Student's *t*-test. The level of statistical significance was set at $p < 0.05$.

Results. Table 1 shows the comparative demographic and clinical profiles of patients treated with either risperidone or haloperidol. There were no significant differences between the two groups with respect to age, sex, diagnostic profile, mean BPRS score before treatment or at discharge, average daily APD dosage, duration of APD use, or length of admission. There was a significantly greater use of adjunctive selective serotonin reuptake inhibitor (SSRI) med-

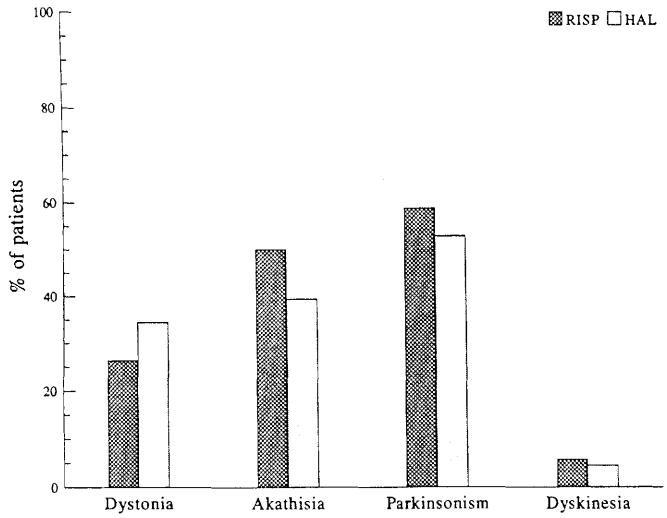

Figure. Comparative incidence of neurologic side effects in neuroleptic-naive patients treated with risperidone (n = 34) or haloperidol (n = 212). Chi-square analysis showed no significant differences in side effect profile between the two groups for any of the neurologic side effects that were assessed.

ication in the risperidone-treated patients ($p < 0.03$), but concurrent use of lorazepam, lithium, benztropine, and tricyclic antidepressants was comparable in the two groups.

Figure 1 shows the comparative incidence of dystonic reactions, akathisia, parkinsonism, and dyskinesia for the risperidone and haloperidol groups during hospitalization. The incidence of acute dystonia, parkinsonism, and akathisia was high for both groups, with no significant differences between them for any of the side effects. There was a nonsignificant trend toward increased dystonia in haloperidol-treated patients and toward increased akathisia in the risperidone group. The comparative severity ratings for akathisia and parkinsonism in the risperidone and haloperidol treated patients are shown in table 2.

***Table 2** Comparative severity ratings of akathisia and parkinsonism for patients treated with risperidone or oral haloperidol*

	Risperidone, n = 34, n (%)	Haloperidol, n = 212, n (%)
Akathisia		
Not present	17 (50)	126 (61)*
Mild	5 (14)	42 (20)
Moderate	8 (24)	29 (14)
Marked/severe	4 (12)	11 (5)
Parkinsonism		
Not present	14 (41)	95 (48)†
Mild	13 (38)	57 (28)
Moderate	7 (21)	39 (19)
Severe	0 (0)	11 (5)

* Excluding four patients with pretreatment akathisia.
† Excluding 10 patients with pretreatment evidence of parkinsonism.

Discussion. We found a comparable incidence of neurologic side effects in acutely ill inpatients treated with either low-dose risperidone or low-dose haloperidol. This similarity in side effect profile suggests that previous reports of negligible side effects in risperidone-treated patients with chronic schizophrenia may not be generalizable to other patient groups. These early multicenter trials using risperidone involved patients with chronic, treatment-resistant schizophrenia,[1-5] most of whom had been off neuroleptics for less than 1 week before being randomized to either risperidone or haloperidol. Subsequent assessments over the 7- to 8-week duration of those studies would have been contaminated by either the ongoing effects or the withdrawal effects of the previously prescribed APD. The washout period of less than 1 week before randomization that has characterized most studies comparing risperidone with typical neuroleptics is problematic, given that neuroleptics are known to produce brain changes that persist long after the drug has been discontinued.[9-11]

Our findings are consonant with emerging evidence that the incidence of neurologic side effects in patients treated with risperidone may be higher than has previously been reported.[12-16] A comparative prevalence study of extrapyramidal side effects (EPS) in patients on stable dosages of clozapine, risperidone, or conventional antipsychotics found no significant differences between risperidone and conventional antipsychotics.[15] A recent study[12] comparing risperidone to haloperidol plus amitriptyline in the treatment of patients with psychosis and mood disturbance found the incidence of EPS to be 37.1% and 31.1%, respectively, in the two groups. Other prospective trials of low-dose risperidone in elderly patients with dementia, EPS were found in 50% to 53%.[13,14]

To our knowledge, the only other prospective study of risperidone in a neuroleptic-naive population involved 22 predominantly male inpatients with schizophrenia who were assessed for side effects before treatment and just before discharge approximately 7 weeks later, with no intervening assessment.[17] The investigators found no "clinically significant" EPS for patients taking risperidone 2 to 4 mg/d and "mild" EPS in 32% of those taking 5 to 8 mg/d. The lack of regular assessments may have accounted for the low rate of EPS that was observed. Such an approach would almost certainly result in underestimation of the actual frequency of side effects, which may vary from one day to another depending on changes in antipsychotic dosages, use of other medications, time of day the assessment is carried out, and factors such as stress, fatigue, or substance abuse.[18]

A somewhat surprising finding in the current study was the higher rate of akathisia, albeit nonsignificant, in risperidone-treated patients. This may be related to the more frequent use of SSRIs, which themselves have been associated with a broad range

of EPS, particularly akathisia,[19-21] perhaps reflecting the inhibitory effect of serotonin on ventral tegmental and substantia nigra neurons.[22]

The side effect profiles observed in this study occurred on a regimen of low-dose medication. There has been an effort in recent years to reduce APD dosage in the treatment of psychosis. This recommendation has been based on the assumption that lower dosages would result in a more benign side effect profile. Our data suggest that this assumption may not be justified: the incidence of neurologic side effects in our patients was over 50% despite mean daily dosages of 3.2 mg in the risperidone group and 3.7 mg in haloperidol-treated patients. This indicates that dosage reduction alone will not be sufficient to obviate this troublesome effect of APDs.

These findings are of considerable relevance to neurologists who are treating patients with PD and psychosis. A well recognized problem of dopaminergic agents is their propensity to induce or exacerbate psychotic symptoms. Typical neuroleptic agents may treat the psychosis but worsen the parkinsonism. The early reports that risperidone may be able to treat psychosis without producing parkinsonism raised hopes that it may be a useful agent in the treatment of patients with PD and psychosis. Our findings, and those of several other recent studies,[23-25] indicate that the side effect profile of risperidone may be very similar to that of typical APDs, and that risperidone may therefore not be a useful alternative in the treatment of patients with PD and psychosis.

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