Aggression and Schizophrenia: Efficacy of Risperidone

Peter F. Buckley, MD, Zafar Y. Ibrahim, MD, Beth Singer, BA, Bruce Orr, Karl Donenwirth, MA, and Parminder S. Brar, MD

The advent of novel antipsychotic medications has raised treatment expectations for patients with severe mental illness. In this regard, clozapine has been particularly effective in reducing aggressive behavior in patients with schizophrenia. This study compared the efficacy of risperidone and conventional antipsychotic medications in the management of hostile patients. Improvements in the level of aggression were evident over time in both treatment groups, and a similar response between risperidone and typical antipsychotics was observed. Future studies should address the relative role of typical antipsychotics, adjunctive agents, and novel antipsychotic medications in the pharmacological management of persistent aggression in patients with schizophrenia.

Although patients who exhibit aggressive behavior are very much in the minority among those diagnosed with schizophrenia, they are nevertheless notoriously difficult to treat.[1] Moreover, they account substantially for the needs and expense associated with prolonged hospitalization in state facilities. Efforts to ameliorate such disruptive behavior through behavioral and/or cognitive-behavioral techniques have shown some success.[2] However, the cognitive deficits that are intrinsic to schizophrenia and the recalcitrant nature of psychotic symptoms in these severely ill patients are serious obstacles to successful behavioral intervention.[3]

Until relatively recently, pharmacological management of aggression in these patients had met with, at best, partial and inconsistent success.[2] Conventional neuroleptics possess broad antianxiety and antipsychotic effects. However, they do not appear to have a preferential and specific antiaggressive action. Moreover, doses that are typically used to treat aggressive behavior in patients with schizophrenia are often excessive and result in treatment complications which themselves may cause further deterioration in behavior.[4] Claims have been made for the role of adjunctive agents in treating aggression.[2,5] The role of benzodiazepines in aggression is limited by their cumulative sedative effects and by the docu-

Dr. Buckley, Dr. Ibrahim, Ms. Singer, Mr. Orr, Mr. Donenwirth, and Dr. Brar are all affiliated with Northcoast Behavioral Healthcare System, Cleveland, OH. Drs. Buckley and Ibrahim are also affiliated with the Department of Psychiatry, Case Western Reserve University, Cleveland. Address correspondence to: Peter F. Buckley, MD, Medical Director, Northcoast Behavioral Healthcare System, 1756 Sagamore Rd., Northfield, OH 44067.

mented risk of paradoxical enhancement of aggression. Beta blockers and carbamazepine may be used, but the results to date are conflicting. Selective serotonin reuptake inhibitors have also received attention for their potential to reduce aggressive behavior.

Clozapine, the prototypic atypical antipsychotic, is the latest (and arguably the most effective) agent that has been tested for the management of aggression in patients with schizophrenia.[6] This drug was introduced to the United States in 1990, following the report of a pivotal study wherein clozapine was shown unequivocally to have superior efficacy over a conventional antipsychotic in the treatment of patients with neuroleptic-refractory schizophrenia.[7] Subsequent studies confirmed clozapine's advantage in the treatment of a broad range of symptoms including positive, negative, affective, and suicidal symptoms.[8] These benefits were most pronounced when clozapine came into widespread use in state hospitals. Patients with recalcitrant psychoses showed dramatic improvements and were able to be discharged even after prolonged hospitalization.[9, 10]

The improvement in aggression has been, perhaps, the most demonstrable effect of clozapine in this inpatient population.[6] A consistent and compelling literature attests to marked reductions in the use of seclusion and restraint with clozapine therapy (see Table 1).[6, 11–17] Intriguingly, this effect does not appear to be tightly coupled with diminished psychotic symptoms but, rather, may represent a selective and superior effect of clozapine on hostility itself. Accounts of clozapine's efficacy in reducing rage in other conditions are consistent with this notion.[18] Two studies have examined response to clozapine in hostile schizophrenic patients using serial Brief Psychiatric Rating Scale (BPRS) evaluation to determine whether there may be some specificity to its antiaggressive effect.[6, 15] Both studies concluded that clozapine was effective in reducing violent behavior by way of a selective antiaggressive action.

Risperidone is another putative atypical antipsychotic medication, which became available in 1994 for the treatment of psychosis.[19] It is a benzisoxazole compound whose predominant pharmacologic profile is that of combined dopaminergic-serotonergic blockade.[20] This blocking effect on both receptors is more marked than that of clozapine. Risperidone's affinity for noradrenergic receptors is also stronger than clozapine's. That apart, risperidone lacks the broader range of binding (cholinergic, histaminergic) seen with clozapine. This shared "atypicality" and some similarity to clozapine (rather than conventional antipsychotics) in profile is accompanied by proven antipsychotic efficacy. The results of large, multicenter trials and subsequent clinical studies confirm that risperidone is an effective antipsychotic that can improve global, positive, and (more speculatively) negative symptoms of schizophrenia (see Table 2).[19, 21–26]

Thus far, three reports have focused on the efficacy of risperidone in state hospital patients.[28–30] Keck and colleagues demonstrated that risperidone treatment can produce sufficient improvement to

Table 1
Representative Studies of the Effect of Clozapine on Aggressive Behavior

Authors	Sample Size	Clozapine, Mean Daily Dose	Design	Results/Comments
Maier *et al.* (1992)[11]	25	450 mg	Patient review over 6 to 15 months; no formal measures apart from privileges attained	Less aggression; 28% of patients were discharged or moved to a less restrictive unit
Wilson (1992)[12]	37	597 mg	Review of S&R, BPRS, privileges at 6 months	General improvement (privileges, social function, community visits); less seclusion; fewer violent incidents
Ratey *et al.* (1993)[13]	5	Unspecified	BPRS, S&R, nursing records	Reduced S&R
Michals *et al.* (1993)[14]	9	450 mg	Clinical review of all records	Marked improvement in aggression in two patients, but minimal response in three
Volavka *et al.* (1993)[15]	223	Unspecified	Statewide pilot program-serial BPRS evaluations	Improvement in psychosis plus selective effect on hostility subscale of BPRS; selective antiaggressive effect of clozapine?
Chiles *et al.* (1994)[16]	115	700 mg	12-Week evaluations	Reduced S&R, effect evident and maximal in 2nd and 4th week (sustained also)
Ebrahim *et al.* (1994)[17]	27	550 mg	6-Month evaluation; BPRS, S&R, privileges	Increased privileges (1→19 patients); decreased S&R (12.4 days→0 days); 70% of patients showed ≥15% reduction in BPRS scores
Buckley *et al.* (1995)[6]	30	636 mg	S&R, BPRS evaluations	Reduction in aggression; selective antiaggressive effect with clozapine?

S&R, seclusion and restraint; BPRS, Brief Psychiatric Rating Scale.

allow community discharge for many patients who have been hospitalized with neuroleptic-refractory schizophrenia for greater than one year.[28] Negron and colleagues also found risperidone to be an effective treatment for the state hospital population, although theirs was a more acute-stay sample.[27] In an earlier study of risperidone in clearly defined treatment-refractory patients at our state facility, we observed that 25 percent of these patients made a 20 percent or greater improvement in symptoms during treatment with risperidone.[30] However, neither this nor the two other state hospital studies addressed the effect of risperidone on aggression in this population. The only study to date to examine this issue noted a modest superiority for risperidone over haloperidol in the hostility subscale of the

Table 2
Representative Studies of Risperidone Treatment in Schizophrenia

Authors	Duration of Treatment: Sample	No. Weeks	Design	Outcome/Comments
Marder and Meibach (1994)[19]	338 patients, acute and chronic illness	8	U.S. multicenter placebo-controlled, double-blind; 2, 6, 10, 16 mg risperidone versus 20 mg haloperidol	6 and 16 mg dose of risperidone most effective, more side effects with 16 mg; 6 mg, optimum dose
Chouinard *et al.* (1993)[21]	135 inpatients, acute and chronic	8	Canadian multicenter (6 sites), same protocol as U.S. study	Similar outcome suggested benefit for negatives; improvement in tardive dyskinesia (TD) ratings suggestive of low TD liability with risperidone?
Hoyberg *et al.* (1993)[22]	107 patients, chronic illness	8	Multicenter, double-blind risperidone, 5–15 mg versus perphenazine, 16–48 mg	Risperidone, 4–8 mg, more effective than perphenazine
Peuskens (1995)[23]	Over 1,000 patients, mainly chronic illness	8	Multicenter, double-blind risperidone, 1, 4, 8, 12 mg versus haloperidol, 10 mg	4–8 mg of risperidone most effective, lower EPS than haloperidol
Claus *et al.* (1992)[24]	44 patients, chronic illness	12	Double-blind comparison of risperidone versus haloperidol	Similar findings to larger European study (Peuskens)[23]
Kronig *et al.* (1994)[25]	12 schizophrenia/3 schizoaffective disorder patients, treatment-refractory by criteria of Kane *et al.*	6	Follow-up, 6 mg-dose of risperidone, 20% reduction in BPRS as response criterion	Three patients did not complete 6-week trial; 8 of 15 treatment-refractory patients responded to risperidone for both positive and negative symptoms
Klieser *et al.* (1995)[26]	59, treatment-refractory	4	Randomized, double-blind clozapine, 400 mg, versus risperidone, 6–12 mg	Equal efficacy; however short trial, treatment-refractory status of sample unspecified
Bondolfi *et al.* (1995)[27]	86, treatment-refractory	8	Randomized, double-blind, risperidone, 6.4 mg (3–10 mg) versus clozapine, 291 mg (150–400 mg)	67% Risperidone group, 65% clozapine group were responders; no group differences evident in symptoms or side effects

Positive and Negative Syndrome Scale (PANSS).[31] This report was based upon a *post hoc* analysis of the U.S.-Canadian multicenter comparative study of risperidone and haloperidol. There is also a recent case report of risperidone's efficacy for dementia-related aggression.[32]

Given the recent emergence of risperidone as a new treatment option for psychosis and the preliminary findings of an effect on aggression, we sought here to examine (in a case-controlled design) the efficacy of risperidone in reducing aggression in patients with schizophrenia who exhibited persistent, aggressive behavior.

Method

The South Campus Hospital of Northcoast Behavioral Healthcare System (NBHS) is a 250-bed state facility for the care of severely mentally ill patients. Seventy percent of the patients have a diagnosis of schizophrenia; the majority of these have treatment refractory illnesses. Staff psychiatrists began prescribing risperidone in March 1994. Data on the use of seclusion and restraint (S&R) were evaluated for patients receiving risperidone and for patients receiving conventional antipsychotics. Data were routinely completed jointly by physicians and nurses and were collated by the hospital's information and risk management services. Patients were identified as either violent or nonviolent on the basis of having spent at least nine hours in S&R during the six months preceding risperidone therapy, a classification similar to that previously employed when studying clozapine at NBHS.[6] The effect of risperidone on aggression was then assessed by comparing S&R data for the six months prior to and during treatment with risperidone and also with respect to a matched comparison group receiving conventional antipsychotic medications. Patients for the control group were selected by examining initial S&R data for the six months prior to the initiation of risperidone in the risperidone-treated group. Thus, at that six-month baseline period, both groups were receiving conventional antipsychotics. Patients were matched with regard to age, gender, and severity of S&R during this six-month baseline period. The subsequent six months, during which one group received risperidone (the experimental group) and the other remained on conventional antipsychotics (the control group), represents the study period of observation. Medication doses were standardized to chlorpromazine equivalents (CPZ equivalent) according to established norms.[7, 33] Comparisons among demographic, clinical, and S&R variables between both groups were performed with *t* test statistical procedures. Time-by-group effects were assessed by repeated measures analysis of variance.

Results

Data on S&R for the six months preceding and during risperidone therapy for a risperidone-treated group (n = 15) were compared with a corresponding time period in a group of patients (n = 12) who were being treated with conventional antipsychotic medication. These groups were matched clinically and were also matched for contemporaneous S&R review. The mean (± standard deviation)

Table 3
Comparison of Risperidone-Treated Patients and Patients Receiving Conventional Antipsychotic Medication

Variable	Risperidone (n = 15)	Conventional Antipsychotic (n = 12)
Age (years)	42 ± 9	45 ± 13
Gender (M/F)	12/3	6/6
Diagnosis		
Schizophrenia	12	9
Schizoaffective	3	0
Other	0	3
Length of stay (years)	12 ± 7.3	10.9 ± 11.0
No. of previous hospitalization	8.5 ± 5.8	7.1 ± 5.6
No. of hours (±SE) in seclusion in 6 months before risperidone	50 ± 19	79 ± 23
No. of hours (±SE) in seclusion during 6 months of treatment	26 ± 17	33 ± 12
Dose of risperidone	6.8 ± 2.0	
Dose of conventional antipsychotic (in chlorpromazine equivalent)		1,295 ± 789

dose of risperidone during the six months of observation was 6.8 ± 2.0 mg, and the dose of conventional antipsychotics was 1,295 ± 789 mg (CPZ equivalent). The demographic and clinical characteristics of each group are summarized in Table 3.

When compared with the prior six-month period, there was a notable reduction in S&R over the six-month period of observation during treatment with either risperidone (50.2 ± 74.1 hours versus 25.5 ± 66.7 hours) or conventional antipsychotics (79.4 ± 78.7 hours versus 33.2 ± 42.1 hours). This result was statistically confirmed on a repeated measures analysis of variance of S&R reduction over time, which revealed a significant time effect ($F = 9.7$, $df = 1,25$, $p = .007$). However, there was no evidence of superiority in S&R reduction between either treatment group. This absence of a differential effect of treatment was statistically confirmed by the lack of any time by group interaction on repeated measures analysis of variance.

Discussion

The relative effects of risperidone and conventional antipsychotic medications upon aggressive behavior in patients with schizophrenia were examined using S&R data. Risperidone was similar to conventional antipsychotics in treating aggression in this sample. Indeed, both groups had less S&R over time and both showed a close similarity in reduction in S&R during the six-month period of observation.

Our choice of a case-controlled design to evaluate risperidone's efficacy for treating aggression is an important methodological point. It is well documented that changes in S&R practices over time, as well as administrative decisions, can

have a powerful impact on the S&R statistics at state hospitals.[34] This is likely to have contributed to the overall decline in the use of S&R, evident in both groups, during the period of observation. Thus, had we merely examined risperidone's efficacy in the absence of a contemporaneous control group, we may have concluded that risperidone treatment is the sole or primary effect responsible for observed reduction in S&R. The data from this controlled study do not substantiate this conclusion. The uncontrolled approach has predominated in the studies of clozapine that have addressed aggressive behavior; this is an important methodological limitation, which must be considered. On the other hand, pre/post-comparisons of S&R are very instructive, and the consistency and clinical significance of clozapine's amelioration of aggression that is evident in the literature argues strongly against this effect as merely a methodological confound (see Table 1). Nevertheless, we sought to apply some rigor to the evaluation of aggression in this study by choosing patients who were on conventional antipsychotic medications at the same time period as those patients who were being treated with risperidone. This approach allowed us to control for time-dependent or other effects on S&R and to examine the direct and comparative effects of each medication upon aggression. In this manner, we found a comparable improvement in S&R for both medication groups.

It should be noted, however, that this study was not of prospective design and was small in sample size. In addition, the group receiving conventional antipsychotics was on a high dosage of these medications. The circumstances governing which patients were changed to risperidone and which were maintained on conventional antipsychotics may be of relevance here to the topic of aggression. These are important methodological limitations of the present study.

The absence of a superiority of risperidone over conventional antipsychotics in treating aggression in patients in this study is, at first glance, in conflict with the results of an earlier report on this topic.[31] In that study, data were examined from 139 patients with schizophrenia who participated in the U.S.-Canadian placebo-controlled multicenter study of risperidone versus haloperidol. Aggression was measured on the hostility item of the PANSS; hostility item scores may range from 1 (absent) to 7 (physical violence). Changes in hostility were evaluated relative to changes in total PANSS scores. A greater reduction in hostility was observed in risperidone-treated patients compared with the haloperidol-treated group. This effect was reported as being (at least in part) selective, since the effect on hostility persisted even when improvements in psychosis scores were statistically taken into account. However, it is noteworthy that the mean hostility scores for both the risperidone and haloperidol groups were low (3.73 ± 1.12 and $3.50 \pm .72$, respectively). Accordingly, it is likely that agitation rather than overt hostility or aggression was being studied here. We contend that S&R is a more meaningful and clinically relevant measure to evaluate aggression in this population. In addition, since the U.S.-Cana-

dian study comprised a carefully selected, clinical trial population (in which aggressive patients were more likely to have been excluded *ab initio* from participation in this study),[19] direct comparison with this present study is less meaningful. Thus, the seemingly disparate findings may reflect more fundamental differences in the definition and measurement of aggression and sample selection between these two studies.

On the basis of this present study (bearing in mind the methodological issues and the modest sample), we suggest that risperidone may be an effective antipsychotic that helps moderate aggressive behavior in schizophrenia. This benefit occurs to an extent that is comparable with (and no better than) that observed with conventional antipsychotics. In view of the difficulty in managing these patients, further studies of risperidone are needed to either confirm or refute our preliminary observations and these tentative conclusions. Moreover, a direct comparative study of risperidone and clozapine in aggressive patients would be most helpful in informing clinicians as to the best manner of incorporating these novel antipsychotics into a treatment algorithm for aggressive behavior in patients with schizophrenia.

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