Risperidone in the Management of Violent, Treatment-Resistant Schizophrenics Hospitalized in a Maximum Security Forensic Facility

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This study examines the effectiveness of risperidone compared with traditional neuroleptic medications in the areas of clinical functioning and aggressive behaviors in a sample of inpatients diagnosed with chronic schizophrenia. Similar to the methodology of Menditto *et al.* (Psychiatr Serv 47:46–51, 1996), two groups of 10 patients were selected from those being treated in a comprehensive psychosocial rehabilitation program. Group 1 subjects were placed on risperidone at various times during their treatment. Group 2 subjects, who were matched with Group 1 subjects on pre-study levels of clinical functioning as measured by the Time-Sample Behavioral Checklist (TSBC), remained on traditional neuroleptics throughout the study period. For each subject, scores on six TSBC subscales were examined at four time points; data were analyzed with repeated-measures multivariate analyses of variance and univariate analyses of variance. Frequency counts of aggressive behaviors (threats and assaults) were compiled into two six-month time periods and analyzed with nonparametric techniques. The risperidone group did not differ from the traditional neuroleptic group on measures of clinical functioning and aggressiveness measured over time. Both groups evidenced improvements in bizarre motor behaviors over the study period. The risperidone group evidenced some deterioration in measures of appropriate interpersonal interaction over time. No differences in aggressive behaviors were noted for either group. The study concludes that for forensic patients with chronic schizophrenia, risperidone failed to produce therapeutic effects in overall clinical functioning and aggressive behaviors that were significantly different from traditional neuroleptics. Descriptive comparisons are made between the receptor-binding profiles and clinical effectiveness of risperidone and clozapine in an attempt to explain these findings.

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In a recent review of the literature, funded by the Agency for Health Care Policy and Research, Umbricht and Kane[1] reviewed nine published double-blind studies that compared risperidone with traditional neuroleptic medications and/or placebo. The efficacy of risperidone in these studies was shown to be consistently superior to that of placebo and at least comparable with that of conventional antipsychotics.

Risperidone is an atypical antipsychotic, having both a chemical structure and a receptor-binding profile that is quite different from conventional antipsychotic agents. In contrast to conventional antipsychotics, risperidone has a high affinity for serotonergic, alpha-adrenergic, and histaminergic receptors. In addition, risperidone differs from clozapine, another atypical agent, through higher affinity for dopamine D_2 receptors and lower affinity for D_1 receptors.

Umbricht and Kane's review[1] indicated that while the preponderance of experimental evidence suggests that risperidone is both safe and effective in the treatment of schizophrenia, most current controlled studies were conducted on acutely schizophrenic patients.* In addition, with few exceptions, the length of time over which the effects of risperidone were examined tended to be short (4 to 12 weeks). Data are also sparse regarding important questions such as whether risperidone is effective as a maintenance treatment and/or in the treatment of chronic schizophrenia. Although there are some suggestive data indicating that risperidone may be effective in the treatment of negative symptoms and deficit-state patients,[1] additional documentation of these effects is necessary.

From a risk management standpoint, risperidone's absence of potentially life-threatening side effects (such as agranulocytosis, seen in about one percent of clozapine users) would appear to support its use prior to attempting a trial of clozapine in a given patient. However, with a few exceptions, studies that directly compare the effects of risperidone and clozapine are lacking.[2, 3] In addition to the fact that clozapine appears to have a significant positive impact on treatment-resistant schizophrenic patients, there is also evidence that it may possess antiaggression effects as well. For instance, a recent study completed by Menditto *et al.*[4] found that treatment with clozapine resulted in a 10-fold reduction in behaviors involving assaults or threatened assaults by patients against staff or other patients. While there is some evidence to suggest that risperidone may also possess antiaggression properties,[1] additional verification of this effect is needed, as most of the current data relating to the antiaggression effects of risperidone come from the Brief Psychiatric Scale's[5] hostility inventory.

The antiaggression effects of any putative pharmacological treatment for schizophrenia are particularly important

*Since the publication of Umbricht and Kane's review, two recent reports from Europe have emerged that purport to examine the effects of risperidone on chronic schizophrenia. The first report[2] appears to be a more extensive version of a report originally presented by Heinrich *et al.*[17]; and it is doubtful that this study contained patients who were chronic schizophrenics, as about half of the sample had not been previously treated with neuroleptic medications.[2] The second report[3] compared two groups of "treatment-resistant outpatients" recruited at seven psychiatric clinics in Switzerland and France who were provided with risperidone and clozapine, respectively.

Table 1
Demographic and Treatment Characteristics

Variable[a]	Control Mean (SD)	Risperidone Mean (SD)
Length of hospitalization (months)	151.50 (76.09)	101.90 (59.97)
Weight (pounds)	169.30 (24.18)	177.30 (34.47)
Age (years)	40.20 (8.39)	39.30 (4.50)
Education (years)	10.70 (1.64)	10.10 (2.28)
Diagnosis (Sz/SzAf)	6/4	7/3
Race (B/W)	7/3	3/7

[a] Sz/SzAf, schizophrenic/schizoaffective; B/W, black/white.

in the management of forensic patients, because in forensic settings continued aggressive behavior is a key factor in decisions to continue hospitalization.[6] Less aggressive patients can often be maintained in less restrictive and less costly community settings.[7]

The present study represents an effort to extend the work of Menditto *et al.*,[4] who followed two groups of 11 patients selected from a population of highly aggressive chronic schizophrenics. The first group of subjects had been placed on clozapine after the introduction of a social learning-based rehabilitation program.[8] The second group remained on traditional antipsychotic drugs throughout the study period. The groups were matched on pretreatment levels of functioning. Data regarding aggressive behaviors, as well as levels of adaptive functioning, were examined. Results of Menditto *et al.*[4] indicated that prior to the introduction of clozapine, the first group of subjects lagged behind the traditional neuroleptic group in their response to the psychosocial rehabilitation program. However, soon after the administration of clozapine, these patients began to manifest improvements that ultimately resulted in their "catching up" with subjects who had remained on traditional antipsychotics. Dramatic reductions in aggressive behaviors in the clozapine group were also documented.

Method

Subjects Subjects in the present study consisted of 20 adults with chronic schizophrenia hospitalized on three forensic treatment wards at a state mental hospital. All subjects had histories of long-term hospitalizations, and the average length of continuous hospitalization in this sample was approximately 10 years (Table 1). All subjects were male, their average age was 40 years, and the average educational level was approximately 10.5 years. A number of subjects had high rates of aggressive behavior that entailed assaults or threatened assaults on patients and/or staff. All subjects had DSM-IV diagnoses of chronic schizophrenia or schizoaffective disorder (Table 1).

Treatment Setting As in Menditto *et al.*,[4] subjects in this study were residents on wards that involved a fully integrated network of psychosocial treatment interventions.[8] The program is structured around a closed, fixed-token economy

system, which entails individual, small group, and unitwide interventions that target self-care skills, interpersonal and communication skills, cognitive functioning, leisure skills, medication management, functional academic skills, community awareness, and vocational skills. As patients meet treatment goals, they progress through a series of steps that involve increasing responsibilities and privileges, with the ultimate goal of reintegration into the community following discharge.

Measures The primary level-of-functioning measure was the Time-Sample Behavioral Checklist (TSBC),[9] a system of planned observations of individual adults in residential treatment settings. This measure yields detailed level-of-functioning data for use in ongoing clinical decision-making and program evaluation. The TSBC consists of 69 specific behavioral codes grouped into seven categories: physical location, physical position, facial expression, eyes open/closed, social orientation, concurrent activities, and bizarre behavior.

Weekly TSBC summary reports are based on 80 to 100 two-second observations made by highly trained, independent, noninteractive observers who record the presence or absence of each behavior according to highly standardized coding rules. Observations of residents are conducted on a treatment unit during all waking hours (15 hours a day, 7 days a week) through the use of a stratified, hourly time-sampling scheme. Previous research on the TSBC has found exceptional levels of reliability and has documented its validity for use with hospitalized psychiatric patients.[9] Excellent convergent and discriminant validity data have also been obtained with the TSBC relative to conventional psychiatric checklists and rating scales.[9] Six of the TSBC higher-order scores were selected for use as outcome measures based on their clinical relevance[4]; these included the Total Appropriate Behavior Index, the Instrumental Activity Index, the Interpersonal Interaction Index, the Total Inappropriate Behavior Index, the Bizarre Motor Behavior Index, and the Bizarre Facials and Verbals Index.

Aggressive behavior was measured via frequency counts of assaults on other patients or staff, threatened assaults, or serious property destruction. These data were obtained through careful reviews of patients' charts and examination of seclusion/restraint records from the study period.

Procedures At the onset of the study, all patients were enrolled in the psychosocial rehabilitation program[8] and were being treated with traditional neuroleptic drugs. Although a variety of neuroleptics were in use, the average patient was on 2,000 chlorpromazine units (milligrams) of medication.[10] Although all patients continued to participate in the rehabilitation program throughout the course of the study, some patients were taken off traditional neuroleptic regimens at various intervals during the study and placed on risperidone. Ten patients (Group 1) who were ultimately titrated to a minimum level of six mg of risperidone per day comprised the first group of subjects. On average, it took these Group 1 patients 45

days to be titrated to 6 mg of risperidone daily.

The second group (Group 2, which remained on traditional neuroleptics throughout the course of the study) consisted of a matched group of 10 patients (Table 1). These 10 patients were matched to patients in Group 1 on the basis of their levels of clinical functioning at the onset of the study, using scores on the TSBC Total Appropriate Behavior Index and Total Inappropriate Behavior Index.

To assess behavior changes in response to changes in drug regimens over time, the six TSBC higher-order scores were examined at four time intervals. These intervals consisted of one-week TSBC summarized data reports taken (1) six months prior to the start of risperidone therapy for Group 1 subjects, (2) three months prior to the start of risperidone, (3) three months following the achievement of a daily dose of six mg of risperidone, and (4) six months following the six-mg dose criterion. Comparative TSBC data sets for subjects in Group 2 were assembled by selecting TSBC weekly reports from time frames matched to those of Group 1 subjects.

As indicated by Menditto *et al.*,[4] although statistically sufficient data can be collected from weekly summaries of TSBC observations, larger blocks of time are needed to collect reliable data on aggressive acts, which are typically low-frequency behaviors. Therefore, data on aggressive behavior were aggregated into two time periods, each representing a six-month interval. The first of these periods represented a six-month block of time prior to the introduction of a risperidone regimen; the second time period represented a six-month block of time immediately following attainment of a six-mg daily dose.

Results

Appropriate parametric and nonparametric tests were performed to examine the equivalency of the two groups prior to the introduction of risperidone. A two (groups) by six (TSBC higher-order scores) multivariate analysis of variance (MANOVA) performed on TSBC scores six months prior to the introduction of risperidone failed to achieve significance ($F = 1.01$, $df = 6,13$, $p < .46$), indicating that the groups did not differ significantly at the onset of the study with regard to levels of adaptive and maladaptive behaviors. Furthermore, a series of t tests and χ^2 tests indicated that subjects did not differ significantly with regard to age, race, diagnosis, educational level, or length of current hospitalization (Table 1).

Data regarding differential functioning between the groups over time were analyzed with a MANOVA that consisted of a two (groups) by four (time intervals) by six (TSBC higher-order scores) factorial design. Results of this analysis indicated that the group main effect failed to achieve significance ($F = 1.77$, $df = 16,139$, $p < .18$), as did the interaction between group and time ($F = 0.48$, $df = 18,139$, $p < .96$). However, the main effect of time was significant ($F = 3.55$, $df = 18,139$, $p < .0001$).

Follow-up univariate analyses of variance (ANOVAs) were then conducted on each of the six TSBC dependent variables

to further explicate the nature of the time effect. These ANOVAs indicated significant time effects for the Interpersonal Interaction ($F = 8.55$, $df = 3,18$, $p < .001$) and Bizarre Motor ($F = 2.86$, $df = 3,18$, $p < .046$) higher-order scores. F tests examining the significance of the time effect for the other TSBC variables failed to achieve significance.

Additional F tests and mean contrasts performed on the Interpersonal Interaction and Bizarre Motor higher-order scores indicated that both groups' Bizarre Motor scores tended to decrease (improve) over time ($p < .0078$). However, in the risperidone group there was evidence that the adaptive behaviors measured by the Interpersonal Interaction Index deteriorated over time (time 1 > time 4, $p < .0012$); no such effects were noted in the traditional neuroleptic group.

As explained previously, data on aggressive behavior were compiled to reflect two time periods: a six-month time period immediately prior to the introduction of risperidone and a six-month time period following achievement of a therapeutic dose level. A series of Wilcoxon rank sum and signed rank tests indicated that neither the risperidone nor the traditional neuroleptic group changed significantly in terms of aggression levels during the course of the study, nor did the groups differ significantly when compared with one another at any point in the study (Figure 1).

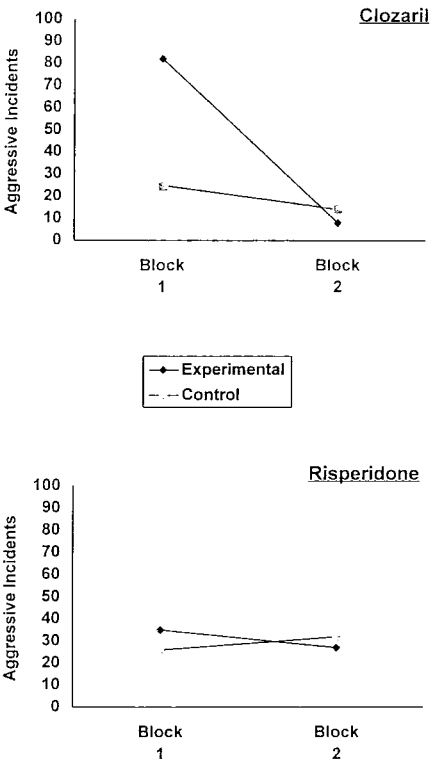

Figure 1. Effectiveness of risperidone versus clozapine[4] in aggressive behaviors, measured in two six-month blocks.

Discussion

The design of this study was essentially retrospective and quasi-experimental in nature,[11] and thus the results need to be interpreted with appropriate caution. For instance, although subjects in the risperidone and traditional neuroleptic groups were matched on levels of adaptive functioning, there is no way of knowing whether the groups differed significantly on other unknown and/or unmeasured variables. Certainly, the results of Menditto *et al.*[4] and the current study need to be replicated, particularly with prospective designs that randomly assign persons diagnosed with chronic and acute schizophrenia to risperidone and clozapine treatment conditions. Several studies of this kind, funded by the National Insti-

tutes of Health, are currently underway.[12, 13]

On the other hand, this study does possess a number of valuable design features that make a discussion of its results reasonable and meaningful, not the least of which is the fact that the groups were equivalent at the onset of the study on a number of important level-of-functioning measures.

Keeping these cautions in mind, results of this study indicate that at least in the context of a severely impaired forensic sample, risperidone does not appear to have the unique effects previously documented with clozapine. Menditto *et al.*[4] found that on three of the six TSBC indexes, clozapine appeared to have a significant therapeutic effect. The current study failed to document significant therapeutic effects for risperidone on any of the six TSBC higher-order scores. Furthermore, the Menditto *et al.* data indicated that clozapine produced a 10-fold decrease in aggressive behavior, whereas the results of the current study indicated that levels of aggression in the risperidone-treated subjects remained essentially unchanged.

The apparent differences between the clozapine and risperidone aggression data are dramatic (Figure 1). While it is tempting to attribute the effect entirely to the antiaggression properties of clozapine, the initial, greatly elevated level of aggression in patients who eventually received clozapine suggests the possibility that some of the effect may be due to the regression-to-the-mean phenomenon.[11]

A number of interesting and potentially significant explanations for the differential effects of clozapine and risperidone on chronic schizophrenia documented by Menditto *et al.*[4] and the current study can be formulated. With regard to interactions between neuroleptic drugs and psychosocial treatment interventions, the results of Menditto *et al.* suggest that clozapine facilitated psychosocial rehabilitation efforts, whereas the current study could not find evidence of similar effects with risperidone. Several biobehavioral hypotheses could be proposed to explain these findings, including differential effects of these two drugs with regard to characteristics such as control over positive symptoms, sedative effects and/or interference with the process of social, self-care, and occupational skill acquisition.[14–16]

An examination of the receptor-binding profiles of clozapine and risperidone reveals that although they are very different from traditional antipsychotic agents, they also differ rather significantly from each other as well.[2] The roles that these receptors and associated neurotransmitters play in the various symptoms of schizophrenia are poorly understood, although it is tempting to attribute clozapine's greater effectiveness to some specific differences in its receptor-binding profile. In particular, clozapine's strong affinity for 5-HT_2 receptors, combined with relatively weak affinity for D_2 receptors, sets it apart from risperidone, which has strong affinities for both 5-HT_2 and D_2 receptors. An additional difference is the greater affinity of clozapine for cholinergic muscarinic receptors, while risperidone apparently lacks any activity on such receptors.

The next few years will likely see the

release of a significant number of additional novel antipsychotics into the marketplace.[17] The results of the current study, as well as those of Menditto *et al.*,[4] suggest that rapid control of positive symptoms is only one criterion for the establishment of a treatment of choice in this area. Sedative effects, impact on negative symptoms, control over aggressive behavior, and interaction with psychosocial rehabilitation efforts also need to be considered.

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