Does Risperidone Improve Verbal Working Memory in Treatment-Resistant Schizophrenia?

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Objective: *Treatment efficacy in schizophrenia is typically defined in terms of symptom reduction. However, new antipsychotic medications could potentially have an impact on aspects of disability, such as neurocognitive deficits. The authors evaluated the effects of risperidone on verbal working memory, a memory component of theoretical interest because of its link to prefrontal activity and of practical interest because of its link to psychosocial rehabilitation.* *Method:* *Verbal working memory of 59 treatment-resistant schizophrenic patients was assessed as part of a randomized, double-blind comparison of treatment with risperidone and haloperidol. Verbal working memory was measured under both distracting and nondistracting conditions at baseline and after 4 weeks of both fixed- and flexible-dose pharmacotherapy.* *Results:* *Risperidone treatment had a greater beneficial effect on verbal working memory than haloperidol treatment across testing conditions (with and without distraction) and study phases (fixed and flexible dose). The treatment effect remained significant after the effects of benztropine cotreatment, change in psychotic symptoms, and change in negative symptoms were controlled. Neither benztropine status nor symptom changes were significantly related to memory performance.* *Conclusions:* *Treatment with risperidone appears to exert a more favorable effect on verbal working memory than treatment with a conventional neuroleptic. The beneficial effect appears to be due, at least partially, to a direct effect of the drug, possibly through antagonism of the 5-HT_{2A} receptor. Results from this study suggest that pharmacotherapeutic efficacy in schizophrenia treatment could be broadened to include impact on neurocognitive abilities.*

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If a schizophrenic patient enters a hospital hearing voices and leaves the hospital without hearing voices, that patient is usually considered to be a treatment success. Pharmacotherapeutic efficacy for schizophrenia has almost exclusively been defined by symptom reduction. However, schizophrenia is associated with disability across a wide range of domains (e.g., neurocognition) that are distinct from symptoms and could present a potential target for pharmacotherapy. As a group, schizophrenic patients have neurocognitive deficits in perception, memory, attention, and problem solving, among others. Some of these neurocognitive deficits appear to exact a toll in outcomes such as community functioning, social problem solving, and psychosocial skill acquisition (1). Presently, there is enthusiasm about the effectiveness of new antipsychotic medications in the reduction of the symptoms of schizophrenia, but do these new medications have any role in the treatment of schizophrenia's neurocognitive deficits?

Conventional neuroleptics with primary affinity for the dopamine (D_2) receptor have a minimal effect on neurocognitive abilities. Acute administration of these agents (i.e., less than 3 days) is sometimes associated with a detrimental effect on visuomotor abilities and vigilance, whereas chronic administration appears to be associated with a beneficial effect on vigilance (reviewed in refer-

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This study is part of a research project that was conceived and initiated by Theodore Van Putten, M.D. He died before the first patient entered the study. The authors dedicate this paper to his memory.

ences 2 and 3). In general, conventional medications do not yield consistent significant changes for most aspects of neurocognition, including verbal working memory, which is the focus of the current study.

Several published studies of the novel antipsychotic agents have examined the neurocognitive effects of clozapine. Of these studies, only one included a specific measure of verbal working memory (4). Hagger et al. administered a neurocognitive battery of tests after 6 weeks and 6 months of open-label clozapine treatment and reported that clozapine had a detrimental effect on performance on a measure of verbal working memory (the consonant trigram test) at the 6-week, but not at the 6-month, assessment. In terms of other types of memory, clozapine does not appear to have a significant effect on secondary memory (5, 6) but appears to offer a beneficial effect on retrieval from semantic memory, as measured by verbal fluency (4, 5, 7). In general, clozapine's effects on most aspects of neurocognition appear to be minimal.

With the rather limited effects of conventional neuroleptics and clozapine on neurocognition, it is natural to wonder about the neurocognitive effects of other antipsychotic agents. Risperidone is a relatively new antipsychotic agent (8). In contrast to clozapine, risperidone has higher affinity for both D_2 and serotonin ($5\text{-}HT_{2A}$) receptors and lower affinity for cholinergic (m1) receptors (9). The current study was conducted to examine the effects of risperidone on a selected aspect of neurocognition, verbal working memory.

Working memory involves the maintenance of information "on line." According to Baddeley's model (10), working memory has three components: a central executive that can manipulate information, and two "slave" systems (an articulatory loop for maintenance of verbal information and a visuospatial scratch pad for spatial information). In this report, verbal working memory refers to the integrity of the articulatory loop—the type of memory that would be used to accurately retain a new telephone number long enough to make the call. Verbal working memory was selected for both theoretical and practical reasons. Human studies that used the lesion method (11) and functional imaging technologies such as positron emission tomography (12) and functional magnetic resonance imaging (13) have confirmed that measures of verbal working memory involve prefrontal structures. Beyond the neuroanatomical relevance of working memory to schizophrenia, there is a pragmatic reason for its selection. Verbal working memory, as measured in the current study, is consistently associated with skill acquisition in psychosocial rehabilitation programs (1). Hence, a deficit in verbal working memory may act as a neurocognitive rate-limiting factor for skill acquisition.

If risperidone has a beneficial effect on verbal working memory performance, it could be mediated by direct or indirect mechanisms. A direct mechanism would involve an action of the agent itself on verbal working memory. Although risperidone differs in several respects from conventional antipsychotic medications, perhaps the characteristic of greatest relevance to the current study is its rather substantial affinity for the $5\text{-}HT_{2A}$ receptor. Under certain conditions, $5\text{-}HT_2$ antagonists can improve learning in laboratory animals (14).

Alternatively, an indirect mechanism would involve an effect that was mediated by some aspect of risperidone treatment but not by risperidone per se. The most obvious indirect mechanism would be the effect of benztropine mesylate (Cogentin), a potent anticholinergic agent. Risperidone generally requires less cotreatment with benztropine than haloperidol (8). Benztropine and other anticholinergic agents have a negative effect on performance on measures of secondary memory, i.e., memory for lists of words and stories that exceed the immediate memory span (15–18). Anticholinergic effects on verbal working memory, however, are not consistent. Since verbal working memory also can be associated with psychiatric symptoms (19–21), another possible indirect mechanism on memory performance would be through treatment-related changes in symptoms. The present study was designed to test whether risperidone has a greater beneficial effect on verbal working memory than a conventional antipsychotic and whether this effect is mediated by direct or indirect mechanisms.

METHOD

Design

The current report is part of a double-blind study of the efficacy, side effect liability, and neurocognitive effects of risperidone versus haloperidol therapy for treatment-resistant schizophrenia. The major efficacy data from this study will be reported separately.

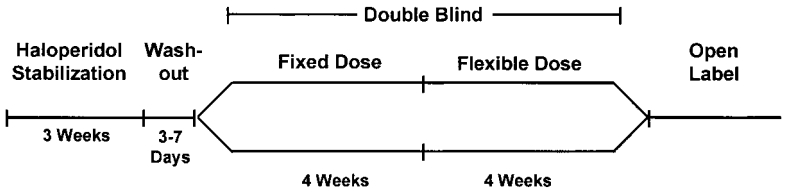
The study was conducted at two sites: the UCLA Clinical Research Unit at Camarillo State Hospital and the West Los Angeles Veterans Administration (VA) Medical Center. Written informed consent was obtained from all participants; when a conservator was assigned, informed consent was obtained from the conservator as well. Subjects for the current study were 59 patients who met DSM-III-R criteria for schizophrenia as determined by the Structured Clinical Interview for DSM-III-R (22). Interviewers were trained at the Diagnosis and Psychopathology Unit of the UCLA Clinical Research Center for the Study of Schizophrenia, and agreement for ratings of key psychotic and mood items was good (minimum kappa=0.75). All patients were considered treatment-resistant according to the criteria of Kane et al. (23). Patients were excluded if they had experienced a period of good functioning within the past 5 years, which was defined as a score on the DSM-III-R Global Assessment of Functioning scale of 70 or above. In addition, treatment-resistance criteria included at least three 6-week treatment periods with neuroleptics from at least two different classes (at doses of at least 1000 mg/day of chlorpromazine equivalents) in the past 5 years that resulted in either no significant symptomatic relief or an inability to tolerate such doses. Absence of significant symptomatic relief was defined as either no or only slight improvement that did not alter need for care of patient. All patients also met symptom severity criteria at the initial screening that included 1) total score of at least 45 on the 18-item Brief Psychiatric Rating Scale (BPRS) (24); 2) minimum score of 4 on two of the following BPRS items: conceptual disorganization, suspiciousness, hallucinations, and unusual thought content; and 3) Clinical Global Impression (25) rating of at least 4.

Presence of the following resulted in exclusion from the study: 1) clinically significant neurologic disease (including seizure disorder) as determined by physical examination, laboratory tests, and review of medical history; 2) a history of head injury; 3) physical, cognitive, or language impairment of such severity as to adversely affect the

validity of clinical ratings; 4) a history of substance abuse, as defined by DSM-III-R, within the past 6 months; 5) a previous trial of risperidone that was sufficient to determine clinical response; 6) treatment with investigational drugs or clozapine within the previous 4 weeks or depot neuroleptics within the previous 8 weeks; 7) behavior that posed significant danger to self or others; or 8) significant clinical improvement (i.e., 18-item BPRS total score of 35 or less) shown between the intial screening and the start of the study.

During the study, patients could receive lorazepam, propranolol, or chloral hydrate as needed but no other psychoactive medications. For patients who received lorazepam, testing occurred a minimum of 10 hours after administration. Treatment with benztropine was uncontrolled and left to the discretion of the treating psychiatrist. In four instances at the VA site, biperiden hydrochloride was substituted for benztropine. For the purposes of analyses of covariance (ANCOVAS), the two agents were treated as identical.

FIGURE 1. Design of a Randomized, Double-Blind Study in Which 59 Treatment-Resistant Schizophrenic Patients Were Given Risperidone or Haloperidol[a]



[a]During the fixed-dose medication phase, patients were randomly assigned to either risperidone, 6 mg/day, or haloperidol, 15 mg/day. The blind was maintained during the flexible-dose phase, but doses could be adjusted.

Figure 1 depicts the study design. The study included a baseline phase and two double-blind phases. Pharmacotherapy at baseline differed between the two sites. Baseline assessments at the state hospital site were conducted while patients received 15–30 mg of haloperidol, whereas baseline assessments at the VA hospital were conducted during a lead-in period in which no medication was given. This difference potentially could have increased the variability in the pooled cohort at baseline but would have had little influence on any differential treatment effects, since patients were randomly assigned to treatment *within* each site. In the first of the double-blind phases—the fixed-dose phase—patients received either risperidone, 6 mg/day, or haloperidol, 15 mg/day, for 4 weeks. For the following 4 weeks, the blind was maintained, but the treating psychiatrists were able to adjust the dose in either direction. After this flexible-dose phase, the blind was broken, and patients who had been assigned to haloperidol were given an opportunity to try risperidone.

Procedures

Psychophysiological and neurocognitive batteries were administered at baseline, during the final week of the fixed-dose phase, and during the final week of the flexible-dose phase. The current report focuses on two indices of verbal working memory derived from the Digit Span Distractibility Test (26). The test consisted of seven audiotaped trials given under two conditions (with and without auditory distraction). In the condition without distraction, subjects listened to a woman recite six digits. The subjects wrote down the digits on an answer sheet after the series was completed. In the distraction condition, the woman recited five target digits, but four distractor digits spoken by a man were presented between each of the target digits. Subjects were instructed to write down the digits spoken by the woman and to ignore those spoken by the man. Time intervals between the target digits were identical in the two conditions. Trials were mixed by condition and presented in a quasi-random sequence. The conditions have been matched for mean difficulty and internal consistency in normal subjects, and the proportion correct for each condition served as the dependent measures.

Performance on the Digit Span Distractibility Test is usually associated with psychotic symptoms (19, 21) but also has been associated with negative symptoms (20). For this reason, we created a global index of psychotic and negative symptoms from two symptom indexes of the BPRS (the thinking disturbance and the withdrawal/retardation indexes) to determine whether verbal working memory performance was associated with treatment-related changes in symptoms (27). Agreement for ratings on a 24-item version of the BPRS (28) was good (minimum intraclass correlation coefficient=0.80).

Statistical Analyses

The data analytic model was a 2×2×2 factorial repeated measures ANCOVA. The dependent variable was change from baseline on the Digit Span Distractibility Test. The statistical model included one between-groups factor (treatment: risperidone versus haloperidol) and two within-subject or repeated measures factors (dosage phase: fixed versus flexible dose; and testing condition: distraction versus no distraction). Baseline performance on the task was used as a covariate.

A second set of analyses was performed to evaluate whether risperidone's effects might be attributable to either a reduction in symptoms or to the cognitive effects of adjunctive benztropine treatment, rather than to the intrinsic properties of risperidone itself. For these analyses, three time varying covariates assessed at each phase were added to the aforementioned statistical model: 1) a composite rating of change in psychotic symptoms from baseline, 2) a composite rating of change in negative symptoms from baseline, and 3) a dichotomous variable that indexed the presence or absence of benztropine. This use of covariance analyses was not intended to estimate what treatment effects might be with equivalent benztropine administration in the two groups. Rather, these analyses are comparable to stepwise regression in which the question is whether there are treatment effects over and above those mediated by benztropine status (29). Subjects were included if they had complete performance and symptom data at the baseline and fixed-dose phases. Six patients were missing data from the flexible-dose phase. For this reason, all analyses used a general linear mixed model analysis of variance procedure, SAS PROC MIXED (30). This method, which uses maximum likelihood methods to estimate the parameters of the conventional ANCOVA model, does not require complete cases (31). On the basis of preliminary analyses that evaluated the appropriateness of several alternative models for the covariance structure, compound symmetry was selected as optimal. Site was not included in the statistical model because preliminary analyses revealed no meaningful differences between sites after baseline performance was included in the model.

RESULTS

Demographic variables for the 59 patients divided by treatment group are listed in table 1. The two groups were highly comparable in most respects, with no significant differences on any of the variables. The percentage of men in each group was also similar (risperidone group: 80.0% [N=24]; haloperidol group: 86.2% [N=25]). On the basis of data from the multisite American trials (8), we expected the groups to differ in the proportion of patients who were receiving benztropine. During the fixed-dose phase, 65.5% (N=19 of 29) of the patients given haloperidol and 13.3% (N=4 of 30) of the patients given risperidone were receiving benztropine (χ^2=16.9, df=1, p<0.001).

The means for verbal working memory performance under each test condition during both double-blind phases are presented by treatment group in figure 2. An

TABLE 1. Demographic Characteristics of 59 Treatment-Resistant Schizophrenic Patients Treated With Risperidone or Haloperidol

	Patients Given Risperidone (N=30)		Patients Given Haloperidol (N=29)	
Variable	Mean	SD	Mean	SD
Age (years)	41.47	9.75	39.86	8.16
Education (years)	12.30	2.68	12.32	1.87
Age at onset (years)	21.73	5.82	21.03	5.98
Chronicity[a]	19.73	9.58	18.71	7.84

[a]Measured as age minus age at first institutionalization.

ANCOVA revealed a significant effect of baseline ($F=50.09$, $df=1, 158$, $p<0.0001$) and a significant effect of treatment ($F=10.63$, $df=1, 57$, $p<0.002$). The effects of time (fixed versus flexible dose) and test condition (distraction versus nondistraction) were not significant. None of the two- or three-way interactions among treatment, time, and condition was significant with the exception of condition by drug, which was marginally significant ($F=3.96$, $df=1, 158$, $p=0.048$).

Regarding within-group changes, the risperidone-treated patients showed a significant improvement from baseline performance at both the fixed-dose ($t=3.98$, $df=158$, $p<0.0001$) and flexible-dose ($t=3.72$, $df=158$, $p<0.0003$) phases. The haloperidol-treated patients did not change significantly from baseline at either phase. In fact, there was a slight decrease in performance from baseline to the end of the flexible-dose phase for this group. The risperidone-treated patients increased their performance to roughly 70% correct for both conditions. This level is still below the 82%–84% correct that has been reported for normal subjects (26).

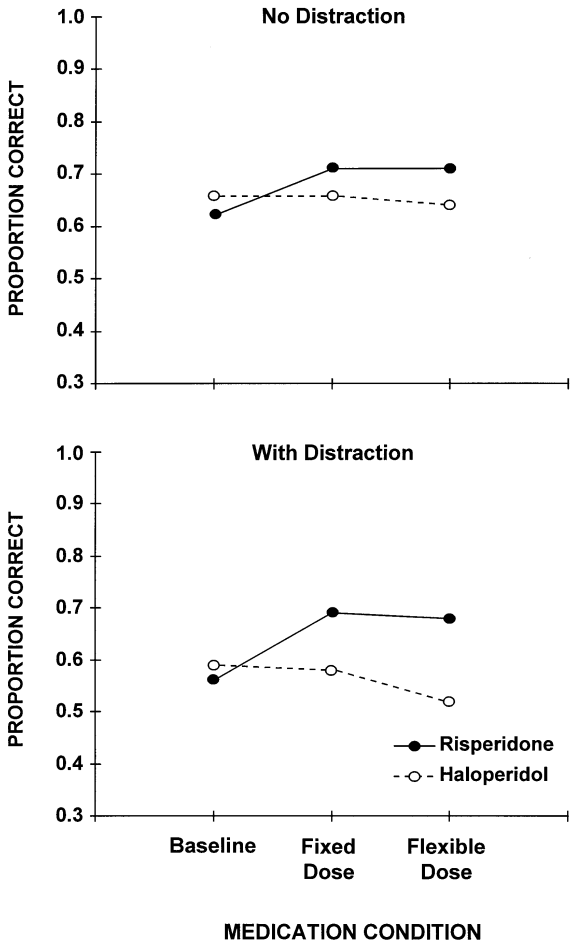
To evaluate whether risperidone's effects were direct or indirect, we conducted the analyses with three covariates: benztropine status, change in psychotic symptoms, and change in negative symptoms. For these analyses, the effect of baseline was significant ($F=48.98$, $df=1, 155$, $p<0.0001$), and treatment was significant ($F=5.61$, $df=1, 57$, $p<0.03$). No significant separate effects on performance were noted for benztropine status, change in psychotic symptoms, or change in negative symptoms.

After we controlled for benztropine and symptoms, within-group changes from baseline were significant for the risperidone-treated group for both the fixed-dose ($t=3.22$, $df=155$, $p<0.002$) and the flexible-dose ($t=3.30$, $df=155$, $p<0.002$) phases. The haloperidol-treated group did not change significantly from baseline at either phase.

DISCUSSION

The central conclusion from this study is that risperidone treatment had a more favorable effect on a key component of verbal working memory (the articulatory loop) than haloperidol treatment. When benztropine status, change in psychotic symptoms, and change in negative symptoms were controlled, the treatment effect remained significant. None of the three covariates was significantly related to performance.

FIGURE 2. Verbal Working Memory Performance of Treatment-Resistant Schizophrenic Patients Given Risperidone or Haloperidol[a]



[a]Fixed-dose phase: risperidone group, N=30; haloperidol group, N=29. Flexible-dose phase: risperidone group, N=26; haloperidol group, N=27.

Risperidone's beneficial effect on verbal working memory stands in contrast to the effects of other antipsychotic medications. Cassens et al. (2) reviewed seven studies that evaluated the effects of conventional antipsychotic medications on other versions of the Digit Span Distractibility Test. Six of the studies reported no significant differences in performance across a range of doses, and one study reported improvement. Among the clozapine studies, the open-label study by Hagger et al. (4) included an alternative measure of verbal working memory (the consonant trigram test). Six weeks of open-label clozapine treatment had a detrimental effect on performance. By 6 months the difference was nonsignificant, since performance had almost, but not quite, returned to baseline levels.

It is unlikely that the treatment effects on verbal working memory can be explained by the administra-

tion of as-needed medications. Chloral hydrate was only given at night, and lorazepam was never given within 10 hours of testing. Only eight patients received propranolol during the fixed- or flexible-dose phase (two in the risperidone group, six in the haloperidol group). Propranolol's effects on neurocognitive abilities are thought to be minimal, if any (32).

Because the effect of treatment remained significant after we controlled for benztropine status, change in psychotic symptoms, and change in negative symptoms, and because these covariates did not have significant effects of their own, it is difficult to explain risperidone's effects entirely through indirect mechanisms. Previous studies have shown benztropine to have a negative effect on secondary (i.e., longer-term) verbal memory in both normal subjects and patients. But verbal working memory constitutes a different memory system, and the effects of anticholinergic agents on this type of memory are not well established. For example, an earlier report failed to find any effects of scopolamine on verbal working memory (33). Perhaps most relevant to the current discussion is a previous evaluation of the effects of benztropine on Digit Span Distractibility Test performance after clinical state and neuroleptic dose were controlled (17); a trend ($p<0.10$) was revealed for an association between benztropine effects and the distraction, but not the no distraction, condition.

The treatment effects on verbal working memory were not explained by symptoms, either. In general, previous studies of the symptom correlates of verbal working memory have found quite modest associations that are more consistent for psychotic than for negative symptoms (19, 21). Despite modest cross-sectional correlations between symptoms and verbal working memory performance, the finding that performance changes occurred independently of symptoms supports the relative independence of these domains.

The results of the covariance analyses suggest that the favorable effects of risperidone treatment on verbal working memory are due, at least partially, to direct effects of the drug. Risperidone differs from haloperidol in a number of respects, but the feature of greatest interest for the present discussion may be its higher 5-HT_{2A} receptor occupancy. The distribution of 5-HT_2 receptors is noteworthy because their highest density is in the frontal cortex, a region relevant to working memory (14). In addition, data from animal studies suggest a possible role of the 5-HT_2 receptor in memory. Agents that block 5-HT_2 receptors can either impair or facilitate learning, depending on the conditions. Specifically, if mice are trained on an avoidance task, they show better retention of training if they receive 5-HT_2 antagonists either immediately after training or immediately before a retention test. While it is unwise to zealously extrapolate from a different species and a different type of memory test, there is at least some basis to expect that the 5-HT_{2A} antagonism of risperidone could be mediating a beneficial effect on verbal working memory.

In this study there was an intentional focus on a single neurocognitive construct, an approach typically used in experimental psychology. The decision to systematically examine a single construct allowed us to explore the direct and indirect medication effects in some detail. However, the limitation of this approach is that we do not yet know whether the treatment effects of risperidone are selective for this particular construct, or indeed for this particular measure. That issue will be resolved as more becomes known about risperidone's effects on other neurocognitive abilities.

The notion of efficacy in pharmacotherapy is typically used in a relatively restricted fashion. Primarily, the term refers to reduction in psychotic symptoms. With newer agents, negative symptoms have figured prominently as part of treatment efficacy (8, 23). Symptom reduction will remain the primary goal of pharmacotherapy in schizophrenia. Nonetheless, it may soon be possible to broaden the notion of efficacy to include amelioration of neurocognitive deficits. This issue has been largely academic until recently, since neither conventional agents nor clozapine has a substantial impact on neurocognition. Why should reduction of neurocognitive deficits become a goal of treatment? Evidence is accumulating that shows that neurocognitive processes are more closely associated with functional outcome (e.g., community functioning, social problem solving, and skill acquisition) than are psychotic symptoms (1). These neurocognitive deficits may act as "rate limiting factors" that restrict the functional adaptation of the patient. Improvement in these critical deficits could, at least theoretically, translate into functional advantages for patients. Hence, newer pharmacotherapies that reduce neurocognitive deficits could expand the narrow goal of *symptom* reduction into a broader goal of *disability* reduction.

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