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ORIGINAL INVESTIGATION

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Procedural learning in schizophrenia after 6 months of double-blind treatment with olanzapine, risperidone, and haloperidol

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Abstract *Rationale:* First generation antipsychotics induce extrapyramidal motor symptoms (EPS), presumably through dopamine D_2 receptor blockade at the dorsal striatum. This may also produce impairment of cognitive processes, such as procedural learning, that are dependent on this region. Haloperidol and, to a lesser extent, risperidone, are active in the dorsal striatum and may induce EPS and impairment of procedural learning. In contrast, the prototypical second-generation antipsychotic, clozapine, is less active in the dorsal striatum and does not induce EPS or impair procedural learning. Olanzapine is pharmacologically similar to clozapine and has a low incidence of EPS induction. *Objectives:* To assess the hypothesis that olanzapine would not have a deleterious effect on procedural learning. *Methods:* Thirty-nine subjects with early phase schizophrenia were randomly assigned to double blind treatment with haloperidol, risperidone, or olanzapine. They were administered the Tower of Toronto test at an unmedicated baseline and again following 6 weeks and 6 months of treatment. *Results:* Procedural learning, defined as the improvement observed between two blocks of five trials of the Tower of Toronto, was preserved after 6 weeks of all three treatments but showed a substantial decline after 6 months of treatment with haloperidol or risperidone. *Conclusions:* These data are consistent with the differential activity of the three medications in dorsal striatum structures and suggest that the advantages of olanzapine over haloperidol and risperidone in relation to extrapyramidal syndromes may also generalize to procedural learning. The results also suggest that the procedural learning disadvantages of haloperidol and risperidone accrue slowly but are apparent after 6 months of treatment.

Keywords Schizophrenia · Procedural learning · Dorsal striatum · Olanzapine · Risperidone · Haloperidol

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Introduction

In the past decade, four novel antipsychotic medications have been approved in North America for the treatment of schizophrenia, and all appear to benefit some aspects of the cognitive deficits associated with the illness (Keefe et al. 1999; Purdon 1999; Purdon et al. 2000, 2001a, 2001b, 2002). The cerebral mechanism responsible for the cognitive gains has not been confirmed, but an association to the extrapyramidal syndrome advantages of the novel agents has been suggested (Tandon et al. 1999). Extrapyramidal syndromes are relatively common in response to treatment with first generation neuroleptics, and appear to result from detrimental effects on structures in the dorsal striatum. This view has a historical association derived from similarities between the treatment-induced movement disorders in schizophrenia and the inherent movement disorders associated with subcortical dementias, including Huntington's disease and Parkinson's disease (Purdon et al. 1994Obeso et al. 1997). Positron

emission tomography has confirmed and extended this interpretation by showing that relative to earlier treatments, the novel antipsychotic medications have a much lower affinity for dopamine D_2 receptors densely represented in the dorsal striatum (Farde et al. 1992; Kapur et al. 1999). Although it is reasonable to speculate that the unique action of novel treatments on receptors of the dorsal striatum may be related to the unique cognitive benefits, a direct assessment of this possibility has been hampered by a reliance on tests that may not be very sensitive to basal ganglia dysfunction in prospective studies of therapeutic effects. The psychometric examination of differential action on the dorsal striatum, therefore, may require the isolation of a task that is more directly associated with basal ganglia integrity.

Procedural learning appears to be sensitive to the integrity of structures in the dorsal striatum. It denotes the ability to gradually acquire a motor or cognitive routine through repeated exposure to a task governed by invariant rules (Cohen et al. 1985) and it is demonstrated by improvement through practice, often with tests of rotor pursuit, mirror reading or drawing, and, more recently, the Tower of Toronto. Procedural learning in animals is impaired by ablation of dorsal striatum structures (Reading et al. 1991). Previous psychometric and more recent functional neuroimaging studies in humans have also implicated the relevance of structures of the dorsal striatum to procedural learning (Martone et al. 1984; Saint-Cyr et al. 1988; Granholm et al. 1993; Poldrack et al. 1999). For example, the degeneration of structures in the dorsal striatum in Huntington's disease impairs the ability to develop skill in mirror reading (Martone et al. 1984). Moreover, patients with Huntington's disease, and patients with degeneration of the substantia nigra due to Parkinson's disease, demonstrate little improvement from repeated presentations of the Tower of Toronto (Saint-Cyr et al. 1988) or from extended practice with the pursuit rotor test (Heindel et al. 1989; Harrington et al. 1990). Recent applications of neuroimaging have documented a correlation between pursuit rotor performance and shortened caudate T2 relaxation times on magnetic resonance imaging (Granholm et al. 1993) and increased glucose metabolism within a network including the dorsal striatum on positron emission tomography (Grafton et al. 1992). An application of functional magnetic resonance imaging has also demonstrated activation in structures of the dorsal striatum and the frontal lobes during the acquisition of a cognitive routine (Poldrack et al. 1999).

The apparent sensitivity of procedural learning to dysfunction in the dorsal striatum prompted several investigations of possible performance decrements associated with first generation neuroleptic treatment in both healthy normal controls and patients with schizophrenia, as well as several preliminary investigations of second generation treatments. Healthy normal control subjects have exhibited deleterious effects of both chlorpromazine and haloperidol on the pursuit rotor and the Tower Tests (Kornetsky and Humphries 1957; Kornetsky et al. 1959; Danion et al. 1992; Kimura et al. 1997; Peretti et al. 1997). A similar decrement was apparent on a mirror drawing task in a cross-sectional comparison of patients with schizophrenia who received haloperidol, compared to patients that were either neuroleptic-naive or receiving clozapine (Bedard et al. 1996). A cross-sectional comparison between a normal control group, and patients with schizophrenia treated with first generation antipsychotic medications, also reported poor overall Tower of Hanoi performance in the patients on a single day of testing and a slow rate of improvement over successive days of training (Goldberg et al. 1990). This tends to implicate a deficit in procedural learning in medicated patients, but the observed improvements in patients over four days of training suggests some retained ability as well. Similar results have been reported with the pursuit rotor task where impairments in absolute performance and the learning curve have been observed in a mixed medication sample receiving "standard neuroleptics" (Schwartz et al. 1996), in contrast to other studies reporting absolute deficits but no marked reduction in the learning curve over repeated administrations (Clare et al. 1993; Goldberg et al. 1993; Granholm et al. 1993). A putatively normal learning curve in medicated patients with schizophrenia was also reported on a motor sequence task (Schmand et al. 1992), but the result was rendered ambiguous by the absence of a normal control group. A recent open-label, cross-sectional comparison of at least 3 months treatment with haloperidol, risperidone or clozapine suggests that risperidone may also impair the rate of improvement over several presentations of the Tower of Toronto test (Bedard et al. 2000). Although risperidone may have a higher affinity for D_2 receptors than the other novel treatments, it is considered to be a second-generation neuroleptic treatment and thus a diminution relative to clozapine is somewhat unexpected. The observed deficit in procedural learning, however, is concordant with the results of a recent meta-analysis implicating a greater propensity of extrapyramidal syndromes in patients treated with risperidone compared to other second generation antipsychotic treatments including olanzapine (Leucht et al. 1999). A more recent prospective evaluation of a small group of treatment refractory patients showed a marked increase in procedural learning on the Tower of Toronto test after patients were switched to clozapine from either typical neuroleptics or risperidone (Purdon et al. 2002). A similar sparing of procedural learning with olanzapine remains to be fully explored, although its favourable EPS profile (Leucht et al. 1999) suggests that it may be more similar to clozapine than to other treatments in this regard. This possibility was recently reinforced in a cross-sectional comparison of a normal control group to patients with schizophrenia treated with either classical neuroleptics or olanzapine (Stevens et al. 2002). On a serial reaction time task with an implicit learning component, the olanzapine group was equivalent to the normal control group, and both demonstrated improvement over time that was not apparent in the classical neuroleptics group.

Although preliminary, there is sufficient evidence to support the potential value of procedural learning measures in the delineation of subcortical involvement in the cognitive gains postulated for second generation neuroleptic treatments and to begin to differentiate these effects from alterations relating to first generation neuroleptic treatment. There is also preliminary evidence to suggest a differentiation between at least two of the second-generation treatments, risperidone and clozapine, on the basis of procedural learning impairments. If successful, this type of delineation may facilitate the differentiation of a cerebral mechanism for the cognitive benefits anticipated from the novel treatments and perhaps begin to provide a rationale on which to anticipate differences between the novel treatments. In the present application, we undertook an assessment of the effects of haloperidol, risperidone, and olanzapine on procedural learning measured with the Tower of Toronto test within a prospective treatment design that attempted to minimise baseline medication status. We anticipated detrimental effects of haloperidol and risperidone on procedural learning based on the results of prior assessments with normal controls and patients with schizophrenia, as well as the high affinity of haloperidol for D_2 receptors in the dorsal striatum and the relatively greater propensity for extrapyramidal movement disorder in risperidone treated patients compared to other second generation neuroleptics. Based on the relative affinity for D_2 receptors in the dorsal striatum and the incidence of extrapyramidal syndromes, we anticipated no detrimental effects of olanzapine on procedural learning.

Materials and methods

Subjects

Sixty-five clinically stable outpatients within the first 5 years of treatment for schizophrenia were recruited from 19 medical centers across Canada and randomly assigned to 12 months of double-blind treatment with haloperidol, risperidone or olanzapine. The diagnosis of schizophrenia as defined by DSM-IV was confirmed by clinical interview by the principal investigator at each site. The sample included men and women aged 18–65 years with symptom severity in the mild range and who did not have prior medical histories of central nervous system disease or severe head injury. Participants were also excluded if they had active serious illness or substance abuse disorders, or if they were pregnant or lactating females. Further details of the sample are provided in a companion report of the standardized clinical neuropsychological changes observed over treatment (Purdon et al. 2000). The Tower of Toronto was included in the neuropsychological battery as an experimental measure of procedural learning and was not included in the prior report. The Tower of Toronto was administered within the full neuropsychological examination completed after a 30-day down-titration of neuroleptic medication culminating in a medication free period of at least 2 days. The tests were administered again after 6 weeks, 30 weeks, and 54 weeks of treatment. Of the 65 patients originally enrolled in the study, complete data were available on 33 patients from the baseline assessment and both the 6-week and 6-month assessments. There were insufficient data at 1 year, particularly in the haloperidol arm, to include a 12-month comparison, and the data reported below pertain only to the 33 patients with complete data after 6 months of treatment. Attrition over the first 6 months resulted from adverse events (O=1, R=1, H=6), death (R=1), lack of efficacy (O=1, R=2, H=1), subject decision (O=5, R=1, H=4), and physician/sponsor decision (O=1, R=2, H=1). An additional five subjects (O=2, R=1, H=2) failed to complete a valid Tower of Toronto due to test rejection or administrator error. This left 11 olanzapine (52%), 13 risperidone (62%), and nine haloperidol (39%) participants with complete data available for analysis after 6 months of treatment. Additional details of attrition are given in the prior report (Purdon et al. 2000). In addition to the comprehensive clinical neuropsychological evaluation, clinical status was assessed with the Positive and Negative Syndrome Scale (Kay et al. 1992) and motor status was assessed with the Extrapyramidal Syndrome Rating Scale (Chouinard et al. 1993), weekly for the first 6 weeks and monthly thereafter. Sample characteristics are presented in Table 1.

Tower of Toronto task and analysis

The Tower of Toronto was administered according to previously published guidelines (Saint-Cyr et al. 1988). The apparatus for the Tower of Toronto consists of three vertical pegs positioned in a horizontal line directly in front of the participant with three or four coloured disks arranged on the left-most peg in a gradient from dark to light with black on the bottom followed by red, yellow, and white. The participant is asked to reassemble the disks in their original sequence on the right-most peg by moving one disk at a time and never placing a dark colour on a light colour. No further instructions are given aside from a reminder if they attempt to move more than one disk or if they place a dark colour on a light colour. The solution can be reached in seven moves for the three-disk version and 15 for the four-disk version. Three trials of the three-disk version were administered first then ten trials of the four-disk version were given in two blocks of five trials. The two blocks of five trials were separated by 90 min during which time subjects completed a variety of other tests. The three-disk version of the Tower of Toronto is thought to assess problem solving ability and frontal lobe function while the four-disk version is thought to assess

Table 1 Baseline sample characteristics and clinical syndromes

Variable	Haloperidol (*n*=9)	Risperidone (*n*=13)	Olanzapine (*n*=11)
Age	29.89 (6.92)	32.08 (13.36)	25.82 (6.84)
Male sex, no. (%)	5 (56)	9 (69)	10 (91)
Education	12.56 (2.65)	12.92 (1.55)	13.55 (2.70)
Age at onset	23.57 (3.31)	30.08 (13.59)	24.30 (7.06)
Illness duration	3.00 (4.32)	2.00 (1.41)	2.30 (2.21)
PANSS			
Positive	12.56 (4.19)	11.62 (2.72)	13.27 (3.69)
Negative	20.67 (8.02)	15.23 (4.73)	18.73 (6.12)
ESRS			
Parkinsonism	5.56 (6.91)	4.23 (3.37)	6.91 (3.14)
Dyskinesia	0.22 (0.67)	0.77 (2.20)	1.36 (2.01)
Dystonia	0.00 (0.00)	0.62 (1.04)	0.36 (0.81)

procedural skills reliant on the integrity of the basal ganglia (Saint-Cyr et al. 1988). Support for this dissociation comes from observations that patients with Parkinson's disease or early Huntington's disease perform normally on the three-disk version but fail to demonstrate significant improvement over repeated testing on the four-disk version. In contrast, normal controls and amnesia patients demonstrate significant gains on both versions (Saint-Cyr et al. 1988). In accordance with previously published guidelines, a given trial was discontinued after 50 moves and the anticipated improvement in performance between the first block of trials and the second block of trials (i.e. Tower delta) provided the dependent measure of procedural learning (Saint-Cyr et al. 1988). Amnesic patients and normal controls typically demonstrate improvements of 25–40 moves between blocks (Saint-Cyr et al. 1988; Purdon et al. 2002). In addition, amnesic patients have demonstrated improvements comparable to controls in as few as two trials.

Prior to the formal analysis of the data, the scores of each subject were visibly inspected to assess floor (i.e. 50 moves by five trials for a total of 250 moves per block) or ceiling (i.e. 15 moves by five trials for a total of 75 moves per block) effects that might interfere with the sensitivity of the instrument for detecting changes from treatment. The Tower delta score (block 2 minus block 1) was subjected to a multivariate analysis of variance for repeated measures with time (baseline, 6 weeks, 6 months) as the within subjects factor and group (olanzapine, risperidone, haloperidol) as the between subjects factor. Significant main effects and interactions were followed with simple effects analysis when necessary.

Results

There were no significant differences in age, education, age at illness onset, or illness duration between groups, nor was there a significant difference in the gender composition of the three groups [all F values<1.40, P>0.28, $\chi^2(2)$=3.25, P=0.20]. The three treatment groups were also similar in their presentation of clinical and motor syndromes at the baseline assessment (all F values <2.20, P>0.13) (see Table 1).

The total number of moves for each block of the Tower of Toronto test and the mean delta score for each group at each assessment is presented in Table 2. Multivariate analysis of the Tower of Toronto data indicated a significant group by time interaction [$F(4,60)$=3.56, P<0.012], and a significant main effect of group [$F(6,58)$=2.69, P<0.024], but not time [$F(2,29)$=2.93, P>0.069]. Univariate analysis of the group factor at the three levels of the time factor revealed no difference between groups in the Tower delta scores at the baseline [$F(2,30)$=0.15, P>0.86], and 6-week assessments [$F(2,30)$=0.49, P>0.61], but a difference was apparent at the 6-month assessment [$F(2,30)$=7.48, P<0.003]. Repeated measures analysis within each group revealed a significant linear relation between time and Tower delta scores for the risperidone group [$F(1,12)$=5.45, P=0.039], a trend towards a similar relation for the haloperidol group [$F(1,8)$=4.46, P=0.07], and no suggestion of an association in the olanzapine group [$F(1,10)$=0.22, P=0.65]. Independent samples t-tests indicated that the olanzapine group demonstrated greater improvement between block one and two of the Tower of Toronto test at 6 months than both the risperidone [$t(22)$=2.37, P<0.028] and haloperidol [$t(18)$=4.25, P<0.001] groups. The risperidone and haloperidol groups demonstrated comparable performance at the 6-month assessment [$t(20)$=1.56, P>0.13]. Patients within the olanzapine group required significantly fewer moves [mean=−29.5, SD=24.2; $t(10)$=4.04, P=0.003] to complete block two, relative to block one, whereas the risperidone and haloperidol groups demonstrated a non-significant marginal decrease and a trend towards an increase respectively [mean=−2.2, SD=30.9; $t(12)$=0.26, P<0.80 and mean=17.1, SD=24.6; $t(8)$=2.09, P<0.07]. Inspection of Tower of Toronto performance for each subject at the three assessment points revealed ceiling performance in no subjects at the baseline assessment, five subjects at the 6-week assessment (two in the olanzapine group and three in the risperidone group), and six subjects at the 6-month assessment (two in the olanzapine group and four in the risperidone group). The mean Tower delta score of the risperidone group after removal of the four subjects that reached ceiling at 6 months was comparable to that of the entire group of 14 (mean=−3.22, SD=37.8). Given the relatively small number of subjects included in the study and the potential for outliers to significantly alter the results, boxplots of the mean delta score for each group at the 6-month assessment were created (see Fig. 1). One outlier was apparent in the haloperidol group, and four outliers were apparent in the risperidone group, suggesting that extreme scores might have influenced Tower of Toronto performance in the latter.

Table 2 Tower of Toronto performance over 6 months of treatment with olanzapine, risperidone, or haloperidol

Group		Baseline assessment			6-week assessment			6-month assessment		
		Block 1	Block 2	Delta	Block 1	Block 2	Delta	Block 1	Block 2	Delta
Olanzapine	Mean	155.2	133.4	–21.8	115.9	104.2	–11.7	121.7	92.3	–29.5
	n	11	11	11	11	11	11	11	11	11
	SD	26.6	40.8	42.7	28.8	30.8	30.1	33.6	21.6	24.2
Haloperidol	Mean	148.8	124.8	–24.0	135.9	115.1	–20.8	121.3	138.4	17.1
	n	9	9	9	9	9	9	9	9	9
	SD	45.1	30.5	41.3	30.9	35.2	25.2	37.6	44.4	24.6
Risperidone	Mean	148.8	118.2	–30.7	124.6	116.3	–8.3	117.7	115.5	–2.2
	n	13	13	13	13	13	13	13	13	13
	SD	38.0	42.6	42.0	42.5	42.0	31.6	38.1	46.0	30.9

Table 3 Procedural learning and adjunctive anticholinergic treatment in schizophrenia

Visit		Tower delta score		
		Baseline assessment	6-week assessment	6-month assessment[a]
Anticholinergic received				
Yes	Mean	–16.1	–22.4	8.0
	SD	46.4	33.3	34.0
	n	7	14	13
No	Mean	–28.5	–5.8	2.3
	SD	40.0	24.0	23.1
	n	26	19	9

[a] Patients receiving haloperidol and risperidone only

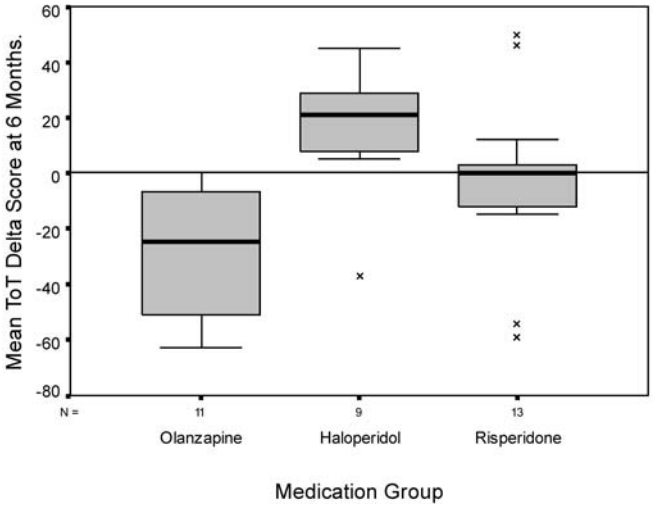

Fig. 1 Boxplots of procedural learning following 6 months treatment with olanzapine, haloperidol and risperidone in schizophrenia. *x* indicates outliers

Potential relationships between clinical symptoms, emergent motor syndromes, medication dosing and anticholinergic supplements were examined with Pearson's correlations and independent *t*-tests. There were no significant relationships between PANSS positive or negative scores and Tower of Toronto change scores at any of the assessments, all *P*-values >0.20. There were also no significant correlations between ESRS measures and Tower of Toronto change scores at any assessment, all *P*-values >0.21. To examine the potential influence of anticholinergic use on Tower of Toronto performance the baseline data were stratified on the basis of whether or not each patient received an anticholinergic supplement within 72 h of testing, and the 6-week and 6-month data were stratified on the basis of whether or not a patient received an anticholinergic supplement within 48 h of testing (see Table 3). There was no difference in Tower of Toronto change scores between the baseline patients that had recently received an anticholinergic supplement and patients that had not received this supplement [$t(31)=0.71$, $P<0.49$]. After 6 weeks of treatment, there was no significant difference in the frequency of anticholinergic supplements within the three treatment groups [$\chi^2(2)=4.89$, $P=0.089$], but there was a numerical increase in the proportion of haloperidol treated patients receiving anticholinergic supplements (67%) relative to the proportion of risperidone (46%) or olanzapine (18%) treated patients receiving the supplement. The stratification analysis gave no indication of a difference in procedural learning between the patients receiving anticholinergic supplements after 6 weeks of treatment relative to the patients that were not receiving anticholinergic supplements [$t(31)=1.67$, $P<0.10$]. After 6 months of treatment, there was a non-significant trend towards a difference in the proportion of patients in each group receiving anticholinergic supplements [$\chi^2(2)=5.10$, $P<0.079$], with the greatest proportion in the haloperidol group (78%), and fewer patients receiving anticholinergic supplements in the risperidone (46%) or olanzapine (27%) groups. The stratification analysis used only the haloperidol and risperidone treatment arms to prevent a bias from the greater representation of the olanzapine patients in the anticholinergic-free group. The 13 patients that were receiving anticholinergic supplements after 6 months treatment with risperidone or haloperidol did not differ in the amount of procedural learning demonstrated by the patients not receiving anticholinergic supplements [$t(20)=0.43$, $P<0.67$] (see Table 3). A contribution of medication dose was examined by comparing the average dose across the three time intervals for each medication. There was no difference in the daily dose of haloperidol after 6 weeks (mean=6.7, mode=5 mg) or 6 months (mean=6.1, mode=5 mg) of treatment, nor was there a difference in the daily dose of risperidone (mean=5.7, mode=6; mean=6.3, mode=6 mg) or olanzapine (mean=10.5, mode=10; mean=10.9, mode=5 mg) at the two follow-up assessment times. The correlations between dose and degree of procedural learning at both the 6-week and 6-month assessments were not significant for any of the groups (all *P*-values >0.21).

Discussion

The predicted dissociation between haloperidol, risperidone, and olanzapine on procedural learning was observed, albeit with an unprecedented temporal association in which the lack of procedural learning with haloperidol and risperidone was not apparent after 6 weeks of treatment but was apparent after 6 months of treatment.

As anticipated, the degree of procedural learning observed in the olanzapine group remained relatively constant throughout 6 months of treatment. The amount of procedural learning was expressed as the reduction in total moves on a second block of five trials of the Tower of Toronto Test relative to an initial block of five trials. The procedural learning at baseline after a minimum of 48 h without neuroleptic treatment (27 moves) and after 6 months of treatment with olanzapine (25 moves) was similar to the improvement we recently documented in a group of normal controls (28 moves) and patients treated for 6 weeks with clozapine (30 moves) (Purdon et al. 2002). The clozapine patients from the prior study had a baseline examination when they were receiving a variety of first generation antipsychotic medications. The procedural learning observed at that baseline (five moves improvement) was similar to the minimal procedural learning observed in the present investigation after 6 months of treatment with risperidone (one move improvement) or haloperidol (17 moves worse). Although the preservation of procedural learning after 6 weeks of treatment with risperidone or haloperidol was unpredicted, it is informative in relation to the relative impairment of procedural learning demonstrated in a prior report of patients treated for at least 12 weeks with risperidone or haloperidol (Bedard et al. 2000). Although cross-study comparisons must be made with caution, there is sufficient evidence from joint consideration of these studies to suggest that procedural learning impairments observed in patients treated with haloperidol or risperidone may be apparent after 12 weeks but not prior to 6 weeks of treatment.

The longstanding consensus that neuroleptic treatment confers no substantial benefit to cognitive skills in schizophrenia (Spohn and Struass 1989) has recently been challenged by demonstrations of gains from a second generation of neuroleptic treatments, including clozapine, quetiapine, and olanzapine (Purdon et al. 2000, 2001a, 2001b), and circumscribed gains from risperidone (Green et al. 1997; Purdon et al. 2000). The earlier consensus also implied the absence of reliable medication-induced cognitive deficits from the first generation of treatments (Spohn and Struass 1989), but this too may have been overstated. The present results show a detrimental influence on procedural learning from risperidone, and a trend towards a detrimental influence from haloperidol that is similar to previous observations of diminished procedural learning with first generation antipsychotic treatments in normal controls and patients (Kornetsky and Humphries 1957; Kornetsky 1959; Danion et al. 1992; Bedard et al. 1996, 2000; Schwartz et al. 1996; Kimura et al. 1997; Peretti et al. 1997; Purdon et al. 2002). The deleterious effects are consistent with expectations derived from procedural learning impairment in subcortical dementia (Martone et al. 1984; Saint-Cyr et al. 1988), functional neuroimaging anomalies in subcortical structures related to procedural learning impairment (Granholm et al. 1993), and the long standing perception that the dopamine receptor affinity of neuroleptic treatments in the dorsal striatum is responsible for some of the movement disorder in schizophrenia (Farde et al. 1992; Kapur et al. 1999). The present results also recapitulate prior investigations of procedural learning in schizophrenia that had revealed impairments on mirror drawing, rotor pursuit, or Tower of Toronto in patients receiving typical neuroleptics (Bedard et al. 1996, 2000; Schwartz et al. 1996) or risperidone (Bedard et al. 2000), and spared Tower of Toronto or mirror drawing performance in patients receiving predominantly atypical neuroleptics (Gras-Vincendon et al. 1994), or clozapine (Bedard et al. 1996, 2000; Purdon et al. 2002). The results suggest that risperidone may have similar effects on procedural learning to first generation neuroleptic treatments, and that olanzapine may be more similar to clozapine in the absence of effects on procedural learning.

We have observed circumscribed benefits from risperidone in both early phase and chronic patients, as well as what appear to be somewhat general improvements in cognitive status from olanzapine in early phase patients, and from clozapine and quetiapine in more chronic patients (Purdon et al. 2000, 2001a, 2001b). Our observations appear to be in general agreement with the results of double-blind studies with clozapine (Buchanan et al. 1994), risperidone (Green et al. 1997, 2002), and olanzapine. The divergence of the novel treatments on cognitive measures from the effects of first generation antipsychotic medication, as well as the apparent differences between the novel treatments, are in keeping with the differences in the metabolic activation of the dorsal striatum (Purdon 1999), and thus do not refute suggestions that the relative cognitive advantages may be related to extrapyramidal syndrome advantages (Tandon et al. 1999). The lack of a direct association between procedural learning and EPS measures in the present study could be related to a differential use of anticholinergic medication, or to the involvement of cerebral structures other than the dorsal striatum. Neuroimaging studies have indicated that several structures in addition to the dorsal striatum, the frontal lobes and cerebellum in particular, are active during performance of procedural learning tasks (Grafton et al. 1992; Poldrack et al. 1999). For example, the Tower of Toronto is presumed to involve a degree of conscious planning that likely requires frontal lobe processes that are replaced by basal ganglia processes with repetition (Gabrieli 1998). Differential medication effects on procedural learning may therefore be related to alterations in frontal lobe processes in the early stages of skill acquisition. However, the larger sample from which the present Tower of Toronto data were extracted did not show differences between medications on the Wisconsin Card Sort Test, a measure presumed sensitive to frontal lobe dysfunction. Moreover, the risperidone and haloperidol groups demonstrated some improvement over time in their performance on the first block of trials of the Tower of Toronto, but they did not demonstrate the relative gains between the first and second block of trials. This may suggest that problem solving ability is not impaired by treatment, and, perhaps

given enough trials, patients receiving haloperidol or risperidone might reach the optimal solution. This is consistent with a prior report indicating that patients could solve the test in the fewest required moves after 4 days of repeated administrations (Goldberg et al. 1990). The mechanism underlying the apparent differential effect of novel antipsychotic medications on procedural learning is likely related to the basal ganglia, but additional investigation will be required to confidently refute a contribution from the movement disorders associated with some treatments or differential effects on other cortical regions. The delayed onset of procedural learning limitations may provide an important parameter to the specification of the neural substrate of the differential effects.

The results of the present study are provocative and will hopefully stimulate further research in the area of procedural learning in particular, and deleterious cognitive effects of different medications in general, but we encourage caution in the generalization of the results until additional research illuminates the application of our findings to a broader sample of patients, additional measurements of procedural learning, and a broader dose range of antipsychotic treatments. Similar to most reports relating to procedural learning in schizophrenia, small sample size and non-significant but numeric inequities in gender composition in the present study will undermine confidence in the results. Also, the relative sparing of procedural learning demonstrated in this study may be specific to the early phase schizophrenia sample that was examined. Previously reported results showing similar effects in treatment resistant patients with clozapine (Purdon et al. 2002) suggest that the present results may generalize to a more chronic sample but this hypothesis will require direct assessment for confirmation. Also, previous work with haloperidol and risperidone has reported similar detrimental effects on procedural learning after at least 12 weeks of treatment (Bedard et al. 2000), but the absence of procedural leaning after 6 months has yet to be independently verified. Also, the lack of difference between haloperidol and risperidone on the Tower of Toronto test after 6 weeks or 6 months of treatment is similar to the lack of difference observed on the pursuit rotor test after 8 weeks of these treatments (Kern et al. 1998). However, the small samples assessed in these studies diminish confidence in the stability of null effects, particularly given the observed outliers that appeared in the risperidone group of the present study, and additional investigation is warranted to assess the validity of the observed results and the possible generalization of results across different measures of procedural learning. The generalization of the present results to other doses of medication should also be made with caution. Each of the medications administered in the present investigation has demonstrated dose/occupancy curves in vivo on positron emission tomography (PET) indicating that higher doses block a greater percentage of striatal D_2 receptors (Kapur et al. 1997, 1998, 1999). The mean of the modal dose was 11.5 mg for olanzapine and approximately 6 mg for risperidone per day after 6 months. Prior PET work has indicated that daily administrations of a 10 mg dose of olanzapine may block 66–75% of dorsal striatum D_2 receptors, whereas 6 mg/day of risperidone may block 73–85% of striatal D_2 receptors. It is therefore possible that a lower dose of risperidone may be less likely to produce deleterious effects on procedural learning. For example, dose ranges from 2 to 4 mg have occluded 60–80% of D_2 receptors within the dorsal striatum (Kapur et al. 1999). Similarly, low percentages of D_2 receptor blockade have been observed in patients treated with 5 mg or less of haloperidol (Kapur et al. 1997). Thus, a lower dose of risperidone or haloperidol might avoid the procedural learning impairment, but this has not been confirmed and it is not clear that the low doses would be sufficiently effective in the treatment of positive and negative symptoms.

There are numerous examples of day-to-day tasks that require procedural learning skills and it is possible that deficits in these skills might have a profound influence on educational and occupational rehabilitation. For example, rudimentary employment, which is often all that is available to our patients, entails numerous repetitive motor and cognitive sequences that must be acquired and developed in order to function successfully. The interference with procedural learning may thus suggest a medication-induced impediment to the acquisition of new skills that to some extent is independent of the direct effects of the psychotic disorder. Novel antipsychotic medications that are capable of reducing the florid symptoms and cognitive impairment associated with psychosis without inducing counter-productive side effects or novel cognitive impairments will be of paramount importance for the treatment of schizophrenia.

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