

Letter to the Editors

Procedural learning improvements after six weeks of clozapine treatment

Dear Editors,

Second generation antipsychotic treatments for schizophrenia may exert clinical and cognitive advantages relative to first generation treatments through a less derogatory effect on neurons in the dorsal striatum. Unique D2 binding profiles have been delineated with PET (Kapur et al. 1999; Farde et al. 1992), and some have speculated that this “EPS advantage” might account for the apparent benefits of novel treatments on cognition, depression, and the negative syndrome (Tandon et al., 1999). Correlation analyses have not supported a direct association between EPS and higher cognitive changes (Purdon, 1999; Purdon et al., 2000), possibly because traditional measures of cognitive skill have insufficient sensitivity to the integrity of the dorsal striatum. This may be overcome by utilization of procedural learning tasks that are impaired in subcortical dementia (Saint-Cyr et al., 1988; Poldrack et al. 1999). Procedural learning is the ability to acquire a motor skill or cognitive routine through repeated exposure (Cohen et al., 1985) and it is measured by improvement through practice, often with the Pursuit Rotor Test (PRT), the Mirror Drawing Test (MDT), and the Tower of Toronto (TOT). Antipsychotic investigations have documented a detrimental effect of chlorpromazine and haloperidol on the TOT and PRT in normal controls (Peretti et al.,

1997; Danion et al., 1992; Kimura et al., 1997). In schizophrenia samples, cross-sectional comparisons have revealed detrimental effects of haloperidol relative to clozapine on the MDT (Bedard et al. 1996), and haloperidol and risperidone relative to clozapine on the TOT (Bedard et al. 2000). A prospective evaluation with a mixed typical-neuroleptic baseline showed no change on the PRT after treatment with haloperidol or risperidone (Kern et al. 1998). First generation antipsychotic medications and risperidone appear to have a negative influence on procedural learning that is not apparent with clozapine, a differential effect that is concordant with estimated relative D2 receptor activity (Leucht et al. 1999). This inference is preliminary given the absence of control group comparisons in the haloperidol and risperidone work and the lack of prospective evaluations of clozapine.

We undertook a prospective pilot study of clozapine effects on the TOT by examining nine stable male inpatients with DSM-IV schizophrenia while they were receiving typical neuroleptic treatment and again after six weeks of clozapine. Patients were similar in age ($M = 29.11 \pm 7.38$) to our healthy control group (35.22 ± 5.89) and had been ill for almost 20 years ($M = 18.22 \pm 5.89$). The Tower was administered in accordance with published guidelines; two blocks of five trials separated by a 90-min interval with procedural learning given by the reduction in total moves to solution between the first and

Table 1
Performance on the Tower of Toronto Test (sum of scores over trials 1 to 5)

	Score		
	Typical $n = 9$	Clozapine $n = 9$	Normal controls $n = 9$
Sum over Block 1	154 ± 37	151 ± 33	131 ± 31
Sum over Block 2	149 ± 38	121 ± 27	103 ± 29
Procedural learning (B1–B2)	–5 ± 40	–30 ± 39	–28 ± 26
Paired t -test	$t(8) = 0.20, p = .85$	$t(8) = 2.31, p = .05$	$t(8) = 3.17, p = .01$

second blocks (Saint-Cyr et al. 1988). As anticipated, the control group showed significant procedural learning, averaging a gain of 28 moves, not apparent in the baseline schizophrenia sample, averaging a gain of 5 moves, but similar to the clozapine sample, averaging a gain of 30 moves (Table 1). Our results are consistent with previous cross-sectional demonstrations of procedural learning, and suggest that the clozapine spares procedural learning from medication-induced impairment and may reverse the impairment produced by other treatments. This result was anticipated from the relatively benign influence of clozapine on the dorsal striatum and provides a rare demonstration of typical neuroleptic deficits on a cognitive skill that can be reversed with a novel treatment.

References

- Bedard, M.A., Scherer, H., Delorimier, J., Stip, E., Lalonde, P., 1996. Differential effects of D2 and D4 blocking neuroleptics on the procedural learning of schizophrenic patients. *Canadian Journal of Psychiatry* 41 (1), S21–S24.
- Bedard, M.A., Scherer, H., Stip, E., Cohen, H., Rodriguez, J.P., Richer, F., 2000. Procedural learning in schizophrenia: further consideration on the deleterious effect of neuroleptics. *Brain & Cognition* 43, 31–39.
- Cohen, N.J., Eichenbaum, H., Deacedo, B.S., Corkin, S., 1985. Different memory systems underlying acquisition of procedural and declarative knowledge. *Annals of the New York Academy Sciences* 444, 54–71.
- Danion, J.M., Peretti, S., Grange, D., Bilik, M., Imbs, J.L., Singer, L., 1992. Effects of chlorpromazine and lorazepam on explicit memory, repetition priming, and cognitive skill learning in healthy volunteers. *Psychopharmacology* 108, 345–351.
- Farde, L., Nordstrom, A.L., Wiesel, F.A., Pauli, S., Halldin, C., Sedval, G., 1992. Positron emission tomographic analysis of central D1 and D2 dopamine receptor occupancy in patients treated with classical neuroleptics and clozapine. *Archives of General Psychiatry* 49, 538–544.
- Kapur, S., Zipursky, R.B., Remington, G., 1999. Clinical and theoretical implications of 5-HT₂ and D2 receptor occupancy of clozapine, risperidone, and olanzapine in schizophrenia. *American Journal of Psychiatry* 156, 286–293.
- Kern, R.S., Green, M.F., Marshall Jr, B.D., Wirshing, W.C., Wirshing, D., McGurk, S., Marder, S.R., Mintz, J., 1998. Risperidone vs. haloperidol on reaction time, manual dexterity, and motor learning in treatment-resistant schizophrenia patients. *Biological Psychiatry* 44, 726–732.
- Kimura, V., Corr, P.J., Mulligan, O.F., Cotter, P.A., Checkley, S.A., Gray, J.A., 1997. Effects of acute administration of d-amphetamine and haloperidol on procedural learning in man. *Psychopharmacology* 129, 271–276.
- Leucht, S., Pitschel-Walz, G., Abraham, D., Kissling, W., 1999. Efficacy and extrapyramidal side-effects of the new antipsychotics olanzapine, quetiapine, risperidone, and sertindole compared to conventional antipsychotics and placebo. A meta-analysis of randomized controlled trials. *Schizophrenia Research* 35, 51–68.
- Peretti, C.S., Danion, J.M., Kauffmann-Muller, F., Grange, D., Patat, A., Rosenzweig, P., 1997. Effects of haloperidol and amisulpride on motor and cognitive skill learning in healthy volunteers. *Psychopharmacology* 131, 329–338.
- Poldrack, R.A., Prabhakaran, V., Seger, C.A., Gabrieli, J.D., 1999. Striatal activation during acquisition of a cognitive skill. *Neuropsychology* 13, 564–574.
- Purdon, S.E., 1999. Cognitive improvement in schizophrenia with novel antipsychotic medications. *Schizophrenia Research* 35, 54–64.
- Purdon, S.E., Jones, B.D.W., Stip, E., Labelle, A., Addington, D., David, S.R., Breier, A., Tollefson, G.D., Canadian Collaborative Group for Research on Cognition in Schizophrenia, 2000. Neuropsychological change in early phase schizophrenia during 12 months of treatment with olanzapine, risperidone, or haloperidol. *Archives of General Psychiatry* 5, 249–258.
- Saint-Cyr, J.A., Taylor, A.E., Lang, A.E., 1988. Procedural learning and neostriatal dysfunction in man. *Brain* 111, 941–959.
- Tandon, R., Milner, K., Jibson, M.D., 1999. Antipsychotics from theory to practice: integrating clinical and basic data. *Journal of Clinical Psychiatry* 60 (8), 21–28.

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