The Effects of Clozapine, Risperidone, and Olanzapine on Cognitive Function in Schizophrenia

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Abstract

Cognitive function is markedly impaired in most patients with schizophrenia. Antecedents of this impairment are evident in childhood. The cognitive disability is nearly fully developed at the first episode of psychosis in most patients. The contribution of cognitive impairment to outcome in schizophrenia, especially work function, has been established. Preliminary results indicate that cognitive function, along with disorganization symptoms, discriminate schizophrenia patients who are able to work full-time from those who are not. Typical neuroleptic drugs lack the ability to improve the various domains of cognitive function impaired in schizophrenia. Atypical antipsychotic drugs pharmacologically related to clozapine—quetiapine, olanzapine, risperidone, sertindole, and ziprasidone—share the ability to produce fewer extrapyramidal symptoms than typical neuroleptic drugs and more potent antagonism of serotonin$_{2a}$ relative to dopamine$_2$ receptors. However, they have a number of different clinical effects. We have identified all the studies of clozapine, olanzapine, and risperidone that provide data on their effects on cognition in schizophrenia. Data for each drug are reviewed separately in order to identify differences among them in their effects on cognition. Twelve studies that report cognitive effects of clozapine are reviewed. These studies provide (1) strong evidence that clozapine improves attention and verbal fluency and (2) moderate evidence that clozapine improves some types of executive function. However, results of the effects of clozapine on working memory and secondary verbal and spatial memory were inconclusive. Risperidone has relatively consistent positive effects on working memory, executive functioning, and attention, whereas improvement in verbal learning and memory was inconsistent. Preliminary evidence presented here suggests that olanzapine improves verbal learning and memory, verbal fluency, and executive function, but not attention, working memory, or visual learning and memory. Thus, atypical antipsychotic drugs as a group appear to be superior to typical neuroleptics with regard to cognitive function. However, available data suggest that these drugs produce significant differences in specific cognitive functions. These differences may be valuable adjunctive guides for their use in clinical practice if cognitive improvements reach clinical significance. The effects of the atypical antipsychotic drugs on cholinergic and 5-HT$_{2a}$-mediated neurotransmission as the possible basis for their ability to improve cognition are discussed. It is suggested that the development of drugs for schizophrenia should focus on improving the key cognitive deficits in schizophrenia: executive function, verbal fluency, working memory, verbal and visual learning and memory, and attention.

Key words: Cognition, clozapine, neuroleptics, olanzapine, risperidone.

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The ability of typical antipsychotic drugs (e.g., chlorpromazine and haloperidol) to reduce delusions, hallucinations, and disorganization (positive symptoms) is such that for many years after their introduction in 1954, the elimination or reduction of positive symptoms to mild levels has been considered the hallmark of good or satisfactory outcome (Davis and Casper 1977). This view obscured the fact that outcome in terms of higher level measures, such as work and social function and the broader construct of quality of life, was in general, very poor (Hegarty et al. 1994; Meltzer 1995*b*). This is because successful treatment of positive symptoms with typical neuroleptic drugs is usually insufficient to restore

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the premorbid ability of schizophrenia patients to work or attend school successfully or to have satisfactory interpersonal function. Thus, although typical neuroleptic drugs are effective in treating positive symptoms in about 70 percent of schizophrenia patients (Meltzer 1997), no more than 30 percent of schizophrenia patients are able to hold part- or full-time jobs (Mulkern and Manderscheid 1989; Rupp and Keith 1993). For example, only 51.8 percent of first-episode schizophrenia patients were reported to recover functionally 1 year after the onset of psychosis (Tohen et al. 1997). Recent-onset patients with schizophrenia (i.e., those with a duration of illness of less than 5 years) are only slightly more able to hold volunteer or paying jobs than chronic, neuroleptic-resistant schizophrenia patients (Meltzer et al., in preparation).

Cognitive Impairment and Functional Deficits in Schizophrenia

Patients with schizophrenia have widespread, multifaceted impairments in many domains of neurocognitive function, including executive function, attention, perceptual/motor processing, vigilance, verbal learning and memory, verbal and spatial working memory, and semantic memory (verbal fluency) (Braff et al. 1991; Kenny and Meltzer 1991; Saykin et al. 1994). There is increasing awareness of the critical importance of cognitive dysfunction in schizophrenia. Evidence suggests that various forms of cognitive impairment, such as verbal learning and memory, executive function, and vigilance, may be of equal or greater importance than positive or negative symptoms in predicting functional outcomes, such as work status, activities of daily living, community outcome, and social problem solving and skill acquisition (Lysaker et al. 1995; Green et al. 1996; Meltzer et al. 1996; Velligan et al. 1997).

Cognition and Work Function in Schizophrenia. The relationship between work function and cognitive function at baseline in a group of 82 neuroleptic-resistant schizophrenia patients (most of whom were medication free, with a few receiving typical neuroleptic drugs) following 12 months of treatment with clozapine has previously been reported (Meltzer et al. 1996). Of this group, 15 patients (18.3%) were employed full time, 13 (15.9%) were employed part time, and 54 (65.9%) were unemployed at 12 months. The baseline (i.e., pre-clozapine) Wisconsin Card Sort Test (WCST; Heaton 1981) Categories score, a measure of executive function, was significantly better in those employed full time compared with those employed part time and the unemployed. There were no differences in eight other cognitive measures. The following test scores were significantly better in those employed full-time at 12 months compared with the unemployed group: the Wechsler Intelligence Scale for Children–Revised (WISC-R; Wechsler 1974) Maze (another test of executive function); the Controlled Word Association Test (CWAT; Benton and Hamsher 1976) and Category Instance Generation Test (CIGT; Newcombe 1969) (tests of verbal fluency); the Digit Symbol Substitution Test (DSST; Wechsler 1981), a test of perceptual/motor processing; and Verbal List Learning–Immediate (VLL-IR), and Verbal List Learning–Delayed Recall (VLL-DR), tests of verbal learning and memory (Bushke and Fuld 1974). Those patients employed part time or in school did not differ from either group. The relationship between cognitive test performance and work status remained the same when 12-month cognitive test scores were evaluated (Meltzer et al., in preparation).

We further examined the relationship between cognition, symptoms, and work status in a group of 243 schizophrenia patients: Of these, 39 were employed or volunteering at least 20 hours per week, and 206 had been unemployed for at least 1 year. The groups did not differ in age, gender, or age at illness onset. Those who were working had a shorter duration of illness (9.2 ± 6.2 (mean ± standard deviation [SD]) vs. 12.9 ± 8.1 years, $p < 0.01$). The employed group had fewer hospitalizations (3.9 ± 5.2 vs. 7.7 ± 8.4, $p < 0.01$), lower Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962) positive symptom scores (9.4 ± 5.6 vs. 11.0 ± 5.4, $p < 0.05$), and lower disorganization scores on the Schedule for Affective Disorders and Schizophrenia–Change (SAD-C; Endicott and Spitzer 1978) (2.1 ± 2.9 vs. 3.1 ± 3.5, $p < 0.05$). Those who were employed had better performance on the WCST–Categories (2.8 ± 2.3 vs. 3.7 ± 2.5, $p < 0.05$) and VLL-DR (6.4 ± 3.3 vs. 7.5 ± 3.2, $p = 0.04$) and tended to have better performance on the VLL-IR (7.5 ± 2.5 vs. 8.3 ± 2.3, $p < 0.06$). After adjusting for duration of illness and BPRS positive symptom scores, WCST–Categories, VLL-IR, and VLL-DR scores were still higher for those patients who were employed (data not presented). Thus, executive functioning and verbal learning and memory, as reported by Green (1996), appeared to be a useful predictor of work status, independent of positive symptoms.

Effect of Antipsychotic Drugs on Cognition

Typical Antipsychotic Drugs. For the purpose of this review, antipsychotic drugs whose predominant initial mode of action is blockade of dopamine (DA) receptors of the D_2 type (i.e., those DA receptors negatively cou-

pled to adenylate cyclase) will be referred to as typical antipsychotics or as neuroleptics, to distinguish them from atypical antipsychotic drugs. Atypical antipsychotics are operationally defined as drugs that produce minimal extra pyramidal symptoms (EPS) at doses that produce effective antipsychotic action (Meltzer 1995*a*). The prototypical atypical antipsychotic drug is clozapine (Meltzer 1997). Other members of the class include olanzapine, quetiapine, risperidone, sertindole, and ziprasidone. These drugs share potent 5-HT_{2a} and relatively weaker D_2 receptor antagonism (Meltzer et al. 1989; Schotte et al. 1996). Other compounds with a similar profile that have had lesser clinical testing include melperone, amperozide, iloperidone, and the selective 5-HT_{2a} antagonist M 100907 (Meltzer and Fatemi 1996). All such compounds cause low EPS at doses that have an antipsychotic action equivalent or superior to haloperidol or similar drugs. Thioridazine, which has the least EPS of any commonly used first-generation antipsychotic drug, is not considered atypical because its potential to produce EPS is significantly greater than that of the atypical antipsychotic drugs listed above (Scholz and Dichgans 1985).

Studies comparing cognitive function in neuroleptic-free schizophrenia patients with patients treated with typical antipsychotics have been reviewed by Heaton and Crowley (1981), Spohn and Strauss (1989), Cassens et al. (1990), King (1990), Bilder et al. (1992), and Mortimer (1997). The clear consensus of this body of research is that neither acute nor chronic administration of typical antipsychotics produced much beneficial effect on cognition. Moreover, there is some evidence that they cause selective impairment of some cognitive functions, particularly motor function and memory (Heaton and Crowley 1981; Earle-Boyer et al. 1991). Those antipsychotic drugs, such as thioridazine, with an appreciable anticholinergic effect have more adverse effects on memory (Spohn and Strauss 1989; Eitan et al. 1992). Lee et al. (1994, in press) found no worsening with typical neuroleptic drugs on any measure studied. Transient improvement in VLL-IR was noted during a 12-month treatment period in 29 recent-onset schizophrenia patients, who responded extremely well to these drugs. Their minimal change in cognition, despite near-complete control of positive symptoms in the group as a whole, provides further evidence that cognition is largely independent of positive symptoms.

Atypical Antipsychotic Drugs

Pharmacological differences in relation to clinical effects. All atypical antipsychotic drugs produce an antipsychotic effect at doses that do not cause significant EPS in the majority of patients with schizophrenia. However, there are differences in these drugs' ability to spare the motor system. Thus, clozapine appears least likely to produce EPS or even tardive dyskinesia (Lieberman et al. 1991), whereas risperidone may produce EPS in the higher range of doses used, for example, ≥ 8 mg/day (Marder and Meibach 1994). Olanzapine, quetiapine, low-dose risperidone, and ziprasidone appear to be more similar to clozapine with regard to EPS potential. However, at this time, it is not clear to what extent they may produce tardive dyskinesia (Beasley et al. 1996; Arvanitis and Miller 1997; Davis and Markham 1997; Tandon et al. 1997). There is some evidence that olanzapine may have a lower risk of causing tardive dyskinesia than does haloperidol (Tollefson et al. 1997*a*).

Differences in the potential to produce EPS reflect differences in pharmacology of these agents (Meltzer et al. 1989; Roth et al. 1992, 1994, 1995; Schotte et al. 1996), which have been reviewed elsewhere (Meltzer and Fatemi 1996; Schotte et al. 1996). Considering only in vitro based affinities, clozapine has the broadest spectrum of action of any of these agents, including high affinities (< 50 nM) for 5-HT_{2a}, 5-HT_{2c}, 5-HT_6, 5-HT_7, M_1–M_5, $alpha_1$-adrenergic, histamine H_1, and D_4 receptors. Olanzapine has high affinity for 5-HT_{2a}, 5-HT_6, D_2, M_1–M_5, and H_1 receptors. Risperidone has high affinity for the 5-HT_{2a}, 5-HT_7, D_2, D_3, $alpha_1$- and $alpha_2$-adrenergic, and H_1 receptors. Ziprasidone has high affinities for the 5-HT_{1a}, 5-HT_{2a}, 5-HT_{2c}, 5-HT_{1d}, 5-HT_7, D_2, and D_3 receptors and moderate affinities for $alpha_1$-adrenergic and H_1 receptors and for the 5-HT and norepinephrine (NE) reuptake transporters (Roth et al. 1995; Seeger et al. 1995). Quetiapine is a low-potency agent with high affinity only for the H_1 receptor (19 nM). Its affinities for the alpha, adrenergic, and 5-HT_{2a} receptors are slightly less—58 and 120 nM, respectively (Schotte et al. 1996). These effects are summarized in table 1. It is apparent that the only receptors for which all the agents have a high in vitro affinity are the H_1 receptor and, with the exception of quetiapine, the 5-HT_{2a} receptor.

As we have discussed elsewhere (Stockmeier et al. 1993), knowledge of the in vitro profiles of the atypical antipsychotic drugs may be insufficient to predict their in vivo effects. At high enough doses, they are capable of affecting other receptors as well. There may also be many regional differences in vivo that may reflect differences in the ability of these agents to modulate the release and reuptake of neurotransmitters at whose receptors they are usually antagonists, but sometimes agonists, through direct or indirect agonist actions. As indicated above, ziprasidone and clozapine have multiple effects on the serotonergic system, including antagonism at 5-HT_{2a}, 5-HT_{2c}, and 5-HT_7 (and in the case of ziprasidone, 5-HT_{1d}) but also direct or indirect 5-HT agonist effects at 5-HT_{1a} receptors. We discuss below how clozapine,

Table 1. High affinities of novel antipsychotic drugs

Receptor	Clozapine	Olanzapine	Quetiapine	Risperidone	Ziprasidone
5-HT_{1a}	—	—	—	—	1
5-HT_{1d}	—	—	—	1	1
5-HT_{2a}	1	1	3	1	1
5-HT_{2c}	1	1	—	—	1
5-HT_{6}	1	1	—	—	1
5-HT_{7}	1	—	—	1	1
DA_1	—	—	—	—	—
DA_2	—	1	—	1	1
DA_3	—	—	—	1	1
DA_4	1	1	—	1	1
H_1	1	1	1	1	1
$alpha_1$	1	2	2	1	1
$alpha_2$	—	—	—	1	—
M_1–M_5	1	1	—	—	—
5-HT transporter	—	—	—	—	1
NE transporter	—	—	—	—	1

[1] $K_i \leq 50$ nM.
[2] 60 nM.
[3] 120 nM.

which is often thought of as a potent antimuscarinic agent (Miller and Hiley 1974), may, in vivo, act more as an indirect cholinomimetic agent. Simplistic pharmacological predictions based on considerations of the effects of specific agents on target receptors (e.g., selective 5-HT_{2a} antagonists such as M 100907) are belied by the complex interactions of 5-HT, DA, NE, glutamate, gamma-aminobutyric acid (GABA), and acetylcholine (ACh), which vary in different brain regions.

The differences in pharmacology are likely to be the basis for important clinical differences among the newer atypical antipsychotic drugs. For example, clozapine is the only atypical antipsychotic drug that so far has been more effective than typical neuroleptic drugs in treatment-resistant patients in a double-blind trial with an active comparator. Clozapine was better able to decrease positive and negative symptoms in treatment-resistant schizophrenia patients (Kane et al. 1988). This is not to say that other atypical antipsychotic drugs are not effective in some of these patients as well, but clinical experience suggests their efficacy in this patient group is less frequent than that of clozapine. In addition, withdrawal of clozapine is more likely to produce an exacerbation of psychosis than is withdrawal of typical neuroleptics, risperidone, olanzapine, or quetiapine (Meltzer et al. 1996). Clozapine is much better tolerated in patients with Parkinson's disease who have an L-dopa-induced psychosis than is either risperidone or olanzapine (Pfeiffer and Wagner 1994; J.H. Friedman personal communication, 4/1/98). Clozapine is the least likely of these drugs to produce tardive dyskinesia (Lieberman et al. 1991). Clozapine, quetiapine, olanzapine, and ziprasidone do not significantly increase serum prolactin levels in patients when given chronically (Meltzer et al. 1979; Arvanitis and Miller 1997; Davis and Markham 1997; Tran et al. 1997), but risperidone does (Peuskens 1995). Olanzapine and clozapine are most likely to produce large weight gain; risperidone is less so (Peuskens 1995; Meltzer 1997), and ziprasidone has little effect on weight (Davis and Markham 1997; Tandon et al. 1997).

These important pharmacological differences may be relevant to effects on cognition. Various cognitive measures have been shown to be sensitive to the action of 5-HT (Buhot 1997), DA (Sawaguchi and Goldman-Rakic 1991; Murphy et al. 1997), ACh (Sarter and Bruno 1997), and glutamate (Abi-Dargham et al. 1997). The pharmacological profiles of the current generation of atypical antipsychotic drugs have some similarities (e.g., relatively potent 5-HT_{2a} compared with D_2 affinity) but, as noted above, important differences as well (e.g., antimuscarinic properties). The complex pharmacology of cognition, many components of which require motor function that may be impaired by EPS, suggests that these agents could have important differences in their effects on cognition.

The rest of this article will evaluate published studies on clozapine and risperidone, and present preliminary

reports of data from this laboratory on olanzapine and risperidone, to determine whether the prediction of unique effects on cognition is, in fact, confirmed. Elsewhere in this issue, the consideration of the differential effect of the atypical antipsychotic drugs complements and extends the approach of Keefe et al. (1999, this issue), who considered these drugs as a class, as were the typical neuroleptic drugs in the reviews cited above. Keefe et al. (1999, this issue) combined cognitive performance study data across drugs in a meta-analysis. It is our hypothesis that differences between atypical antipsychotic drugs with regard to cognition are of central importance for both theoretical and clinical reasons.

Clozapine. We identified 12 studies, published or in press, in which the effects of clozapine on various cognitive measures have been evaluated (table 2). The study of Lee et al. (1994) was a preliminary report based on a partial sample of recent-onset patients with schizophrenia. Data on the full sample is now available (Lee et al., in press) and will be commented on where differences have emerged. Of the 12 studies, 5 included a comparison group treated with another antipsychotic drug (Buchanan et al. 1994; Lee et al. 1994; Daniel et al. 1996; Meyer-Lindenberg et al. 1997; Lindenmayer et al. 1998), 1 was a single-blind crossover study (Daniel et al. 1996), and 7 were open trials with no comparator. The Zahn et al. (1994) study was a crossover study involving fluphenazine and clozapine. The sample sizes ranged from 10 to 36. The total number of subjects treated with clozapine was 263. Two studies included neuroleptic-responsive patients (Lee et al. 1994; Galletly et al. 1997), whereas the others evaluated only neuroleptic-resistant patients. The baseline cognitive assessment was conducted on neuroleptic-treated patients in all but two of the studies (Hagger et al. 1993; Lee et al. 1994). Only one study was conducted in a double-blind fashion (Buchanan et al. 1994) and that was only for the first phase of the study, which was 10 weeks in duration. In seven studies, treatment lasted from 6 to 12 weeks. Five studies examined the effects of clozapine at longer intervals, ranging from 6 to 14 months. One study (Goldberg et al. 1993) included subjects treated with multiple drugs in addition to clozapine. Specific neuropsychological assessments were grouped according to the following cognitive domains: (1) attention, (2) executive function, (3) working memory, (4) verbal learning and memory, (5) visual learning and memory, (6) semantic memory, (7) perceptual/motor processing, and (8) reaction time. The specific tests and a summary of results are listed in table 3. Several studies selected identical measures to assess the domains of perceptual/motor processing (e.g., DSST) and executive function (e.g., WCST).

Before summarizing the results, several methodological issues require comment. First, it is our opinion that drug comparison studies require a double-blind, randomized design. We are not aware of any evidence that suggests that cognitive test results in schizophrenia patients will be biased if the investigator knows what medication the patient is receiving. However, such knowledge could differentially affect how comparative studies are conducted and which patients persist in a trial. It is often very difficult to persuade early terminators to repeat the cognitive assessments. Therefore, cognitive studies are overrepresented with subjects who complete the study, most of whom would more likely be responders in terms of psychopathology or other key outcome measures. Investigators should report the number of dropouts in studies comparing two or more antipsychotic agents, especially studies sponsored by industry. A disparity in dropout rates between groups in a nonblinded study might reflect bias due to selective termination of one group of patients.

The second methodological issue is the duration of the trials. Those studies that examined the effects of atypical antipsychotic drugs usually found significant short-term benefits (e.g., 4–10 weeks), with a different pattern and a slightly greater extent of response after 6 to 12 months. Short-term studies nevertheless appear to be highly informative as to what domains of cognition, if any, are affected by the agents. A shorter study lends itself well to randomized, double-blind efficacy studies. However, longer studies are clearly the most relevant in determining the clinical significance, if any, of cognitive changes that emerge during treatment.

Finally, concomitant medications are likely to seriously confound these studies. Drugs likely to be combined with atypical antipsychotics (e.g., other antipsychotics, antidepressants, mood stabilizers, benzodiazepines, anticholinergics, and beta-blockers, many of which are 5-HT_{1a} antagonists) may have independent effects on cognition. These drugs are also likely to influence critical effects of atypical antipsychotics on neurotransmitters, such as DA, 5-HT, and ACh, which are the most likely basis for the effects these drugs have on cognition. The negative results of Goldberg et al. (1993), with regard to the effects of clozapine on cognition, may be an example of this.

Perceptual/motor processing, attention, and reaction time. As shown in table 3, 6 of 10 studies (60%) found significant improvement in perceptual/motor processing, as measured by the DSST; in attention, as measured by the Digit Span subtest of the Wechsler Adult Intelligence Scale–Revised (WAIS-R; Wechsler 1981); or in reaction time. It should be noted that the Digit Span is considered by some to be a measure of working memory.

Table 2. Study design and subjects in studies of clozapine effect on cognition

Investigator	Baseline	Number of subjects and neuroleptic responsivity	Study design	Comparison group	Concomitant meds	Duration of treatment	Dose of clozapine (mg/day)
Goldberg et al. 1993	Typical neuroleptic	13, resistant	Open	None	6/13 lithium, valproate, fluoxetine, lorazepam, primidone	6–14 mos	420[1]
Hagger et al. 1993	27/36 drug free	36, resistant	Open	Normal controls	None reported	6 wks, 6 mos	403 ± 208[2]
Buchanan et al. 1994	Fluphenazine	19, resistant	Blind; open extension	19 haloperidol	Anticholinergics	10 wks, 12 mos	200–600
Lee et al. 1994, in press	Mostly neuroleptic free	35, responsive	Open	29 neuroleptic treated	Mostly none	6 wks, 6, 12 mos	344 ± 140[2]
Zahn et al. 1994	Fluphenazine or placebo	25, resistant	Open	Crossover	Anticholinergics	6 wks	444 ± 89[2]
Daniel et al. 1996	Clozapine	>20, resistant	Crossover, single blind	Risperidone	No	6 wks	375[2]
Grace et al. 1996	Typical neuroleptic	22, resistant	Open	None	Unknown	3 yrs	Not given
Hoff et al. 1996	Typical neuroleptic and other drugs	30, resistant	Open	No controls	Unknown	12 wks	668 ± 164[2]
Fujii et al. 1997	Typical neuroleptic	10, resistant	Open	None	No	6 wks, 1 yr	643[2]
Galletly et al. 1997	4 risperidone, 1 drug free, 14 typical neuroleptic	19, responsive	Open	None	None reported	6.5 ± 2.0 mos	393 ± 182[2]
Meyer-Lindenberg et al. 1997	Typical neuroleptic	13, resistant	Open	13 zotepine	None reported	6 wks	150–450
Lindenmayer et al. 1998	Typical neuroleptic	21, resistant	Open	14 risperidone	Anticholinergics for EPS	12 wks	363 ± 91[2]

Note.—EPS = extrapyramidal symptoms.

[1] Mean dose.
[2] Mean dose ± standard deviation.

Table 3. Effect of clozapine on cognition

Investigator	Test	Results
Perceptual/Motor processing		
Goldberg et al. 1993	WAIS-R DSST	Not improved
Hagger et al. 1993	WAIS-R DSST	Improved
Lee et al. 1994	WAIS-R DSST	Improved
Grace et al. 1996	WAIS-R DSST	Improved
	Trails A	Improved
	WAIS-R Digit Span Forward	Improved
Hoff et al. 1996	Digit Symbol Modalities	Improved
Fujii et al. 1997	WAIS-R DSST	Improved
Galletly et al. 1997	WAIS-R DSST	Not improved
Lindenmayer et al. 1998	WAIS-R DSST	Not improved
Attention		
Daniel et al. 1996	CPT	Not improved
Grace et al. 1996	WAIS-R Digit Span Forward	Improved
Reaction time		
Zahn et al. 1994	Reaction Time	Improved
Executive functioning		
Goldberg et al. 1993	WCST	
	Categories and	Not improved
	% Perseveration	Not improved
	Category Test	Not improved
	Trails B	Not improved
Hagger et al. 1993	WCST	Not improved at 6 wks
	Categories and	or 6 mos
	% Perseveration	Improved at 6 mos
	WISC-R Mazes	
Buchanan et al. 1994	WCST	
	Categories and	Not improved at 10 wks
	% Perseveration	(both)
	Stroop Color-Word	Worsening at 12 mos
	Interference	
	Trails B	Improved[1]
Lee et al. 1994, in press	WCST	
	Categories	Not improved
	% Perseveration	Improved
	WISC-R Mazes	Improved
Daniel et al. 1996	WCST	Not improved
	Trails B	Not improved
Grace et al. 1996	Trails B	Improved
	WAIS-R Similarities	Improved
Hoff et al. 1996	WCST	
	Perseveration Errors	Not improved
	Categories	Worsening
	Total error	Not improved

Table 3. Effect of clozapine on cognition (Continued)

Investigator	Test	Results
Fujii et al. 1997	Trails B	Not improved
	Similarities	Improved
	WCST	
	Categories and	Improved[1]
	Perseverative Errors	Improved[1]
Galletly et al. 1997	WISC-R Maze	Not improved
Meyer-Lindenberg et al. 1997	Computer Mazes	Improved
Lindenmayer et al. 1998	Trails B	Improved[1]
	Stroop Color-Word	Not improved
Verbal working memory		
Hagger et al. 1993	ACTT	Not improved
Lee et al. 1994; in press	ACTT	Not improved
Grace et al. 1996	WAIS-R Digit Span Backward	Improved
Galletly et al. 1997	ACTT	Improved
Verbal learning and memory		
Goldberg et al. 1993	WMS-R Paired Associates	Not improved
Hagger et al. 1993	VLL-IR	Improved
	VLL-DR	Improved
Lee et al. 1994, in press	VLL-IR	Improved
	VLL-DR	Improved
Daniel et al. 1996	WMS	Not improved
Grace et al. 1996	Five Word List	Improved
	Immediate Recall	Not improved
	Delayed Recall	Improved
Hoff et al. 1996	Associative Learning	Not improved
	California Verbal Learning	Improved
Lindenmayer et al. 1998	Paragraph Memory Test	Not improved
Visual learning and memory		
Goldberg et al. 1993	WMS-R Visual Reproduction	Worsening
	Facial Recognition	Not improved
Buchanan et al. 1994	Mooney Faces	Improved at 12 mos
Hoff et al. 1996	Benton Visual Retention	Worsening
	WMS-R Visual Reproduction	Not improved
Daniel et al. 1996	Rey Complex Figure	Not improved
Grace et al. 1996	Rey Complex Figure	Improved
Fujii et al. 1997	WAIS-R Picture Arrangement	Not improved
	WAIS-R Block Design	Not improved
Galletly et al. 1997	WAIS-R Block Design	Improved
Lindenmayer et al. 1998	Pattern Memory Test	Not improved
Verbal fluency		
Goldberg et al. 1993	Category Test	Not improved
Hagger et al. 1993	CWAT	Improved at 6 wks and
	CIGT	6 mos

Table 3. Effect of clozapine on cognition (Continued)

Investigator	Test	Results
Buchanan et al. 1994	Category Fluency	Improved at 10 weeks, not improved at 12 mos
	CWAT	Not improved at 10 weeks, improved a 12 mos
Lee et al. 1994	CWAT CIGT	Improved at 6 wks and 6 mos
Grace et al. 1996	CWAT CIGT	Improved in both
Hoff et al. 1996	CWAT	Improved
Galletly et al. 1997	CWAT	Improved
Visual spatial skills		
Goldberg et al. 1993	Line Orientation	Not improved
Grace et al. 1996	Block Design	Improved
Fine motor control		
Hoff et al. 1996	Finger Tapping	Improved
Fujii et al. 1997	Finger Tapping	Not improved
Confrontational naming		
Hoff et al. 1996	Boston Naming	Not improved

Note.—WAIS-R = Wechsler Adult Intelligence Scale–Revised; DSST = Digit Span Substitution Test; CPT = Continuous Performance Test; WCST = Wisconsin Card Sorting Test; WISC-R = Wechsler Intelligence Scale for Children–Revised; ACTT = Auditory Consonant Trigrams Test; VLL-IR = Verbal List Learning–Immediate Recall; VLL-DR = Verbal List Learning–Delayed Recall; WMS-R = Wechsler Memory Scale–Revised; CWAT = Controlled Word Association Test; CIGT = Category Instance Generation Test.

[1]Trend ($p < 0.10$).

One study, which included a continuous performance test (CPT), found no improvement (Daniel et al. 1996). The average effect size was about 0.5 SD, and the mean improvement was 15 to 20 percent over baseline. No study found worsening; however, because these effects are mean group differences, it is likely that some patients did worsen. The final scores were still significantly lower than normal control levels when the latter data were provided. The three studies that did not find an effect on any of these measures—Goldberg et al. (1993), Daniel et al. (1996), and Lindenmayer et al. (1998)—also found no improvement with clozapine on any other type of cognitive measure.

Executive function. Of the 12 studies listed in table 2, 11 examined at least one measure of executive functioning. Five studies (45.4%) found improvement, two studies found a trend (Buchanan et al. 1994; Fujii et al. 1997), and four found no improvement or worsening. Only one study (Lee et al. 1994) found significant improvement in the WCST–Percent Perseveration. However, this was not confirmed in the full sample (Lee et al., in press; Lindenmeyer et al. 1998). One study (Fujii et al. 1997) found a trend for improvement in the WCST on both Categories and Perseverative Errors. Altogether, five studies examining the effect of clozapine on the WCST–Categories or Percent Perseveration found no improvement. Fujii et al. (1997) also found a significant improvement in the Similarities subtest of the WAIS-R. Mixed results were found with the Trails B test (The Adjutant General's Office 1944). Two of three studies that examined the ability to perform maze tasks showed improvement with clozapine treatment. Gallhofer et al. (1996) provided cross-sectional data consistent with a beneficial effect of clozapine on maze performance. No improvement, and even some worsening, on the Stroop Color-Word Interference test was found. We can conclude that clozapine may improve some types of executive functioning, but not WCST–Categories (see below).

Working memory. Four studies examined the effect of clozapine on verbal working memory, using the Auditory Consonant Trigrams Test (ACTT; Peterson and Peterson 1959) (table 3). Two reported improvement, and two did not. Hagger et al. (1993) and Lee et al. (1994) found slight worsening of verbal working memory after 6 weeks of treatment. However, scores reverted to baseline levels after 6 months of treatment. Lee et al. (in press) found no effect on working memory at either 6 weeks or 6 months in a larger sample of neuroleptic-responsive,

clozapine-treated patients than was included in the earlier report. Galletly et al. (1997), however, reported significant improvement in the ACTT after a mean of 6.5 months of treatment. Grace et al. (1996) also reported improvement in verbal working memory using the WAIS-R Digit Span Backward subtest after 2 years of treatment. It may be that a beneficial effect of clozapine on working memory is apparent only after a prolonged period of treatment. It seems unlikely that neuroleptic resistance is a major factor in this domain of cognition because the patients of Lee et al. (1994) responded well to typical neuroleptics prior to clozapine.

Verbal and visual learning and memory. Four of seven studies (57.1%) reported significant improvement on measures of verbal learning and memory (table 3), including immediate and delayed recall. The improvement due to clozapine was approximately 0.5 SD, but it did not normalize scores. The studies that found clozapine ineffective used relatively more complex assessments of verbal learning and memory, such as paired associates and paragraph memory tests.

Eight studies examined the effect of clozapine on visual learning and memory (table 3). The results ranged from significant worsening in two studies (25%) to significant improvement in three studies (37.5%). Three studies (37.5%) reported no effect. Two of the studies with positive effects had longer duration of treatment (Buchanan et al. 1994; Grace et al. 1996). The one positive study with a relatively short duration (Galletly et al. 1997) included nontreatment-resistant patients. We can conclude that clozapine may improve verbal memory tasks of lesser difficulty and possibly after a longer duration of treatment.

Verbal fluency. Six of seven studies (85.7%) that examined the effect of clozapine on verbal fluency reported significant improvement (table 3). All six positive studies utilized the CWAT, which involves letter fluency (generating words beginning with the letters F, A, or S). Improvement was noted in four of five studies for the CIGT, a test of category fluency. Improvements in both tests were approximately 0.5 SD and brought the performance levels to less than 0.5 SD below the mean for the normal controls included in the study. For example, in the Hagger et al. (1993) study, which was the first to report this effect of clozapine, scores on the CWAT increased from 30.4 ± 14.1 to 37.6 ± 14.2 at 6 months, a 23 percent improvement. Normal control scores were 43.9 ± 12.2. This is the most robust and consistent effect on cognition reported with clozapine or any other antipsychotic drug reported thus far.

Motor functioning. Two studies evaluated the effects of clozapine on a measure of motor functioning, the Finger Tapping Test. Hoff et al. (1996) found significant improvements on this task following clozapine treatment, whereas Fujii et al. (1997) did not.

Summary. Clozapine was found to have a robust effect on two cognitive domains, verbal fluency and attention. There was also evidence for its ability to improve some types of executive function and verbal learning and memory. There was little evidence of improvement in working memory. No study found improvement in every cognitive domain. On the other hand, three studies failed to find a significant effect of clozapine on any cognitive measure. These studies differed in some ways from the studies with positive findings. Of the 15 patients in the Goldberg et al. (1993) study, 12 received one of the following psychotropic agents:. lithium, fluoxetine, lorazepam, valproate, primidone, or levothyroxine. Patients in the Daniel et al. (1996) study received valproic acid, fluoxetine, paroxetine, sertraline, clonazepam, or clorazepate. The interaction these drugs may have had with clozapine could have influenced cognitive performance. However, the Fujii et al. (1997) study, in which clozapine was found to improve executive function and attention, included two patients who were receiving valproic acid and one receiving clonazepam. The Daniel et al. (1996) study may have been compromised by the fact that patients were already receiving clozapine when they were randomized to risperidone or to continue on clozapine. Thus, no baseline on typical neuroleptic drugs or neuroleptic withdrawal was ever obtained, and the baseline for 10 of the 20 subjects evaluated was obtained when these patients had already received clozapine for an unknown period of time. Thus, they may have achieved maximum improvement from clozapine treatment at the time the ratings were initiated. Lack of cognitive response to clozapine was unrelated to good symptom response. However, a previous history of good response to typical neuroleptic drugs appears to be a good predictor of improvement in cognition with clozapine: The three studies that found the most robust improvement in cognition in association with clozapine (Lee et al. 1994; Fujii et al. 1997; Galletly et al. 1997) included patients who responded best to typical neuroleptic drugs. In contrast, it appears that the most treatment-resistant patients (e.g., in Lindenmayer et al. 1998) had the least robust improvement in cognition. This suggests that the capacity to respond to typical neuroleptic drugs in terms of psychopathology may predict the capacity to demonstrate significant improvement in cognition when treated with clozapine. If this is confirmed in future studies, it would provide additional rationale for the use of clozapine in patients whose positive symptoms had responded to typical neuroleptic drugs.

Clozapine's ability to improve attention and verbal fluency, which appears to be quite robust, has been found

in the majority of studies to date. There is no evidence that practice effects account for the beneficial effects of clozapine on cognition. Even in the case of verbal fluency, where clozapine has been found to produce improvement in six of seven studies, no improvement has been found with risperidone (Meltzer, unpublished data). Moreover, Kenny and Meltzer (1992) found no evidence of a practice effect on any of the cognitive measures in the studies of Hagger et al. (1993) or Lee et al. (1994). The apparent improvement of verbal learning and memory may affect three areas of outcome identified by Green (1996): community outcome, social problem solving, and skill acquisition. As previously mentioned, these outcome measures are related to performance on measures of verbal learning and memory. We found significant relationships between improvement in cognitive measures with clozapine and quality of life (Meltzer et al., unpublished data).

The effects of baseline performance, gender, duration of illness, duration of treatment, dosage, and adjunctive therapies on the effect of clozapine on cognition require further study. It is also unclear which cognitive changes occurring from clozapine treatment are associated with changes in psychopathology. Hagger et al. (1993) did find that improvement in negative symptoms was associated with improvement in attention, executive function, verbal learning and memory, and verbal fluency. It is interesting that improvement in positive symptoms did not predict improvement in cognitive function. However, Galletly et al. (1997) also found that improvement in psychopathology, including positive symptoms, correlated with improvement in various cognitive measures. Clearly, some changes in cognitive performance are associated with changes in psychopathology.

Risperidone. Risperidone is the second atypical antipsychotic drug introduced into clinical practice. Its effects on EPS and psychopathology are much more dose-dependent than clozapine and possibly olanzapine as well (Marder and Meibach 1994; Peuskens 1995). At doses ≤ 6 to 8 mg/day, it usually produces few EPS. At higher doses, the frequency of EPS increases and there is some evidence for lesser efficacy as well (Lindstrom and von Knorring 1994; Marder and Meibach 1994; Simpson and Lindenmayer 1997). Whether cognitive effects of risperidone are also dose-related has not yet been determined.

Baseline cognitive data are available in three published studies of the effect of risperidone on cognition (Green et al. 1997; McGurk et al. 1997; Rossi et al. 1997) (table 4). Data from the same study of risperidone vs. haloperidol in treatment-resistant schizophrenia have been published by the UCLA group in several publications (Green et al. 1997; Kern et al. 1998, 1999 [this issue]). In addition, we will provide a preliminary report on an open study of the effect of risperidone in schizophrenia. The UCLA study (Green et al. 1997) was the only double-blind study and included haloperidol as a comparator. The total number of subjects treated with risperidone in these studies was 123, with individual sample sizes ranging from 13 to 29. The studies of Green et al. (1997) and Rossi et al. (1997) included neuroleptic-resistant patients with schizophrenia. The other two studies included both neuroleptic-resistant and neuroleptic-responsive patients (Stipp and Lussier 1996; Meltzer et al., in preparation). The duration of treatment ranged from 4 weeks to 6 months. A small proportion of subjects treated with risperidone received anticholinergic medications for EPS in all the studies.

The preliminary results of our open study of risperidone on cognition in 29 patients with schizophrenia will be reported here. The methods of diagnosis and assessment were identical to those of Hagger et al. (1993) and Lee et al. (1994). There were 22 males and 7 females (mean age 29.3 ± 7.5 years; duration of illness, 9 ± 3.4 years). Of these, 6 patients were hospitalized during an acute exacerbation at the time of study entry and 23 were outpatients. Eleven of the patients met the criteria of Kane et al. (1988) for neuroleptic resistance. Cognition was assessed at baseline and repeated after 6 weeks of risperidone treatment. At that time, three patients were receiving benztropine for EPS. Other psychotropic medications at 6 weeks included phenergan (3 patients) and lorazepam (2 patients). There was no significant change in BPRS total, positive, or withdrawal/retardation scores at 6 weeks, reflecting in part the neuroleptic-resistant nature of this group. Improvement in the ACTT, a measure of verbal working memory, at 6 weeks (29.3 ± 8.0 to 32.3 ± 11.6; $p < 0.05$) was the only significant change. There was a trend for an improvement in the WCST–Categories ($p < 0.09$).

Before we review all the studies that have evaluated the effects of risperidone on cognitive functioning in schizophrenia, we will comment on two studies not included in this review. Gallhofer et al. (1996) evaluated the comparative effects of risperidone, clozapine, and typical antipsychotics on maze performance. The evaluation was done after treatment with these medications for an unspecified amount of time. No baseline assessments on other medications were obtained prior to study entry; therefore, change from baseline on cognitive measures was not known, and any time-dependent effects of these medications were not evaluated. Daniel et al. (1996) randomized treatment-resistant schizophrenia patients who had been stable on clozapine to receive either clozapine or risperidone. Again, no baseline assessments prior to clozapine or risperidone treatment were obtained. Subjects who were randomized to receive clozapine had

Table 4. Study design and subjects in studies of risperidone effect on cognition

Investigator	Baseline	Number of subjects and neuroleptic responsivity	Study design	Comparison group	Concomitant medications	Duration of treatment	Dose of risperidone
Rossi et al. 1997	Typical neuroleptic	25, resistant	Open	None	Benzodiazepines Orphenadrine	4 wks	2–6 mg (mean = 4.6 mg)
Stipp and Lussier 1996	Typical neuroleptic	13, resistant and responsive	Open	None	Benztropine Procyclidine	8 wks/6 mos	3–10 mg (mean = 6.9 ± 2.3)
Green et al. 1997	Typical neuroleptic	29, resistant	Double blind	Typical	Benztropine Lorazepam Propranalol	8 wks	6 mg
McGurk et al. 1997	Off meds	28, resistant	Double blind	Typical	Benztropine Lorazepam Biperiden	4 wks	6 mg
Kern et al. 1998	Typical neuroleptic	27, resistant	Double blind	Typical	Benztropine Lorazepam Biperiden	8 wks	6 mg
Meltzer et al., in preparation	No meds, Typical neuroleptic	29, resistant and responsive	Open	None	Benztropine Lorazepam Phenergan	6 wks	3–9 mg (mean = 6.9 ± 2.1)

already been receiving it for an unstated amount of time; therefore, change from baseline and time-dependent effects were not obtained.

Perceptual/motor processing, attention, and reaction time. As shown in table 5, one of two studies found improvement in perceptual/motor functioning. Selective attention was improved (Stipp and Lussier 1996), but two other measures of attention, Divided Attention and Digit Span Forward, did not improve (Rossi et al. 1997; Stipp and Lussier 1996). Reaction time was reported to be improved by risperidone (Stipp and Lussier 1996; Kern et al. 1998). Improvements compared to baseline levels ranged from approximately 10 percent on the DSST to approximately 20 percent on the serial reaction time test. However, despite significant improvements, performance remained impaired compared to normal control subjects.

Executive function. Two of three studies (table 5) found improvement in measures of executive function, which included the WCST–Categories and Total Errors and Trail Making B (McGurk et al. 1997; Rossi et al. 1997). The improvement in the WCST–Categories reported by Rossi et al. (1997) was 0.5 categories; how-

Table 5. Effects of risperidone on cognition

Investigator	Test	Results
Perceptual/Motor processing		
Rossi et al. 1997	WAIS-R DSST	Improved
Meltzer et al., in preparation	WAIS-R DSST	Not improved
Attention		
Stipp and Lussier 1996	Selective Attention	Improved
	Divided Attention	
	Simultaneous Visual Pursuit/Digit Span Test	Worsening
Rossi et al. 1997	WAIS-R Digit Span Forward	Not improved
Reaction time		
Stipp and Lussier 1996	Reaction Time:	
	Alertness	Improved
	Sustained	Not improved
Kern et al. 1998	Serial Reaction Time	Improved
Executive functioning		
Rossi et al. 1997	WCST	
	Categories	Improved
	Total Errors	Improved
McGurk et al. 1997	Trails B	Improved
Meltzer et al., in preparation	WCST	
	Categories	Not improved
	% Perseveration	Not improved
	WISC-R Mazes	Not improved
Working memory		
McGurk et al. 1996	Computerized Spatial Working Memory Test	Improved
Green et al. 1997	Digit Span Distractibility	Improved
Rossi et al. 1997	WAIS-R Digit Span Backward	Improved
Meltzer et al., in preparation	ACTT	Improved
Verbal learning and memory		
Stipp and Lussier 1996	Word Pairs	Not improved
	Word Stem Priming	Improved
Kern et al. 1999 (this issue)	California Verbal Learning and Memory Test	Improved
Meltzer et al., in preparation	List Learning	Not improved

Table 5. Effects of risperidone on cognition (Continued)

Investigator	Test	Results
Verbal fluency		
Meltzer et al., in preparation	CWAT	Not improved
	CIGT	Not improved
Motor functioning		
Kern et al. 1998	Pin Test	Improved
Motor learning		
Kern et al.1998	Serial Reaction Time	Not improved
	Pursuit Rotor	Not improved

Note.—Improved = $p < 0.05$. WAIS-R = Wechsler Adult Intelligence Scale–Revised; DSST = Digit Span Substitution Test; WCST: Wisconsin Card Sorting Test; ACTT = Auditory Consonant Trigrams Test; CWAT = Controlled Word Association Test; CIGT = Category Instance Generation Test.

ever, performance remained in the impaired range. A trend for improvement in the WCST was found in the study of Meltzer et al. (in preparation). Similarly, performance on Trail Making B improved approximately 15 percent from baseline in the study of McGurk et al. (1997) but remained in the clinically impaired range.

Working memory. All three studies that evaluated the effect of risperidone in verbal working memory (Rossi et al. 1997; Green et al. 1997; Meltzer et al., in preparation) (table 5) demonstrated improvement following risperidone treatment. It is interesting that each of these studies used a different measure of this construct. The degree of improvement in each study was about 10 to 15 percent above baseline levels. Despite improvement, performance in all cases remained impaired compared to normal scores.

Only one study evaluated the effects of risperidone on spatial working memory, which was also improved by risperidone treatment (McGurk et al. 1997). The number of correctly identified target locations improved approximately 10 percent from baseline levels but remained significantly impaired compared to a control group matched for education.

Verbal learning and memory. Two of three studies (table 5) found improvement in verbal learning and memory (Stipp and Lussier 1996; Kern et al. 1999, this issue). The improvement in total words acquired in the Kern et al. study was a full SD above baseline levels. For the haloperidol group, an increase of 0.25 SD from baseline was found. There were no measures of visual learning and memory included in any study.

Verbal fluency. Verbal fluency (table 5) as measured by the CWAT and CIGT was not improved in the study by Meltzer et al. (in preparation). No other study included measures of verbal fluency.

Motor functioning. One study evaluated the effects of risperidone on a test of fine motor control, the Pin Test (table 5). Fine motor control improved following risperidone treatment (Kern et al. 1998). Risperidone-treated patients improved 15 percent from baseline; those treated with haloperidol improved only 6 percent.

Motor learning. Kern et al. (1998) evaluated the effects of risperidone on motor learning using the pursuit rotor and the serial reaction time test (table 5). No improvement was found on either test.

Summary. Risperidone was found to have statistically significant effects on some measures of perceptual/motor processing, reaction time, executive function, working memory, verbal learning and memory, and motor function, but not verbal fluency or motor learning. In the UCLA study (McGurk et al. 1996; Green et al. 1997; Kern et al. 1999, this issue), which was a randomized comparison of risperidone and haloperidol in treatment-resistant patients, changes in psychopathology did not account for the observed improvements in neurocognitive performance. Similarly, risperidone-induced improvement in working memory in the Meltzer et al. (in preparation) study was unrelated to improvement in BPRS total scores.

Olanzapine. Olanzapine is an atypical antipsychotic drug that has been found to be equal or superior to haloperidol in efficacy and to produce significantly fewer EPS than haloperidol (Beasley et al. 1996; Tollefson et al. 1997*b*; Tran et al. 1997). There are, to our knowledge, no published studies of the efficacy of olanzapine on cognition in schizophrenia. We report here data from 20 schizophrenia patients, 5 of whom were hospitalized on a research unit and 15 outpatients at baseline. Of the 20 patients, 10 (6 females, 14 males) met Kane et al. (1988) criteria for neuroleptic-resistant schizophrenia. The other 10 were at least partial responders to neuroleptic drugs. Mean age of the subjects was 41 ± 9.0 years. Age at onset was 25 ± 6.0 years, and the mean duration of illness was 16.0 ± 7.3 years. The average education of the subjects was 13.3 ± 2.5 years.

The initial evaluation of cognitive function was conducted while patients were receiving typical neuroleptic drugs and included two patients who received thioridazine. Ancillary medication at baseline included lorazepam and benztropine. The cognitive domains assessed included executive functioning, working memory, verbal and visual learning and memory, motor functioning, and perceptual/motor processing. Cognitive testing was repeated after 6 weeks of treatment. The mean dose of olanzapine was 12.5 ± 5.2 (range 5–20) mg/day. No other antipsychotic drug was given. Three subjects received lorazepam; two, sertraline; one, benztropine; and one, valproate at the 6-week assessment.

There was a trend for improvement in BPRS total score ($p < 0.06$) but no significant effect on BPRS positive or negative symptoms, perhaps reflecting the facts that half the patients in the study were neuroleptic resistant and the dose in this study was relatively low. The positive results are listed in table 6. A full published report is forthcoming. Olanzapine produced significant improvement on one measure of executive function, verbal learning and memory, verbal fluency, and reaction time. There was a 30 percent decrease in serial reaction time, which placed performance in the range of normal control subjects (Green et al. 1996). The improvement in the Stroop Color-Word Interference Test was approximately 45 percent of baseline, which is one of the larger effects on cognition reported for any of the atypical antipsychotic drugs. The 6-week score on the Stroop test was within the range of normal controls (Hoff et al. 1992). The improvement in the California Verbal Learning Test (Delis et al. 1983) List A trials 1 to 5 was 21 percent above baseline, whereas that in the Long Delay Free Recall was 17 percent. The improvement in verbal fluency as measured by the CWAT and the CIGT was 23 percent and 21 percent, respectively. This compares favorably with that seen with clozapine in neuroleptic-resistant patients: 15.1 percent and 5.5 percent, respectively (Hagger et al. 1993). Olanzapine had no effect on the WCST–Categories or Percent Perseveration, the WISC–R Mazes, or Trail Making A and B, all of which are measures of executive functioning. It also had no

Table 6. Effects of olanzapine on cognition

Test	Baseline	At 6 Weeks	*p*
Executive function			
Stroop Color-Word Interference	148 ± 55.5	105.8 ± 22	0.009
Executive functioning			
Categories	2.53 ± 2.32	2.69 ± 2.69	0.25
Percent perseverative errors	29.9 ± 20	25.0 ± 12.7	0.1
Trail Making B	161 ± 132	99 ± 45	0.18
Verbal learning and memory			
California Verbal Learning Test			
Total words list 1–5	38.5 ± 14.4	46.1 ± 11.2	0.002
Long delayed free recall	8.4 ± 3.7	9.8 ± 3.1	0.003
Visual learning and memory			
Visual Reproduction (WMS-R)			
Immediate recall	27.5 ± 9.0	29.5 ± 7.2	0.2
Delayed recall	19.8 ± 10.8	22.0 ± 9.1	0.5
Verbal fluency			
Controlled Word Association Test	27.1 ± 14.1	34.1 ± 12.5	0.004
Category Instance Generation Test	14.3 ± 6.1	18.5 ± 5.3	0.009
Working memory			
Verbal Working Memory			
ACTT (60 items)	41.0 ± 11.4	43.3 ± 9.2	0.64
Spatial Working Memory			
Spatial Working Memory Test (15 sec)	20.7 ± 7.5	21.8 ± 5.4	0.67
Attention/reaction time			
Serial reaction time test (Block 1)	743 ± 285	493 ± 107	0.005
Perceptual/motor processing			
DSST	32.2 ± 16	30.4 ± 18	0.4

Note.—Data are mean ± standard deviation. WMS-R = Wechsler Memory Scale–Revised; ACTT = Auditory Consonant Trigrams Test; DSST = Digit Span Substitution Test.

effect on verbal and spatial working memory or the DSST and Digit Span tests, which are measures of perceptual/motor processing and attention. It is unlikely that the positive effects on cognition reflect practice effects because typical neuroleptic drugs at 6 weeks did not produce improvement in these same tests of executive function, verbal learning and memory, or verbal fluency. These findings, of course, need to be verified in an independent sample.

In summary, olanzapine was found to have a significant effect on some measures of reaction time, executive function, verbal learning and memory, and verbal fluency. The magnitude of these effects was generally greater than that previously reported for clozapine and risperidone. However, these are the results of only one study and must be confirmed by other laboratories, in comparison with other atypical agents, using a double-blind, randomized experimental design.

Quetiapine. There are no published data on the effect of quetiapine on cognition except for a single case study, which reported significant improvement in attention and verbal memory and learning (Stipp and Lussier 1996).

Comparison of Clozapine, Risperidone, and Olanzapine. Even at this early stage of research, there are similarities as well as differences among these three atypical antipsychotic drugs with regard to which domains of cognition are improved after short-term treatment. It is important to point out that each of the drugs produced some improvement in cognition, whereas the data for typical neuroleptic drugs suggest no consistent improvement in any cognitive measure across many studies.

Clozapine appears to favorably affect most cognitive domains, albeit to varying extents. Olanzapine did not improve visual learning and memory, although it did improve verbal learning and memory. There are no data with regard to risperidone and visual learning and memory. Risperidone improved all cognitive domains except verbal fluency. Clozapine, olanzapine, and risperidone all appear to improve some, but not all, tests of perceptual/motor processing, attention/reaction time, executive function, and verbal learning and memory. Clozapine and olanzapine, but not risperidone, were found to improve verbal fluency. The major beneficial effects of both clozapine and olanzapine were on verbal fluency, followed by verbal learning and memory. Overall the effects of the two drugs on cognition were similar. The lack of effect of risperidone on verbal fluency has been reported by only one laboratory so far. It will be necessary to replicate this study in other laboratories before this difference with clozapine and olanzapine can be accepted.

Our laboratory (Hagger et al. 1993; Lee et al. 1994) failed to observe improvement with either clozapine or olanzapine on verbal working memory, but Galletly et al. (1997) did report improvement with clozapine. Risperidone differed from both other drugs in having its most robust effect on working memory, but it also improved attention and verbal learning and memory. There was stronger evidence for risperidone to improve executive function, including the WCST, than for either of the other two drugs.

The fact that clozapine and olanzapine have anticholinergic properties, while risperidone does not, is a possible basis for their differential impact on working memory. Clozapine and olanzapine have a greater ability to increase the concentration of extracellular DA in awake, freely moving rats than does risperidone (Kuroki et al. 1998). However, all three drugs produce high occupancy of cortical 5-HT_{2a} receptors in the human cortex (Farde et al. 1992; Nyberg et al. 1993, 1997). These results suggest that ACh may be more important than DA or 5-HT for working memory function. This is in accord with previous data from rodents, which indicates that ACh is more important than DA for short-term memory (McGurk et al. 1992; Broersen et al. 1994, 1995).

The differences among drugs noted here did not arise from direct comparisons in randomized, double-blind trials. Thus, it is possible that reported differences reflect differences in patient populations, medication status at baseline, drug dosage, duration of trials, choice of specific cognitive tests, and concomitant medication. However, the fact that key differences on working memory and verbal fluency reflect studies from multiple laboratories, at least for some of the drugs, suggests these differences may be real.

Clinical Significance. The studies reviewed here could have rich significance for clinical practice if the results are confirmed and extended by further research. It is not yet clear if the magnitude of the improvement in cognition reported here for any of these drugs is clinically significant. There is evidence that verbal learning and memory, in particular, is important for occupational and community functioning, as summarized by Green (1996). All three atypical antipsychotic drugs have a comparable beneficial effect on this cognitive domain. Risperidone appears to have a robust effect on working memory, a cognitive dimension thought to be of great importance to the entire schizophrenia syndrome (Goldman-Rakic 1991). Although the average improvement in cognitive measures appears to be about 0.5 SD, this may be sufficient to improve cognition in many patients to the point where they could function in many situations at an accept-

able level. Data from Lindstrom (1988) and Meltzer (1992) indicated that a significant proportion of patients on clozapine are able to work part- or full-time after 1 or more years of treatment. The differential contributions to improved outcome of the enhanced cognitive functioning, decreased psychopathology, and lower EPS produced by the atypical antipsychotic drugs are not known.

The available data suggest that the improvement in cognitive function produced by the atypical antipsychotic drugs is, in general, independent of the improvement in psychopathology. This is consistent with the evidence that cognitive measures generally correlate poorly with psychopathology, especially positive symptoms (Hagger et al. 1993). It also suggests that the cognitive impairment in schizophrenia is to some extent the result of brain abnormalities independent of those that produce major psychopathology.

If it is confirmed that specific atypical antipsychotic drugs have unique profiles of action on various domains of cognition, several interesting conclusions emerge. First, it may be desirable to characterize patients with schizophrenia on the basis of their deficits in specific domains of cognition and choose the antipsychotic drug most likely to correct that deficit, providing it is in the range where the drug is effective. For example, risperidone may be prescribed for patients with particular deficits in working memory and executive function, and clozapine or olanzapine for patients with deficits in verbal fluency. Of course, the patterns of cognitive deficits that patients exhibit may differ from the pattern the drugs affect. This raises the second issue: Would it be useful to combine atypical antipsychotic drugs for such patients to attempt to obtain the advantages of both? Such a strategy would have to consider the combined side-effect burden and the cost. Anecdotal reports of advantages of clozapine plus risperidone or olanzapine have been difficult to explain pharmacologically. Additive effects on cognition could be the basis for the beneficial effects of such combinations. However, expense and side-effect profiles make this strategy one to pursue with caution. It is also possibile that in combination, the drugs' effects will negate each other. Third, there is a strong need to determine which factors affect the ability of the atypical antipsychotic drugs to improve cognition—for example, gender, duration of illness, age, concomitant medications, and neuroleptic-resistant status. These and other such issues will require extensive clinical study.

Cholinergic and Serotonergic Basis for Effects of Atypical Antipsychotic Drugs on Cognition. Keefe et al. (1999, this issue) reviewed some of the literature concerning the importance of ACh, DA, 5-HT, NE, and glutamate to the cognitive effects of antipsychotic drugs. Several issues concerning ACh and 5-HT not addressed there will be highlighted here. The first is the common belief that the sole effect of clozapine on cholinergic transmission is as a potent muscarinic antagonist. On this basis, clozapine has been predicted to interfere with various cognitive functions, especially the encoding of new information as required in tests of verbal memory (Harvey and Keefe 1997). However, clozapine was reported to be a full agonist at the M_4 receptor in Chinese hamster ovary cells transfected with the human cloned M_1–M_5 receptor genes (Zorn et al. 1994). It was subsequently shown to be a partial agonist at cloned M_4 receptors and a full antagonist at striatal M_4 receptors (Olianas et al. 1997). Perhaps more important, clozapine has recently been reported to increase extracellular concentrations of ACh in rat prefrontal cortex, nucleus accumbens, and striatum using in vivo microdialysis (Parada et al. 1997). We have confirmed these results for the prefrontal cortex (Ichikawa and Meltzer, unpublished data). The increase is sufficiently large that it might be able to overcome the muscarinic receptor blockade induced by clozapine. Thus, clozapine may be an indirect cholinergic agonist as well as a direct-acting muscarinic agonist or antagonist (Zorn et al. 1994). If so, it might be expected to enhance encoding of memories, but should not affect verbal fluency (Broks et al. 1988).

Second, the hypothesis of Goldman-Rakic and colleagues about the central importance of working memory to the etiology of schizophrenia (Goldman-Rakic 1991; Goldman-Rakic and Selemon 1997) and of a modulatory role of dopaminergic activity (Sawaguchi and Goldman-Rakic 1991) and appropriate levels of D_1 receptor stimulation (Zahn et al. 1994; Williams and Goldman-Rakic 1995) on working memory, in particular, has been very influential in guiding research in this area. It is consistent with the view that working memory depends on the activity of the prefrontal cortex and that increased dopaminergic activity, especially in the prefrontal cortex, is required during working memory (Sawaguchi and Goldman-Rakic 1991; Watanabe et al. 1997). There is evidence for decreased blood flow in the dorsolateral prefrontal cortex in schizophrenia during the Wisconsin Card Sorting task, which requires both executive function and working memory (Berman et al. 1986; Weinberger et al. 1986). However, recent discoveries of the localization of 5-HT_{2a} receptors on the apical dendrites of pyramidal neurons in the rat prefrontal cortex (Willins et al. 1997; Jakab and Goldman-Rakic 1998) have resulted in the hypothesis that 5-HT_{2a} receptors may be just as or more important for working memory as are D_1 receptors. It has been postulated that clozapine exerts its beneficial effects on cognition and psychopathology by virtue of its ability to antagonize and downregulate 5-HT_{2a} receptors (Jakab and

Goldman-Rakic 1998). This is an attractive hypothesis, but it fails to explain why clozapine has so little effect on verbal working memory. There are as yet no data on its effects on spatial working memory. Furthermore, downregulation of 5-HT_{2a} receptors is also produced by antidepressants and typical neuroleptics, such as haloperidol and chlorpromazine (Peroutka and Snyder 1980; Andree et al. 1986). We found that a single dose of clozapine will downregulate 5-HT_{2a} receptors and that this effect lasted for more than 5 days (Matsubara and Meltzer 1989). No relationship between affinity for the 5-HT_{2a} receptor of a group of antipsychotic drugs and downregulation of 5-HT_{2a} receptors was found (Matsubara and Meltzer 1989). Further study is needed to determine the integrated effect of 5-HT, DA, and ACh on working memory and other cognitive measures.

In order to further study the pharmacological basis of the cognitive effects of the atypical antipsychotic drugs, valid data on which of the cognitive measures each drug affects in specific types of schizophrenia patients, and the time course of that effect, are essential. These findings must then be related to a comprehensive understanding of the in vivo effects of these drugs.

Conclusions

The studies of the effects of atypical antipsychotic drugs on cognitive function in schizophrenia reviewed here are the first efforts in this regard. There are clear limitations in the design of these studies, including patient selection, sample size, choice of cognitive tests, absence of comparators, lack of double-blind evaluations, duration of treatment, and concomitant medications. Nevertheless, the frequency with which positive effects have been reported contrasts strikingly with the results from studies of typical neuroleptics, where there have been few positive effects. Buchanan et al. (1994), Lee et al. (1994), Green et al. (1997), and McGurk et al. (1997) compared clozapine or risperidone with typical neuroleptic drugs and found advantages for the atypical agents over the typicals in a number of the cognitive measures. Together with data indicating that cognitive function is highly important to schizophrenia outcome, it is possible to conclude that the cognitive enhancing effects of atypical antipsychotic drugs represent a clinically important advantage over typical antipsychotic drugs. It is interesting to note that the atypical antipsychotic drugs were originally developed to enhance tolerability through diminished EPS, rather than to target cognitive functions.

The possibility that atypical antipsychotic drugs have differing patterns of effects on cognition while sharing some overall benefit implies differences in mechanism of action, which can be exploited to understand the pathophysiology of cognitive impairment in schizophrenia and its remediation. We suggest that cognitive improvement be made an explicit target of drug development for schizophrenia. Agents that improve working memory, executive function, attention, and verbal learning and memory should be possible with the aid of appropriate animal models, using a wide range of species. Whether such agents will prove to be antipsychotic in the traditional sense, that is, whether they decrease delusions and hallucinations as well, will be of great interest. Still, this would be of secondary importance because it might be possible to combine antipsychotic agents and cognitive enhancers to treat these two aspects of the syndrome. It is also intriguing to speculate that efforts to develop cognitive enhancing agents for senile dementia and age-associated cognitive decline may provide treatments valuable in schizophrenia and vice versa.

References

Abi-Dargham, A.; Laruelle, M.; Aghajanian, G.K.; Charney, D.; and Krystal, J. The role of serotonin in the pathophysiology and treatment of schizophrenia. *Journal of Neuropsychiatry and Clinical Neurosciences,* 9:1–17, 1997.

The Adjutant General's Office, War Department. *Army Individual Test Battery: Manual of Directions and Scoring.* Washington, DC: The Office, 1944.

Andree, T.H.; Mikuni, M.; Tong, C.Y.; Koenig, J.I.; and Meltzer, H.Y. Differential effect of subchronic treatment with various neuroleptic agents on serotonin$_2$ receptors in rat cerebral cortex. *Journal of Neurochemistry,* 46:191–197, 1986.

Arvanitis, L.A., and Miller, B.G. Multiple fixed dose of "Seroquel" (quetiapine) in patients with acute exacerbation of schizophrenia: A comparison with haloperidol and placebo. The Seroquel Trial 13 Study Group. *Biological Psychiatry,* 42(4):233–246, 1997.

Beasley, C.M. Jr.; Tollefsen, G.; Tran, P.; Satterlee, W.; Sanger, T.; and Hamilton, S. Olanzapine versus placebo and haloperidol: Acute phase results of the North American doubleblind olanzapine trial. *Neuropsychopharmacology,* 14:111–123, 1996.

Benton, A.L., and Hamsher, K.D. *Multilingual Aphasia Examination.* Iowa City, IA: University of Iowa, 1976.

Berman, K.F.; Zec, R.F.; and Weinberger, D.R. Physiological dysfunction of dorsolateral prefrontal cortex in schizophrenia: 2. Regional cerebral blood flow (rCBF) evidence. *Archives of General Psychiatry,* 43:126–135, 1986.

Bilder, R.M.; Turkel, E.; Lipschutz-Broch, L.; and Lieberman, J.A. Antipsychotic medication effects on neuropsychological functions. *Psychopharmacology Bulletin,* 28:353–366, 1992.

Braff, D.L.; Heaton, R.; Kuck, J.; Cullum, M.; Moranville, J.; Grant, I.; and Zisook, S. The generalized pattern of neuropsychological deficits in outpatients with chronic schizophrenia with heterogeneous Wisconsin Card Sorting Test results. *Archives of General Psychiatry,* 48:891–898, 1991.

Broersen, L.M.; Heinsbroek, R.P.; de Bruin, J.P.; Joosten, R.N.; van Hest, A.; and Olivier, B. Effects of local application of dopaminergic drugs into the dorsal part of the medial prefrontal cortex of rats in delayed matching to position task: Comparison with local cholinergic blockade. *Brain Research,* 645(1–2):113–122, 1994.

Broersen, L.M.; Heinsbroek, R.P.; de Bruin, J.P.; Uylings, H.B.; and Olivier, B. The role of the medial prefrontal cortex of rats in short-term memory functioning: Further support for involvement of cholinergic, rather than dopaminergic mechanisms. *Brain Research,* 674(2):221–229, 1995.

Broks, P.; Preston, G.C.; Traub, M.; Poppelton, P.; Ward, C.; and Stahl, S.M. Modeling dementia: Effects of scopolamine on memory and attention. *Neuropsychologia,* 26:685–700, 1988.

Buchanan, R.W.; Holstein, C.; and Breier, A. The comparative efficacy and long-term effect of clozapine treatment on neuropsychological test performance. *Biological Psychiatry,* 36:717–725, 1994.

Buhot, M.C. Serotonin receptors in cognitive behaviors. *Current Opinion in Neurobiology,* 7:243–254, 1997.

Buschke, H., and Fuld, P.A. Evaluating storage, retention, and retrieval in disordered memory and learning. *Neurology,* 11:1019–1025, 1974.

Cassens, G.; Inglis, A.K.; Appelbaum, P.S.; and Guthell, T.G. Neuropsychological function in chronic schizophrenia patients. *Schizophrenia Bulletin,* 16:477–499, 1990.

Daniel, D.G.; Goldberg, T.E.; Weinberger, D.R.; Kleinman, J.E.; Pickar, D.; Lubick, L.J.; and Williams, T.S. Different side effect profiles of risperidone and clozapine in 20 outpatients with schizophrenia or schizoaffective disorder: A pilot study. *American Journal of Psychiatry,* 153:417–419, 1996.

Davis, J.M., and Casper, R. Antipsychotic drug: Clinical pharmacology and therapeutic use. *Drugs,* 14:260–282, 1977.

Davis, R., and Markham, A. Ziprasidone. *CNS Drugs,* 8:153–159, 1997.

Delis, D.C.; Kramer, J.H.; Kaplan, E.F.; and Ober, B.A. *California Verbal Learning Test, Manual.* New York: The Psychological Corporation (Harcourt Brace Jovanovich), 1983.

Earle-Boyer, E.A.; Serper, M.R.; Davidson, M.; and Harvey, P.D. Continuous performance tests in schizophrenic patients: Stimulus and medication effects on performance. *Psychiatry Research,* 37:37–46, 1991.

Eitan, N.; Levin, Y.; Ben-Artzi, E.; Levy, A.; and Neumann, M. Effects of antipsychotic drugs on memory functions of schizophrenic patients. *Acta Psychiatrica Scandinavica,* 35:74–76, 1992.

Endicott, J., and Spitzer, R.L. The diagnostic interview: The Schedule for Affective Disorders and Schizophrenia (SADS). *Archives of General Psychiatry,* 35:837–844, 1978.

Farde, L.; Nordström, A.L.; Wiesel, F.A.; Pauli, S.; Halldin, C.; and Sedvall, G. PET analysis of central D_1- and D_2-dopamine receptor occupancy in patients treated with classical neuroleptics and clozapine—relation to extrapyramidal side effects. *Archives of General Psychiatry,* 49:538–544, 1992.

Fujii, D.E.; Ahmed, I.; Jokumsen, M.; and Compton, J.M. The effects of clozapine on cognitive functioning in treatment-resistant schizophrenic patients. *Journal of Neuropsychiatry and Clinical Neurosciences,* 9:240–245, 1997.

Galletly, C.A.; Clark, C.R.; McFarlane, A.C.; and Weber, D.L. Relationships between changes in symptoms ratings, neuropsychological test performance, and quality of life in schizophrenic patients with clozapine. *Psychiatry Research,* 72:161–166, 1997.

Gallhofer, B.; Bauer, U.; Lis, S.; Krieger, S.; and Gruppe, H. Cognitive dysfunction in schizophrenia: Comparison of treatment with atypical antipsychotic agents and conventional neuroleptics drugs. *European Neuropsychopharmacology,* 6:14–20, 1996.

Goldberg, T.E.; Greenberg, R.D.; Griffin, S.J.; Gold, J.M.; Kleinman, J.E.; Pickar, D.; Shulz, S.C.; and Weinberger, D.R. The effect of clozapine on cognition and psychiatric symptoms in patients with schizophrenia. *British Journal of Psychiatry,* 162:43–48, 1993.

Goldman-Rakic, P.S. Prefrontal cortical dysfunction in schizophrenia: The relevance of working memory. In: Carrol, B.I., and Barrett, J.E., eds. *Psychopathology and the Brain.* New York, NY: Raven Press Ltd., 1991. pp. 1–21.

Goldman-Rakic, P.S., and Selemon, L.D. Functional and anatomical aspects of prefrontal pathology in schizophrenia. *Schizophrenia Bulletin,* 23:437–458, 1997.

Grace, J.; Bellus, S.P.; Raulin, M.L.; Herz, M.L.; Priest, B.L.; Brenner, V.; Donnelly, K.; Smith, P.; and Gunn, S. Long-term impact of clozapine and psychosocial treatment of psychiatric symptoms and cognitive functioning. *Psychiatric Services*, 4:41–45, 1996.

Green, M.F. What are the functional consequences of neurocognitive deficits in schizophrenia? *American Journal of Psychiatry*, 153:321–330, 1996.

Green, M.F.; Kern, R.S.; Williams, O.; McGurk, S.R.; and Lee, K. Procedural learning in schizophrenia: Evidence from serial reaction time. *Cognitive Neuropsychiatry*, 2(2):123–134, 1996.

Green, M.F.; Marshall, B.D., Jr.; Wirshing, W.C.; Ames, D.; Marder, S.R.; McGurk, S.R.; Kern, R.S.; and Mintz, J. Does risperidone improve verbal working memory in schizophrenia? *American Journal of Psychiatry*, 154:799–804, 1997.

Hagger, C.; Buckley, P.; Kenny, J.T.; Freidman, L.; Ubogy, D.; and Meltzer, H.Y. Improvement in cognitive function and psychiatric symptoms in treatment-refractory schizophrenic patients receiving clozapine. *Biological Psychiatry*, 34:702–712, 1993.

Harvey, P.D., and Keefe, R.S.E. Cognitive impairment in schizophrenia and implication of atypical neuroleptic treatment. *CNS Spectrums*, 2:41–53, 1997.

Heaton, R.K. *Wisconsin Card Sorting Test Manual*. Odessa, FL: Psychological Assesment Resources, 1981.

Heaton, R.K., and Crowley, T.J. Effect of psychiatric disorders and their somatic treatments on neuropsychological test results. In: Filskov, S., and Boll, T.J., eds. *Handbook of Clinical Neuropsychology*. New York, NY: John Wiley & Sons, 1981. pp. 481–525.

Hegarty, J.D.; Baldessarini, R.J.; Tohen, M.; Waternaux, C.; and Oepen, G. One hundred years of schizophrenia: A meta-analysis of the outcome literature. *American Journal of Psychiatry*, 151:1409–1416, 1994.

Hoff, A.L.; Faustman, W.O.; Wieneke, M.; Espinoza, S.; Costa, M.; Wolkowitz, O.; and Csernansky, J.C. The effects of clozapine on symptom reduction, neurocognitive function, and clinical management in treatment-refractory state hospital schizophrenic inpatients. *Neuropsychopharmacology*, 15:361–369, 1996.

Hoff, A.L.; Riordan, H.; O'Donnell, D.W.; Morris, L.; and DeLisi, L.E. Neuropsychological functioning of first-episode schizophreniform patients. *American Journal of Psychiatry*, 149:898–903, 1992.

Jakab, R.L., and Goldman-Rakic, P.S. 5-Hydroxytryptamine 2A serotonin receptors in the primate cerebral cortex: Possible site of action of hallucinogenic and antipsychotic drugs in pryamidal cell apical dendrites. *Proceedings of the National Academy of Sciences of the United States of America*, 95: 735–740, 1998.

Kane, J.; Honigfeld, G.; Singer, J.; Meltzer, H.; and the Clozaril Collaborative Study Group. Clozapine for the treatment-resistant schizophrenic: A double-blind comparison with chlorpromazine. *Archives of General Psychiatry*, 45:789–796, 1988.

Keefe, R.S.E.; Silva, S.G; Perkins, D.O.; and Lieberman, J.A. The effects of atypical antipsychotic drugs on neurocognitive impairment in schizophrenia: A review and meta-analysis. *Schizophrenia Bulletin*, 25(2):201–222, 1999.

Kenny, J.T., and Meltzer, H.Y. Attention and higher cortical functions in schizophrenia. *Journal of Neuropsychiatry and Clinical Neurosciences*, 4:269–275, 1991.

Kern, R.S.; Green, M.F.; Marshall, B.D.; Wirshing, W.C.; Wirshing, D.; McGurk, S.R.; Marder, S.R.; and Mintz, J. Risperidone vs. haloperidol on reaction time, manual dexterity, and motor learning in treatment-resistant schizophrenia patients. *Biological Psychiatry*, 44:726–732, 1998.

Kern, R.S.; Green, M.F.; Marshall, B.D.; Wirshing, W.C.; Wirshing, D.; McGurk, S.R.; Marder, S.R.; and Mintz, J. Risperidone vs. haloperidol on secondary memory: Can newer antipsychotics medications aid learning? *Schizophrenia Bulletin*, 25(2):223–232, 1999.

King, D.J. The effect of neuroleptics on cognitive and psychomotor function. *British Journal of Psychiatry*, 157:799–811, 1990.

Kuroki, H.; Meltzer, H.Y.; and Ichikawa, J. Effect of antipsychotic drugs on extracellular dopamine levels in rat medial prefrontal cortex and nucleus accumbens. *Journal of Pharmacology and Experimental Therapeutics*, 288:774–781, 1998.

Lee, M.A.; Meltzer, H.Y.; and Jayathilake, K. A comparison of the effect of clozapine with typical neuroleptics on cognitive function on neuroleptic responsive schizophrenia. *Schizophrenia Research*, in press.

Lee, M.A.; Thompson, P.; and Meltzer, H.Y. Effects of clozapine on cognitive function in schizophrenia. *Journal of Clinical Psychiatry*, 55(Suppl. B):8–14, 1994.

Lieberman, J.A.; Saltz, B.L.; Johns, C.A.; Pollack, S.; Borenstein, M.; and Kane, J. The effects of clozapine on tardive dyskinesia. *British Journal of Psychiatry*, 158:503–510, 1991.

Lindenmayer, J.P.; Iskander, A.; Park, M.; Apergi, F.S.; Czobor, P.; Smith, R.; and Allen, D. Clinical and neurocognitive effects of clozapine and risperidone in treatment-refractory schizophrenics: A prospective study. *Journal of Clinical Psychiatry*, 59:521–527, 1998.

Lindstrom, E., and von Knorring, L. Changes in single symptoms and separate factors of the schizophrenic syndrome after treatment with risperidone or haloperidol. *Pharmacopsychiatry,* 27:108–113, 1994.

Lindstrom, L.H. The effect of long-term treatment with clozapine in schizophrenia: a retrospective study in 96 patients treated with clozapine for up to 13 years. *Acta Psychiatrica Scandinavica,* 77:524–529, 1988.

Lysaker, P.; Bell, M.; and Beam-Goulet, J. Wisconsin Card Sorting Test and work performance in schizophrenia. *Psychiatry Research,* 56:45–51, 1995.

Marder, S.R., and Meibach, R. Risperidone in the treatment of schizophrenia. *American Journal of Psychiatry,* 151:825–835, 1994.

Matsubara, S., and Meltzer, H.Y. Effect of typical and atypical antipsychotic drugs on 5-HT_2 receptor density in rat cerebral cortex. *Life Sciences,* 45:1397–1406, 1989.

McGurk, S.R.; Green, M.G.; Wirshing, W.C.; Ames, D.; Marshall, B.D.; and Marder, S.M. "The Effects of Risperidone vs. Haloperidol on Spatial Working Memory in Treatment-Resistant Schizophrenia." Paper presented at 51st Annual Meeting of the Society of Biological Psychiatry, New York, NY, 1996.

McGurk, S.R.; Green, M.F.; Wirshing, W.C.; Ames, D.; Marshall, B.D.; Marder, M.D.; and Mintz, J. The effects of risperidone vs. haloperidol on cognitive functioning in treatment-resistant schizophrenia: The Trail Making Test. *CNS Spectrums,* 2:60–64, 1997.

McGurk, S.R.; Levin, E.D.; and Butcher, L.L. Dopamine modulation of cholinergic mediated memory deficits following lesions of the cholinergic medial pathway. *Neuroscience,* 50:129–135, 1992.

Meltzer, H.Y. Dimensions of outcome with clozapine. *British Journal of Psychiatry,* 160 (Suppl. 17):46–53, 1992.

Meltzer, H.Y. The concept of antipsychotic drugs. In: den Boer, J.A.; Westenberg, H.G.M.; and van Praag, H.M., eds. *Advances in the Neurobiology of Schizophrenia.* Vol. 1. London, England: Wiley & Sons, 1995*a*, pp. 265–273.

Meltzer, H.Y. Multiple outcome criteria in schizophrenia: An overview of outcome with clozapine. *European Psychiatry,* 19 (Suppl. 10):19S–25S, 1995*b*.

Meltzer, H.Y. Treatment-resistant schizophrenia—The role of clozapine. *Current Medical Research and Opinion,* 14(1):1–20, 1997.

Meltzer, H.Y., and Fatemi, S.H. The role of serotonin in schizophrenia and the mechanism of action of antipsychotic drugs. In: Kane, J.M.; Möller, H.Y.; and Awouters, F., eds. *Serotonin in Antipsychotic Treatment: Mechanisms and Clinical Practice.* New York, NY: Marcel Dekker, Inc., 1996. pp. 77–107.

Meltzer, H.Y.; Goode, D.J.; Schyve, P.M.; Young, M.; and Fang, V.S. Effect of clozapine on human serum prolactin levels. *American Journal of Psychiatry,* 136:1550–1555, 1979.

Meltzer, H.Y.; Lee, M.; and McGurk, S.R. Effects of risperidone on cognitive function in schizophrenic patients. In preparation.

Meltzer, H.Y.; Matsubara, S.; and Lee, M. Classification of typical and atypical antipsychotic drugs on the basis of dopamine D-1, D-2, and serotonin 2 pKi values. *Journal of Pharmacology and Experimental Therapeutics,* 251:238–246, 1989.

Meltzer, H.Y.; Thompson, P.A.; Lee, M.A.; and Ranjan, R. Neuropsychologic deficits in schizophrenia: Relation to social function and effect of antipsychotic drug treatment. *Neuropsychopharmacology,* 14(35):275–335, 1996.

Meyer-Lindenberg, A.; Gruppe, H.; Bauer, U.; Lis, S.; Krieger, S.; and Gallhofer, B. Improvement of cognitive function in schizophrenic patients receiving clozapine or zotepine: Results from a double-blind study. *Pharmacopsychiatry,* 30(2): 35–42, 1997.

Miller, R.J., and Hiley, C.R. Anti-muscarinic properties of neuroleptics and drug-induced Parkinsonism. *Nature,* 248(449):596–597, 1974.

Mortimer, A.M. Cognitive function in schizophrenia—Do neuroleptics make a difference? *Pharmacology, Biochemistry and Behavior,* 56:789–795, 1997.

Mulkern, V.M., and Manderscheid, R.W. Characteristics of community support program clients in 1980 and 1984. *Hospital and Community Psychiatry,* 40:165–172, 1989.

Murphy, B.L.; Roth, R.H.; and Arnsten, A.F. Clozapine reverses the spatial working memory deficits induced by FG7142: Clozapine reverses the spatial working deficits induced by FG7142 in monkeys. *Neuropharmacology,* 16:433–437, 1997.

Newcombe, F. *Missile Wounds of the Brain.* New York, NY: Oxford University Press, 1969.

Nyberg, S.; Farde, L.; Eriksson, L.; Halldin, C.; and Eriksson, B. 5-HT2 and D2 dopamine receptor occupancy in the living human brain: A PET study with risperidone. *Psychopharmacology,* 110:265–272, 1993.

Nyberg, S.; Farde, L.; and Halldin, C. A PET study of 5-HT2 and D2 dopamine receptor occupancy induced by olanzapine in healthy subjects. *Neuropsychopharmacology,* 16:1–7, 1997.

Olianas, M.C.; Maullu, C.; and Onali, P. Effects of clozapine on rat striatal muscarinic receptors coupled to inhibi-

tion of adenyl cyclase activity and on the human clone M_4 receptor. *British Journal of Pharmacology,* 122:401–408, 1997.

Overall, J.E., and Gorham, D.R. The Brief Psychiatric Rating Scale. *Psychological Reports,* 10:799–812, 1962.

Parada, M.A.; Hernandez, L.; Puig de Parada, M.; Rada, P.; and Murzi, E. Selective action of acute systemic clozapine on acetylcholine release in the rat prefrontal cortex by reference to the nucleus accumbens and striatum. *Journal of Pharmacology and Experimental Therapeutics,* 281:582–588, 1997.

Peroutka, J.S., and Snyder, S.H. Long-term antidepressant treatment decreases spiroperidol-labeled serotonin receptor binding. *Science,* 210:88–90, 1980.

Peterson, L.R., and Peterson, M.J. Short-term retention of individual verbal items. *Journal of Experimental Psychology,* 58:193–198, 1959.

Peuskens, J. Risperidone in the treatment of patients with chronic schizophrenia: A multi-national, multi-centre, double-blind, parallel-group study versus haloperidol. Risperidone Study Group. *British Journal of Psychiatry,* 166:712–733, 1995.

Pfeiffer, C., and Wagner, M.L. Clozapine therapy for Parkinson's disease and other movement disorders. *American Journal of Hospital Pharmacy,* 51:3047–3053, 1994.

Rossi, A.; Mancini, F.; Stratta, P.; Mattei, P.; Gismondi, R.; Pozzi, F.; and Casacchia, M. Risperidone, negative symptoms, and cognitive deficit in schizophrenia: An open study. *Acta Psychiatrica Scandinavica,* 95:40–43, 1997.

Roth, B.L.; Ciaraneloo, R.D.; and Meltzer, H.Y. Binding of typical and atypical antipsychotic agents to transiently expressed 5-HT_{1c} receptors. *Journal of Pharmacology and Experimental Therapeutics,* 260:1361–1378, 1992.

Roth, B.L.; Craigo, S.C.; Choudhary, M.S.; Uler, A.; Monsma, F.J.; Shen, Y.; Meltzer, H.Y.; and Sibley, D.R. Binding of typical and atypical antipsychotic agents to 5-hydroxytryptamine 6 (5-HT6) and 5-HT hydroxytryptamine 7 (5-HT7) receptors. *Journal of Pharmacology and Experimental Therapeutics,* 268:1406–1410, 1994.

Roth, B.L.; Tandra, S.; Burgess, L.H.; Sibley, D.R.; and Meltzer, H.Y. D4 dopamine receptor binding affinity does not distinguish between typical and atypical antipsychotic drugs. *Psychopharmacology,* 120:365–368, 1995.

Rupp, A., and Keith, S. The costs of schizophrenia. *Psychiatric Clinics of North America,* 16:413–423, 1993.

Sarter, M., and Bruno, J.P. Cognitive functions of cortical acetylcholine: Toward a unifying hypothesis. *Brain Research—Brain Research Reviews,* 23(1–2):28–46, 1997.

Sawaguchi, T., and Goldman-Rakic, S. D1 dopamine receptors in prefrontal cortex: Involvement in working memory. *Science,* 251:947–950, 1991.

Saykin, A.J.; Shtasel, D.L.; Gur, R.E.; Kester, D.B.; Mozley, L.H.; Stafiniak, P.; and Gur, R.C. Neuropsychological deficits in neuroleptic naïve patients with first-episode schizophrenia. *Archives of General Psychiatry,* 51(2):124–131, 1994.

Scholz, E., and Dichgans, J. Treatment of drug-induced exogenous psychosis in parkinsonism with clozapine and fluperlapine. *European Archives of Psychiatry and Neurological Science,* 235:60–64, 1985.

Schotte, A.; Janssen, P.F.M.; Gommeren, W.; Luyten, W.; Van Grompel, P.; Lesage, A.S.; De Loore, K.; and Leysen, J.E. Risperidone compared with new and reference antipsychotic drugs: In vitro and in vivo receptor binding. *Psychopharmacology,* 124:57–73, 1996.

Seeger, T.F.; Seymour, P.A.; Schmidt, A.W.; Zorn, S.H.; Schulz, D.W.; Lebel, L.A.; McLean, S.; Guanowsky, V.; Howard, H.R.; and Lowe, J.A., III. Ziprasidone (CP-88,059): A new antipsychotic with combined dopamine and serotonin receptor antagonist activity. *Journal of Pharmacology and Experimental Therapeutics,* 275:101–113, 1995.

Simpson, G.M., and Lindenmayer, J.P. Extrapyramidal symptoms in patients treated with risperidone. *Journal of Clinical Psychopharmacology,* 17:194–201, 1997.

Spohn, H.E., and Strauss, M.E. Relation of neuroleptic and anticholinergic medication to cognitive functions in schizophrenia. *Journal of Abnormal Psychology,* 98:367–380, 1989.

Stipp, E., and Lussier, I. The effect of risperidone on cognition in patients with schizophrenia. *Canadian Journal of Psychiatry,* 41(Suppl. 2):S35–S40, 1996.

Stockmeier, C.A.; DiCarlo, J.J.; Zhang, Y.; Thompson, P.; and Meltzer, H.Y. Characterization of typical and atypical antipsychotic drugs based on in vivo occupancy of serotonin 2 and dopamine 2 receptors. *Journal of Pharmacology and Experimental Therapeutics,* 266:1374–1384, 1993.

Tandon, R.; Harrigan, E.; and Zorn, S.H. Ziprasidone: A novel antipsychotic with unique pharmacology and therapeutic potential. *Journal of Serotonin Research,* 4:159–177, 1997.

Tohen, M.; Stoll, A.L.; Strakowski, S.M.; Fadedda, G.I.; Mayer, P.V.; Goodwin, D.C.; Kolbrener, M.L.; and Madigan, A.M. The McLean First-Episode Psychosis Project: Six-month recovery and recurrence outcome. *Schizophrenia Bulletin,* 18:273–282, 1997.

Tollefson, G.D.; Beasley, C.M.; Tamura, R.N.; Tran, P.V.; and Potvin, J.H. Blind, controlled long-term study of the

comparative incidence of treatment-emergent tardive dyskinesia with olanzapine or haloperidol. *American Journal of Psychiatry,* 154:1248–1254, 1997*a*.

Tollefson, G.D.; Beasley, C.M., Jr.; Tran, P.V.; Street, J.S.; Krueger, J.A.; Tamura, R.N.; Graffeo, K.A.; and Thieme, M.E. Olanzepine versus haloperidol in the treatment of schizophrenia and schizoaffective and schizophreniform disorders: Results of an international collaborative trial. *American Journal of Psychiatry,* 154: 457–465, 1997*b*.

Tran, P.; Hamilton, S.H.; Kuntz, A.J.; Ptovin, J.H.; Andersen, S.W.; Beasley, C.; and Tollefson, G.D. Double-blind comparison of olanzapine vs. risperidone in the treatment of schizophrenia and other psychotic disorders. *Journal of Clinical Psychopharmacology,* 17:407–418, 1997.

Velligan, D.I.; Mahurin, R.K.; Diamond, P.L.; Hazelton, B.C.; Eckert, S.L.; and Miller, A.L. The functional significance of symptomatology and cognitive function in schizophrenia. *Schizophrenia Research,* 25:21–31, 1997.

Watanabe, M.; Kodama, T.; and Hikosaka, K. Increase of extracellular dopamine in primate frontal cortex during a working memory task. *Journal of Neurophysiology,* 78:2795–2798, 1997.

Wechsler, D. *Wechsler Intelligence Scale for Children–Revised.* New York, NY: Psychological Corporation, 1974.

Wechsler, D. *WAIS-R Manual.* New York, NY: Psychological Corporation, 1981.

Weinberger, D.R.; Berman, K.F.; and Zec, R.F. Physiological dysfunction of dorsolateral prefrontal cortex in schizophrenia: 1. Regional cerebral blood flow (fCBF) evidence. *Archives of General Psychiatry,* 43:114–125, 1986.

Williams, G.V., and Goldman-Rakic, P.S. Modulation of memory fields by dopamine D1 receptors in prefrontal cortex. *Nature,* 376:572–575, 1995.

Willins, D.L.; Deutch, A.Y.; and Roth, B.L. Serotonin 5-HT_{2a} receptors are expressed on pyramidal cells and interneurons in the rat cortex. *Synapse,* 27:79–82, 1997.

Zahn, T.P.; Pickar, D.; and Haier, R.J. Effects of clozapine, fluphenazine, and placebo on reaction time measures of attention and sensory dominance in schizophrenia. *Schizophrenia Research,* 13(2):133–144, 1994.

Zorn, S.H.; Jones, S.B.; Ward, K.M.; and Liston, D.R. Clozapine is a potent and selective muscarinic M4 receptor agonist. *European Journal of Pharmacology,* 269(3):R1–R2, 1994.

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The 10th Congress of the Association of European Psychiatrists (AEP 2000) will be held in Prague, Czech Republic, from October 28 to November 1, 2000.

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