The Effects of Atypical Antipsychotic Drugs on Neurocognitive Impairment in Schizophrenia: A Review and Meta-analysis

by Richard S.E. Keefe, Susan G. Silva, Diana O. Perkins, and Jeffrey A. Lieberman

Abstract

Cognitive deficits are a fundamental feature of the psychopathology of schizophrenia. Yet the effect of treatment on this dimension of the illness has been unclear. Atypical antipsychotic medications have been reported to reduce the neurocognitive impairment associated with schizophrenia. However, studies of the pattern and degree of cognitive improvement with these compounds have been methodologically limited and have produced variable results, and few findings have been replicated. To clarify our understanding of the effects of atypical antipsychotic drugs on neurocognitive deficits in patients with schizophrenia, we have (1) reported on newly established standards for research design in studies of treatment effects on cognitive function in schizophrenia, (2) reviewed the literature on this topic and determined the extent to which 15 studies on the effect of atypical antipsychotics met these standards, (3) performed a meta-analysis of the 15 studies, which suggested general cognitive enhancement with atypical antipsychotics, and (4) described the pharmacological profile of these agents and considered the pharmacological basis for their effects on neurocognition. Finally, we suggest directions for the development of new therapeutic strategies.

Key words: Antipsychotic drugs, neurocognitive impairment.


Over the past two decades, the syndrome of schizophrenia has been characterized with increasing sophistication and precision. Investigators have come to understand the illness as having multiple symptom dimensions and have described its phenomenology as including positive symptoms, negative symptoms, mood symptoms, and cognitive impairment. Each of these is believed to contribute to the morbidity of the illness and has become a target for therapy. Large numbers of treatment studies have demonstrated that the therapeutic effects of conventional antipsychotic drugs are predominantly limited to the positive symptoms of the illness. These drugs have substantially less impact on negative symptoms, mood symptoms, and cognitive impairment.

In recent years, investigators have focused on the negative and cognitive pathology of schizophrenia and have sought to assess the effects of treatment on these dimensions of the illness. The motivation underlying this effort derives from evidence that the functional disability in schizophrenia is strongly associated with negative symptoms (Keefe et al. 1987) and cognitive deficits (reviewed in Green 1996) and is not correlated with psychotic symptoms. However, the methodological challenges in validly and reliably assessing treatment effects on these symptom dimensions have been formidable.

With the advent of atypical antipsychotic drugs, the motivation to examine the multidimensional treatment outcome in schizophrenia has burgeoned. Members of the pharmaceutical industry have initiated numerous large-scale, multisite investigations of the impact of atypical antipsychotics on cognitive deficits in schizophrenia patients. The investigators of these studies hypothesized that atypical antipsychotics may substantially improve cognitive functioning in patients with schizophrenia. The investigators and pharmaceutical industry representatives have interpreted the results of studies to date as demonstrating that atypical antipsychotics ameliorate cognitive deficits in patients with schizophrenia. Other investigators have suggested that these studies have been methodologically limited and difficult to replicate. Moreover, the pattern and degree of cognitive improvement observed with these compounds have been variable. Finally, conclusions about whether atypical antipsychotics improve cognitive

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function in patients with schizophrenia are susceptible to various biases (Harvey and Keefe, submitted). A particularly important source of bias derives from the tendency of some clinicians and researchers to weigh equally studies with adequate and inadequate research designs.

The purpose of this article is to review critically studies of the impact of atypical antipsychotics on cognitive deficits in patients with schizophrenia. First, we will discuss the development of methodological standards against which studies in this area may be judged. Second, we will use a meta-analysis to evaluate systematically whether the results of these studies indicate that atypical drugs have therapeutic effects on cognitive symptoms. Finally, we will consider the possible pharmacological mechanisms that may be responsible for any putative effects on cognitive function.

Methodological Considerations

Research articles investigating the effects of atypical medications on neuropsychological and neurocognitive functioning were identified using the MEDLINE and Psychology Abstract database systems. Relevant articles published in medical or psychology journals between 1990 and April 1998 were then reviewed. Data from a manuscript accepted for publication that describes additional measures in an already published study were also included. The search yielded 15 studies of the effects of atypical antipsychotics on cognitive function in patients with schizophrenia, schizoaffective disorders, or psychosis not otherwise specified (see table 1). Abstracts were not included. Studies investigating the effects of atypical antipsychotics on neurocognitive functioning in geriatric patients with schizophrenia were excluded from the analysis. Separate publications of different measures from a single study were counted as one study.

Standards for the Assessment of Cognitive Change in Schizophrenia Treatment Studies. A research study that attempts to evaluate the effects of an atypical antipsychotic medication on cognitive functions has several important design features. These features and proposed design standards, listed in table 2, will be described here briefly (see Harvey and Keefe, submitted, for greater detail). Evaluation of how well the published studies met these standards appears in table 1.

Pharmacological status at baseline. Research on the impact of atypical antipsychotics on cognitive function must consider patients' treatment status prior to the initiation of the new medication. Given the limited research previously conducted in this area, the only requirement regarding the pharmacological status at baseline is that the baseline medication be determined. This determination was made in 14 of the 15 studies we reviewed. While medication-free baseline assessments are ideal, they are not practical to obtain and are most feasible in first-episode populations. In more chronic populations, medication-free assessment is not required, since conventional antipsychotics have repeatedly been found to be minimally effective in improving cognitive function (Medalia et al. 1988; Cassens et al. 1990). One possible caveat to this position, however, is that most studies on the effects of conventional antipsychotics have used doses that today are viewed as relatively high. The specific cognitive effects of low-dose (e.g., 2 mg/day haloperidol) conventional antipsychotic treatment strategies have not been adequately explored.

It is an acceptable research practice to include patients who receive adjunctive medication on a regular basis. If treatment with one medication leads to a greater likelihood of patients receiving a particular form of adjunctive medication that has a cognitive effect, then this cognitive effect can be viewed as being indirectly caused by the original medication. For example, if treatment with conventional antipsychotics increases the likelihood that patients will require anticholinergic medication, which has been found to impair memory in some (McEvoy et al. 1987; Strauss et al. 1990) but not all (Tamlyn et al. 1992) studies, then the increase in memory impairments can be fairly attributed to the conventional antipsychotic treatment. However, it may not be an acceptable research practice to include patients who have received medications that are rarely administered to them. This research practice could misrepresent the actual profile of cognitive deficits that are characteristic of patients on the antipsychotic under investigation. For example, one-time administration of benzodiazepines to alleviate anxiety prior to the cognitive testing situation should not be acceptable, since the resultant cognitive state is not representative of the patient's normal cognitive state while on the antipsychotic medication of interest.

Finally, the baseline assessment should be performed following a period of stability in the patient's medication regimen. Patients who have recently experienced a change in medication or dose are more likely to have controlled side effects and acute symptom exacerbation. Thus, acutely admitted patients who have been on their current treatment regimen for only a few days are not ideal for entry into a study of cognitive enhancement. Harvey and Keefe (submitted) recommend a 4- to 6-week period of stable treatment. The exception to this standard is the planned study of patients who have not taken their medication for an unspecified period of time. In this case, it is important to determine baseline levels of various
Table 1. Characteristics of 15 studies of the effect of atypical antipsychotic medication on cognitive functions in patients with schizophrenia

<table>
<thead>
<tr>
<th>Studies</th>
<th>Diagnosis of subjects</th>
<th>Baseline neuro-cognitive assessment (medication status)</th>
<th>Multiple study arms with random assignment</th>
<th>Double-blind condition</th>
<th>Adequate duration</th>
<th>Appropriate dosing (daily dose)</th>
<th>Appropriate test batteries</th>
<th>Adequate sample size</th>
<th>Assessment of neuro-cognitive/clinical relationships</th>
<th>Reported neuro-cognitive improvements after correction for multiple comparisons</th>
<th>Neuro-cognitive improvements after correction for multiple comparisons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Double-blind (n = 3)</td>
<td>Buchanan et al. 1994 (phase I)</td>
<td>Treatment-responsive schizophrenia</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes; 10 wk</td>
<td>Yes; (clozapine: 400mg (200–600), haloperidol: 20mg (10–30))</td>
<td>Yes; 4 cognitive domains tested</td>
<td>No; 19 subjects in each group</td>
<td>Yes</td>
<td>Yes; verbal fluency and visuospatial analysis (corrections for multiple comparisons made in original report)</td>
<td>Yes; verbal fluency and visuospatial analysis (corrections for multiple comparisons made in original report)</td>
</tr>
<tr>
<td>Green et al. 1997; McGurk et al. 1997; and Kern et al., in press</td>
<td>Treatment-resistant schizophrenia</td>
<td>Yes (3- to 7-day washout following 3-wk haloperidol stabilization)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes; 4 wk</td>
<td>Yes; (risperidone: 6mg, haloperidol: 15 mg)</td>
<td>Yes/no; 4 domains overall; 2 measures per publication</td>
<td>Yes; (n = 59)</td>
<td>Yes</td>
<td>Yes; attention, executive, motor functions</td>
<td>Yes; attention, executive, motor functions</td>
</tr>
<tr>
<td>Meyer-Lindenberg et al. 1997</td>
<td>Treatment-resistant schizophrenia</td>
<td>Yes (4-day washout)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes; testing at day 2, then weekly for 6 wk</td>
<td>Yes; (clozapine: 150–450mg; zotepine: 150–450mg)</td>
<td>No; maze tests only</td>
<td>Yes; (n = 26)</td>
<td>No</td>
<td>Executive and fine motor</td>
<td>None</td>
</tr>
<tr>
<td>Open-label (n = 12)</td>
<td>Goldberg et al. 1993 Patients with psychotic disorders</td>
<td>Yes (conventional antipsychotic)</td>
<td>No</td>
<td>No</td>
<td>Yes; 3-24 mo (mean = 15 mo)</td>
<td>Yes; (clozapine: 9 domains; many adjunctive medications)</td>
<td>Yes; (n = 15)</td>
<td>No</td>
<td>No; (n = 26)</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>
Table 1. Characteristics of 15 studies of the effect of atypical antipsychotic medication on cognitive functions in patients with schizophrenia (Continued)

<table>
<thead>
<tr>
<th>Studies</th>
<th>Diagnosis of subjects</th>
<th>Baseline neurocognitive assessment (medication status)</th>
<th>Multiple study arms with random assignment</th>
<th>Double-blind condition</th>
<th>Adequate duration</th>
<th>Appropriate dosing (daily dose)</th>
<th>Appropriate test batteries</th>
<th>Adequate sample size</th>
<th>Assessment of neurocognitive/clinical relationships</th>
<th>Reported neurocognitive improvements after correction for multiple comparisons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hagger et al. 1993</td>
<td>Treatment-resistant schizophrenia</td>
<td>Yes (27 drug-free; 5 conventional; 4 1–3 days clozapine)</td>
<td>No</td>
<td>No</td>
<td>Yes; 6 wk</td>
<td>363 ± 211mg for 6 wk; 403 ± 208mg for 6 mo</td>
<td>Yes; 6 domains</td>
<td>Yes (n = 36)</td>
<td>Yes</td>
<td>Executive function, attention, verbal fluency, digit-symbol</td>
</tr>
<tr>
<td>Buchanan et al. 1994 (phase II)</td>
<td>Treatment-responsive schizophrenia</td>
<td>Yes (fluphenazine)</td>
<td>No</td>
<td>No</td>
<td>Yes; 1 yr</td>
<td>Yes (clozapine: 200–600mg)</td>
<td>Minimal; 3 domains</td>
<td>Yes (n = 33)</td>
<td>Yes</td>
<td>Visuospatial analysis, executive function, verbal fluency</td>
</tr>
<tr>
<td>Lee et al. 1994</td>
<td>Treatment-responsive schizophrenia</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes; 6 wk</td>
<td>Not available</td>
<td>Yes; 6 domains</td>
<td>No; conventional: (n = 23) clozapine: (n = 24)</td>
<td>Yes</td>
<td>Executive, learning/memory, verbal fluency, digit-symbol</td>
</tr>
<tr>
<td>Zahn et al. 1994</td>
<td>Schizophrenia</td>
<td>Yes (fluphenazine or placebo)</td>
<td>No</td>
<td>No</td>
<td>Yes; 6 wk each phase</td>
<td>Yes (fluphenazine: mean = 23 ± 14.8mg clozapine: mean = 444 ± 189mg)</td>
<td>No; 2 tests</td>
<td>No (n = 25)</td>
<td>No; hallucinations only</td>
<td>Attention</td>
</tr>
</tbody>
</table>
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<tr>
<th>Studies</th>
<th>Diagnosis of subjects</th>
<th>Baseline neurocognitive assessment (medication status)</th>
<th>Multiple study arms with random assignment</th>
<th>Double-blind condition</th>
<th>Adequate duration</th>
<th>Appropriate dosing (daily dose)</th>
<th>Appropriate test batteries</th>
<th>Adequate sample size</th>
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<th>Reported neurocognitive improvements after correction for multiple comparisons</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Gallhofer et al. 1996</td>
<td>Schizophrenia</td>
<td>No</td>
<td>No</td>
<td>No; 7 days</td>
<td>Yes;</td>
<td>Yes; (clozapine: 200–400mg, risperidone: 4–8mg, haloperidol: 3–15mg, fluphenazine: 6–24mg)</td>
<td>No; maze tests only</td>
<td>No</td>
<td>No</td>
<td>Executive and fine motor</td>
<td>Verbal fluency and digit symbol</td>
</tr>
<tr>
<td>Hoff et al. 1996</td>
<td>Treatment-resistant schizophrenia</td>
<td>Yes (conventional neuroleptic)</td>
<td>No</td>
<td>No</td>
<td>Yes; 12 wk</td>
<td>Yes; (baseline CPZ equivalents: 1,418 ± 809, clozapine: 425–900mg, mean = 668 ± 164)</td>
<td>Yes; 10 domains</td>
<td>No</td>
<td>Yes</td>
<td>Educational and fine motor</td>
<td>None</td>
</tr>
<tr>
<td>Stip and Lussier 1996</td>
<td>Schizophrenia</td>
<td>Yes (conventional neuroleptic)</td>
<td>No</td>
<td>No</td>
<td>Yes; 8 wk 20–30 wk</td>
<td>No (haloperidol: 1 patient-40mg risperidone: 1 patient-11mg, 2 patients-10mg)</td>
<td>Minimal; 3 domains</td>
<td>No</td>
<td>Minimal; correlations with BPRS and PANSS total scores</td>
<td>Attention</td>
<td>Attention</td>
</tr>
</tbody>
</table>
Table 1. Characteristics of 15 studies of the effect of atypical antipsychotic medication on cognitive functions in patients with schizophrenia (Continued)

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<th>Studies</th>
<th>Diagnosis of subjects</th>
<th>Baseline neurocognitive assessment (medication status)</th>
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<th>Reported neurocognitive improvements after correction for multiple comparisons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Galletly et al. 1997</td>
<td>Schizophrenia</td>
<td>Yes (1 medication-free; 4 risperidone; 14 conventional)</td>
<td>No</td>
<td>No</td>
<td>Yes; 6.5 ± 2.0 mo</td>
<td>Yes; clozapine: mean = 393 ± 182mg</td>
<td>Yes; 7 domains</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Fujii et al. 1997</td>
<td>Treatment-resistant schizophrenia</td>
<td>Yes (conventional neuroleptics)</td>
<td>No</td>
<td>No</td>
<td>Yes; 12–16 mo</td>
<td>Yes; (250–900mg clozapine; mean = 643)</td>
<td>Yes; 7 domains</td>
<td>No</td>
<td>Yes</td>
<td>No; Total IQ: Abstraction, digit-symbol, intelligence (estimated total, verbal, and performance IQ)</td>
</tr>
<tr>
<td>Rossi et al. 1997</td>
<td>Schizophrenia</td>
<td>Yes (1 wk placebo)</td>
<td>No</td>
<td>No</td>
<td>Yes; 4 wk</td>
<td>Yes; (risperidone: mean = 2mg)</td>
<td>No; 3 tests</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Serper and Chou 1997</td>
<td>Schizophrenia</td>
<td>Yes (medication-free; time period unknown)</td>
<td>No</td>
<td>No</td>
<td>Yes; 4 wk</td>
<td>Yes; (CPZ-equivalents: 827 ± 528mg, ziprasidone: n/a, aripiprazole: n/a)</td>
<td>No; 3 measures</td>
<td>No</td>
<td>Attention</td>
<td>None</td>
</tr>
</tbody>
</table>

Note.—BPRS = Brief Psychiatric Rating Scale; PANSS = Positive and Negative Syndrome Scale.
Table 2. Standards for assessment of cognitive change in schizophrenia treatment studies

1. Pharmacological status at baseline assessment
   - Medication-free in first-episode patients
   - Conventional antipsychotic in other patients
   - Allow chronically administered adjunctive medications
   - Discontinue acutely administered or sporadically administered medications before assessment
   - Stable treatment before study entry
2. Multiple study arms with random assignment
3. Double-blind conditions
4. Adequate duration of trial
   - Short- and long-term assessments
5. Clinically appropriate dosing strategies
6. Appropriate neurocognitive test batteries
   A. Measures
      - Correlate with functional outcome
      - Improve with conventional antipsychotics
      - Sensitive to potential adjunctive treatment
      - Assess functional outcome
   B. Properties
      - Available normative data
      - Test-retest reliability
      - Absence of ceiling or floor effects
      - Brief presentation
      - Tailored to patient population being studied
   C. Number
      - Minimum number that can assess all relevant cognitive functions
7. Adequate sample size
   - Minimum number to detect meaningful clinical change
   - Identification of groups with various levels of treatment response
8. Discrimination between cognitive improvement and other clinical changes
   - Negative symptoms
   - Positive symptoms
   - Medication side effects

domains of symptomatology to assess the relationship between baseline psychopathology and cognitive improvement.

Multiple study arms with random assignment. The best design for clinical trials involves multiple treatment arms to which patients are randomly assigned. Using this design, an atypical antipsychotic can be compared with another atypical antipsychotic, a conventional antipsychotic medication, or both, and investigators will be able to identify specific treatment effects independent of other confounding factors such as improvement in cognitive task performance due to practice or novelty effects. This method was utilized in 4 of the 15 studies we reviewed.

Double-blind condition. While open-label studies are common for initial investigations of a medication, most clinical trials use a double-blind study methodology. Assessments that require subjective evaluations, such as symptom ratings, clearly demand double-blind methods, as this prevents subjective measures from being contaminated by the knowledge of the patient's medication status (Rosenheck et al. 1997). However, even objective measures such as cognitive tests are susceptible to these biases. Every effort should be made to safeguard cognitive data from these biases by using double-blind methodology. This method was used in 3 of the 15 studies we reviewed.

Adequate duration of trial. Since psychotic and negative symptom response may extend for months after the initiation of atypical antipsychotic treatment in some studies (Lieberman et al. 1994; Wilson 1996) but not others (Conley et al. 1997), it is certainly possible that cognitive functions may also continue to improve over this time frame. Therefore, studies designed to assess the long-term impact of atypical antipsychotics on cognitive functions are preferable. Furthermore, complex cognitive functions (e.g., executive functions) that depend on several areas of adequate cognitive skill may take longer to improve.

While the long-term evaluation of cognitive improvement is important, very early cognitive changes with atypical antipsychotics may be even more interesting. The effects on cognitive functions of compounds such as methylphenidate are immediate (Bilder et al. 1992). The immediacy of this improvement suggests that these cognitive changes are probably not solely attributable to other clinical changes, such as improvement in negative symptoms. As has been reported on a limited basis with conventional antipsychotics (Serper et al. 1994), early improvement in cognitive functions with atypical antipsychotics may herald future clinical changes. Of the 15 studies we reviewed, 10 investigated the short-term (4-12 weeks) effects of treatment, and 7 studied the long-term (> 20 weeks) effects. Three studies assessed both short-term and long-term effects, and one study assessed patients after only 7 days of treatment.

Clinically appropriate dosing strategies. The comparison of two medications, one of which is appropriately dosed and one of which is inappropriately dosed, could provide an unfair and potentially misleading comparison. Of the 15 studies we reviewed, 12 used appropriate dosing strategies. For example, the inclusion in a clinical trial of patients taking 40 mg per day of haloperidol confers a great advantage to the comparator medication,
since patients taking this much haloperidol are likely to have great difficulty performing any task with a motor component. Likewise, although the initial labeling dose for risperidone was 6 to 16 mg, subsequent studies determined that patients often developed extrapyramidal symptoms (EPS) at the higher end of this dose range, with doses of 2–8 mg now used for most patients with schizophrenia. Studies of cognitive improvement with atypical antipsychotics need to utilize the most recent information on appropriate dose ranges. The current suggested dose ranges for available atypical antipsychotics are presented in table 3.

Appropriate content, properties, and number of neurocognitive measures. To be considered appropriate, a neurocognitive battery must (1) include measures among the many that are impaired in patients with schizophrenia, (2) have statistical and distributional properties that allow improvement with treatment, and (3) have a number of measures that are neither so small that important findings will be easily missed, nor so large that statistical power will be wasted on unimportant measures. Using these criteria, we determined that 7 of the 15 studies included neurocognitive batteries that were appropriate, while 3 additional studies used measures that were acceptable, yet limited in scope. The following are expanded descriptions of the three criteria:

1. Content. Various theoretical considerations, too numerous to detail here, can determine the content of the battery of tests chosen. Measures that predict functional outcome, such as card-sorting, vigilance, and memory (Green 1996), may be particularly relevant clinically. Other potential measures include those that are known to be improved by conventional antipsychotics or worsened by adjunctive treatments.

2. Properties. Tests used in a trial of atypical antipsychotic medications should have the following statistical and distributional properties: available normative data; test-retest reliability; absence of ceiling or floor effects; and brief presentation. These properties will ensure that improvement (or absence of improvement) in patients’ performance is attributable to the actual change (or absence of change) in cognitive status. Tests with ceiling effects are particularly problematic. Patients who perform as well as possible on a test that is too easy will have no room to improve. Thus the medication under investigation will have no opportunity to enhance the cognitive function being measured.

3. Number of Measures. Finally, the number of outcome measures can vary widely. Some studies focus on specific constructs, whereas others attempt to assess the overall pattern of possible improvements among several constructs. We prefer a battery broad enough that the impact of an atypical antipsychotic can be determined on a range of cognitive functions. However, the battery should also be short enough that patients with psychoses can complete the battery without decrements in energy and motivation. This is especially relevant when the battery is administered in a fixed order. Our experience suggests that the primary factor that determines successful completion of a battery is rater expectation, so it is best to ensure that testers feel that they can expect to complete it.

Appropriate sample size. In studies of the effect of atypical antipsychotics on cognition, the acceptance of the null hypothesis (i.e., the drug has no effect) is as important as the acceptance of the alternative hypothesis (i.e., the drug does have an effect). Therefore, it is crucial that these studies have adequate power to reject a false null hypothesis. Otherwise, readers will be led to believe that the drug has no effect when, in fact, the drug has not been given an adequate opportunity to have an effect. Since statistical power is dependent on the size of the sample being studied, along with the effect size, the appropriateness of a sample size can be determined quite easily with the use of a power analysis. The statistical power available in a study (i.e., the likelihood of rejecting a false null hypothesis, conventionally equaling 0.80) is a function of sample size, estimated effect size, and the criterion for statistical significance (usually 0.05). If we hypothesize that atypical antipsychotics produce an effect on cognitive functions that would be considered a “medium” effect size (approximately 0.5 standard deviation [SD] equivalents) (Cohen 1977), and we desire statistical power equaling 0.80, we would require 64 subjects for each medication group. None of the 15 studies were found to have adequate statistical power to test the hypothesis. Thus, adequate samples in these studies may have generated different conclusions. Even when we apply a less conservative criterion of being able to detect a “large” effect size (0.8 SD equivalent difference between groups), which requires 26 subjects per group, only 5 of the 15 studies generate adequate statistical power.

Although larger sample sizes are usually desirable, collecting data on a large number of patients merely to

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**Table 3. Suggested doses for atypical antipsychotic medications**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Daily usual adult dose (range, mg)</th>
<th>Estimated equivalency to haloperidol (dose, mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olanzapine</td>
<td>5–20</td>
<td>10–15</td>
</tr>
<tr>
<td>Risperidone</td>
<td>1–12</td>
<td>2–4</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>150–800</td>
<td>300–600</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>40–160</td>
<td>80–120</td>
</tr>
</tbody>
</table>
detect a significant difference between medications is often not justifiable. If the sample size required to do this is very large, it is likely that the medication of interest is only marginally better than the standard medication, calling into question the clinical relevance of the difference between medications. However, there are other good reasons for using large sample sizes. First, the sample should be large enough that the entire pattern of effects on neurocognitive measures, including measures that do and do not improve, is clinically meaningful. Second, patients may demonstrate responses to the new medication that range from normalization, whereby their performance is within one SD of the normal mean, to performance that is actually worsened. Thus, the sample should be large enough that patients can be stratified according to whether they are normalized, improved but not normalized, minimally improved, not improved, or worsened. Finally, very large sample sizes allow a determination of the relationship between cognitive improvement and measures of functional outcome.

**Discrimination between cognitive enhancement and generalized clinical change.** Cognitive impairment is not completely independent of other aspects of the clinical picture in patients with schizophrenia. Cognitive deficits are associated with negative symptoms of the illness (Addington et al. 1991; Davidson et al. 1995), movement disorders (Sorokin et al. 1988; Spohn et al. 1988), and medication side effects (Walker and Green 1982; Earle-Boyer et al. 1991). In addition, patients with very severe positive or disorganization symptoms may prove to be very difficult to test with a comprehensive assessment battery. Therefore the extent to which cognitive change overlaps with changes in other symptom and side effect domains should be evaluated in each study. The Committee for Proprietary Medicinal Products (CPMP) in Europe requires this type of analysis before antipsychotics can be labeled for specific effects (CPMP 1996).

A minimum strategy would be to assess positive, negative, and disorganized symptoms, as well as side effects and movement disorders, each time the cognitive battery is administered. Changes in scores for cognitive measures can then be examined to determine the extent to which they are explained by changes in other aspects of the illness. Although this specific statistical approach is rare, some aspect of the relationship between cognitive change and clinical symptoms was evaluated in 9 of the 15 studies.

**Meta-analysis and Review of Study Results**

**Selection of Studies.** Results of the 15 studies listed in table 1 were included in the meta-analysis. The analysis was not restricted to studies investigating a particular atypical antipsychotic medication. We divided the studies into those that used double-blind methodology and those that did not. Three of the studies were randomized and double-blind, and 12 were open-label studies. In one study (Serper and Chou 1997), the patients on atypical antipsychotics and a portion of the patients on haloperidol were assessed under double-blind conditions; however, several of the patients on haloperidol were not. One of the open-label studies (Lee et al. 1994) used multiple study arms with random assignment. The number of studies examining the various atypical antipsychotics are as follows: clozapine, 10; risperidone, 4; zotepine, 1; ziprasidone, 1; and aripiprazole, 1. Published data from studies of olanzapine and quetiapine were not yet available.

**Data Reduction.** As reviewed above, the 15 studies utilized a wide range of test measures. Some studies examined only a few neurocognitive measures, while others conducted a more comprehensive neuropsychological assessment. The number of different neurocognitive tests included in each of the double-blind and open-label studies ranged from 1 to 13.

Because of the variability in the type and number of measures used to assess neurocognitive effects, test results were grouped into the following categories: (1) attention subprocesses, (2) executive function, (3) working memory, (4) learning and memory, (5) visuospatial analysis, (6) verbal fluency, (7) digit-symbol substitution, and (8) fine motor function.

**Examination of Study Results.** Each study was examined to determine (1) improvement in the performance of a single test after treatment with atypical antipsychotic medication when compared with conventional antipsychotic treatment (atypical vs. conventional) or (2) a significant positive change in performance after treatment with atypical antipsychotic medication relative to baseline (atypical treatment only). Our definition of improvement was conservative. We corrected for multiple comparisons in each study using an experimentwise p value of < 0.05, even if this statistical procedure was not completed by the study’s authors. For instance, if 10 measures were reported in a study, we assigned a significance criterion of 0.05/10 = 0.005 for each measure.

Table 4 shows the number of studies that assessed each neurocognitive domain and the number that demonstrated significant improvements overall and in each of the cognitive domains.

After we corrected for multiple comparisons, two of the three randomized, double-blind studies demonstrated significant neurocognitive improvement on at least one test measure following treatment with atypical antipsy-
Table 4. Meta-analysis results by study type and neurocognitive domain

<table>
<thead>
<tr>
<th>Neurocognitive Domains</th>
<th>Total studies, n</th>
<th>Studies reporting clinical improvement, n</th>
<th>Studies demonstrating improvement after correction for multiple comparisons, n</th>
<th>Meta-analysis, $\chi^2$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized, Double-Blind Studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any Neurocognitive Domain</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>14.82</td>
<td>0.022</td>
</tr>
<tr>
<td>Attention Subprocesses</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>10.23</td>
<td>0.006</td>
</tr>
<tr>
<td>Executive Function</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>16.93</td>
<td>0.009</td>
</tr>
<tr>
<td>Learning and Memory</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>4.50</td>
<td>0.343</td>
</tr>
<tr>
<td>Visuospatial Analysis</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>7.46</td>
<td>0.024</td>
</tr>
<tr>
<td>Verbal Fluency</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>5.18</td>
<td>0.075</td>
</tr>
<tr>
<td>Open-Label Studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any Neurocognitive Domain</td>
<td>12</td>
<td>11</td>
<td>7</td>
<td>47.59</td>
<td>0.002</td>
</tr>
<tr>
<td>Attention Subprocesses</td>
<td>5</td>
<td>3</td>
<td>1</td>
<td>15.93</td>
<td>0.101</td>
</tr>
<tr>
<td>Executive Function</td>
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<td>6</td>
<td>2</td>
<td>36.06</td>
<td>0.006</td>
</tr>
<tr>
<td>Learning and Memory</td>
<td>7</td>
<td>3</td>
<td>0</td>
<td>21.24</td>
<td>0.095</td>
</tr>
<tr>
<td>Working Memory</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>14.50</td>
<td>0.024</td>
</tr>
<tr>
<td>Visuospatial Analysis</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>17.45</td>
<td>0.026</td>
</tr>
<tr>
<td>Verbal Fluency</td>
<td>5</td>
<td>5</td>
<td>3</td>
<td>35.73</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Digit-Symbol Substitution</td>
<td>7</td>
<td>6</td>
<td>3</td>
<td>70.83</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fine Motor Function</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>17.60</td>
<td>0.007</td>
</tr>
<tr>
<td>Intelligence/IQ</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>16.50</td>
<td>0.035</td>
</tr>
</tbody>
</table>

chotic medication compared with conventional antipsy-
chotics. Seven of the 12 open-label studies demonstrated
improvement following treatment with atypical anti-
psychotics. Overall, 9 of 15 studies demonstrated
improvement.

Meta-analysis

Meta-analytic procedures were used in the statistical
analysis of the study results. Fisher's method (Rosenthal
1978) of combining probabilities ($p$ values) from two or
more independent studies was employed. This method for
combining and comparing research results from studies
yielding multiple effect sizes based on multiple dependent
variables has been reviewed by Rosenthal (1978) and
Rosenthal and Rubin (1986). Fisher's method for combin-
ing $p$ values provides a summary of the statistical signifi-
cance of the results and a test of the null hypothesis that
there is no difference between the effect of atypical
antipsychotics and conventional antipsychotics. The fact
that unpublished findings are not included in this analysis
is particularly relevant since studies showing improve-
ments with medications are more likely to be published
than those that demonstrate no improvements.

Two meta-analyses were conducted to address the
question of whether atypical antipsychotics improved
neurocognitive performance in general. The first analysis
combined the results from the three double-blind studies.
The second analysis combined the results of the 12 open-
label studies. When a given study included multiple test
measures, the average $p$ value for that study was used in
the statistical procedure. If multiple test measures were
included in a single domain of cognitive functioning, the
average $p$ value for that domain was used in the statistical
procedure. When $p$ values were not available, we calcu-
lated them using the published means and SDs. In one
case, we contacted the authors to obtain unpublished
means and SDs.

The meta-analysis of the three double-blind studies
indicated that atypical antipsychotics were significantly
more effective than conventional antipsychotics at
improving cognitive functioning ($\chi^2 = 14.82, p = 0.022$)
(see table 4). Meta-analysis of the 12 open-label studies
supported the results of the double-blind studies. In these
studies, atypical antipsychotics also improved neurocog-
nitive functions ($\chi^2 = 47.59, p = 0.002$). Meta-analytic
procedures that included all 15 studies also supported the
effect of atypical antipsychotics on cognition ($\chi^2 = 62.41,$
$p = 0.0004$).

The effect of novel antipsychotic medication on spe-
cific domains of cognitive function was also examined via
meta-analysis by combining all studies that reported data
for each domain. Corrections for multiple comparisons were not made in these meta-analyses, since this would have required setting a variable $p$ value for each domain. As in the meta-analyses of the general effect of atypical antipsychotics on cognition, Fisher’s method for combining $p$ values was used. In the double-blind studies, these meta-analyses indicated that atypical antipsychotics produce significant improvement in attention, executive functions, and visuospatial analysis (see table 4). In the open-label studies, improvements in executive function, working memory, visuospatial analysis, verbal fluency, digit-symbol substitution, and fine motor functions were indicated (see table 4).

Conclusions from the Meta-analysis and Review of Studies. Despite a conservative statistical approach, correcting the results of each study for the number of statistical comparisons made, the meta-analysis conducted in this study suggests that atypical antipsychotics, when compared with conventional antipsychotics, improve cognitive functions in patients with schizophrenia. Verbal fluency, digit-symbol substitution, fine motor functions, and executive functions were the strongest responders to novel antipsychotics. Attention subprocesses were also responsive; learning and memory functions were the least responsive.

The pattern of responsiveness of these functions suggests that measures with a timed component may be particularly responsive to novel antipsychotics. This pattern may be a result of the absence of EPS from atypical antipsychotic medications compared with conventional antipsychotics. Since timed tests all involve some degree of dependence on motor skills, which are impaired by EPS, the results could partially be a result of the reduced EPS with atypical antipsychotics. Furthermore, the advantage of atypical antipsychotics may also be related to the absence of practice-related improvements in patients taking conventional antipsychotics. Thus, while conventional antipsychotics do not have severely deleterious direct effects on cognition, they may be inferior to atypical antipsychotics in that they impair motor skills and prevent adequate learning effects.

Because of the limited number of studies included in the analysis (and because only three studies employed double-blind methodology), it is difficult to determine conclusively the pattern of specific cognitive improvements that can be expected with any specific atypical antipsychotic treatment. However, there is preliminary support for the notions that motor skills and verbal fluency are improved with clozapine and that risperidone may improve attention and executive functions. As reviewed in Meltzer and McGurk (1999), preliminary unpublished data suggest that olanzapine may also have beneficial cognitive effects.

Although the meta-analytic techniques employed in the current study indicate that overall cognitive improvement with atypical antipsychotics is robust, it should be noted that in no study did the cognitive functions of patients with schizophrenia reach normal levels. Thus, plenty of room remains for additional improvement in the cognitive functions of these patients.

None of the 15 studies that we reviewed met all of the recently developed standards for the assessment of cognitive change in schizophrenia. Most important, only 3 of the 15 studies used double-blind methodology. The strong impact of the various rater biases inherent in open-label studies of patients with schizophrenia, underscored recently in the Department of Veterans Affairs collaborative study of clozapine (Rosenheck et al. 1997), should lead us to temper our enthusiasm for the results of the open-label studies reviewed here. However, these studies have served an important function by lending initial support for the relatively recent notion that cognitive impairment can be improved in patients with schizophrenia. As a result of these initial studies, several large-scale comprehensive investigations of the effect of atypical antipsychotics on cognitive impairment in schizophrenia are underway.

Over the next few years, the results of large-scale clinical trials will begin to refine our understanding of the extent to which specific cognitive deficits in schizophrenia can be improved by the drugs currently available. In the meantime, however, data from studies of the pharmacology of cognitive function in animals and normal humans can help establish the directions for the next generation of cognition-enhancing medications for patients with schizophrenia. It is likely that these directions will be based in part on our understanding of the neurotransmitter mechanisms by which currently available antipsychotics have their enhancing effect. In the next section, therefore, we shall review the ways in which these compounds are believed to interact with various neurotransmitter systems to affect cognitive functions.

Pharmacological Basis of Antipsychotic Drug Effects on Neurocognition

Although all antipsychotic medications currently available share the pharmacological property of antagonizing $D_2$ dopamine receptors, antipsychotic drugs vary substantially in their pharmacological profiles; each affects a variety of neuroreceptors in the central nervous system (table 5). This variation in pharmacological properties...
could have important clinical consequences, including selective effects on cognition of a specific antipsychotic drug. It is very important to note, however, that affinity constants are limited in their ability to determine receptor occupancy and even more limited in their ability to predict the effects of a medication on humans. While the use of these in vitro methods is currently standard, other techniques such as positron emission tomography (PET), which may be more accurate measures of receptor occupancy in vivo, may soon replace in vitro techniques.

The neurotransmitter systems affected by antipsychotic medications include cholinergic, adrenergic, serotonergic, and dopaminergic types. Multiple receptor subtypes have been identified for most of these neurotransmitters (Cooper et al. 1996; Riedel et al. 1996). Five muscarinic cholinergic (M₁–M₅) four alpha-adrenergic (α₁, α₂A, α₂B, α₂C), and five dopaminergic (D₁–D₄) receptor subtypes have been characterized to date. Seven main classes of serotonergic receptors have been identified (5-HT₁A–5-HT₁D), some with distinct subtypes (5-HT₁A₁A/V, 5-HT₁B₁E/I, 5-HT₁C₂), (5-HT₁A₂B₂C₂, 5-HT₁A₅B₅).

It is likely that only some of the neurotransmitter systems whose functions are mediated by these receptor subtypes are involved in cognitive functions. Thus, the variation in receptor affinities provides a potential mechanism for selectivity of therapeutic drug activity generally, and specifically in relation to cognitive function. At present, however, the relationship between receptor subtype and cognitive function is poorly understood. We have attempted to examine the pharmacology of the antipsychotic drugs in terms of their putative effects on cognitive function. While not comprehensive, this review highlights important issues in understanding relationships between cognition and drug activity at specific neuroreceptors.

The effect on neurotransmission of compounds such as atypical antipsychotics is most likely highly complex. A frequent assumption is that a medication with an affinity for a receptor will manifest specific effects. For example, olanzapine might be expected to produce memory impairment due to its high affinity for M₁ receptors, yet this expectation has not been met. The actual clinical effect of a drug is difficult to extrapolate from its cumulative impact on individual neurotransmitter systems. As we will review below, the interaction among neurotransmitter systems appears to carry the lion’s share of the variance in determining the effects of these medications on cognition.

### Muscarinic Cholinergic Receptors

Drugs that antagonize muscarinic cholinergic receptors (e.g., atropine-like drugs) have been consistently shown to impair learning and memory in studies of humans and other animals (see Levin 1988a; Holttum and Gershon 1992 for reviews). This impairment is related to a deficit in encoding new information; retrieval is not affected. For example, healthy humans showed impaired ability to recall word lists when given scopolamine (a nonselective cholinergic antagonist) before learning the lists, but no impaired ability to recall lists learned prior to scopolamine exposure (Ghoneim and Mewaldt 1977; Mewaldt and Ghoneim 1979). Similar decreased performance in tests of verbal memory has been found in healthy humans administered other anticholinergic drugs (e.g., McEvoy et al. 1987; Gelenberg et al. 1989; Vitiello et al. 1997). Similar findings have been reported in studies of rodents and primates. For example, scopolamine administration disrupts associate learning in rabbits (Harvey et al. 1983), episodic visual memory in monkeys (Aigner et al. 1991) and rats (Wishaw 1989), and working memory in rats (McGurk et al. 1988). However, the long-term effects of anticholinergic drugs may be the most relevant issue for the treatment of patients with schizophrenia, and there is evidence from rat studies that the long-term effects of anticholinergic drugs on memory may diminish over time (Rosic et al. 1980; Abdulla et al. 1993).

Drugs with anticholinergic properties may have clinically important effects on learning and memory in patients with schizophrenia. Co-administration of anticholinergic drugs to antipsychotic-treated patients with

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**Table 5. Affinity constants (Kᵢ, nM) for atypical antipsychotics**

<table>
<thead>
<tr>
<th></th>
<th>D₂</th>
<th>D₁</th>
<th>D₄</th>
<th>M₁</th>
<th>M₄₁</th>
<th>H₁</th>
<th>α₁</th>
<th>α₂</th>
<th>5HT₁A</th>
<th>5HT₂A</th>
<th>5HT₃A</th>
<th>5HT₃B</th>
<th>5HT₃C</th>
<th>5HT₃D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>125</td>
<td>85</td>
<td>9²</td>
<td>2</td>
<td>18</td>
<td>6</td>
<td>7</td>
<td>7</td>
<td>770</td>
<td>12</td>
<td>8</td>
<td>69</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haloperidol</td>
<td>1</td>
<td>25</td>
<td>5²</td>
<td>1475</td>
<td>3</td>
<td>3630</td>
<td>46</td>
<td>360</td>
<td>7879</td>
<td>78</td>
<td>3085</td>
<td>&gt;1000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td>11</td>
<td>31</td>
<td>27</td>
<td>2</td>
<td>13</td>
<td>7</td>
<td>19</td>
<td>230</td>
<td>&gt;1000</td>
<td>4</td>
<td>11</td>
<td>57</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quetiapine</td>
<td>160</td>
<td>455</td>
<td>4</td>
<td>120</td>
<td>660</td>
<td>11</td>
<td>7</td>
<td>87</td>
<td>2450</td>
<td>220</td>
<td>615</td>
<td>170</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risperidone</td>
<td>3</td>
<td>75</td>
<td>7</td>
<td>3</td>
<td>3</td>
<td>155</td>
<td>2</td>
<td>3</td>
<td>490</td>
<td>.6</td>
<td>26</td>
<td>3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Note.**—Lower affinity constant indicates tighter binding to the receptor, and thus greater affinity.

¹Similar affinities were seen for M₂ and M₃ receptors.

²Indicates immeasurably low affinity.

³Quetiapine has no affinity for the D₄ receptor.
schizophrenia has been found to be associated with decreased performance on tests of short-term memory in most (Tune et al. 1982; Baker et al. 1983; Calev 1983; Perlick et al. 1986; Fayen et al. 1988; Gelenberg et al. 1989; Strauss et al. 1990; Sweeney et al. 1991; Silver and Geraisy 1995) but not all (Tamlyn et al. 1992) studies. For example, in a placebo-controlled crossover study in stable antipsychotic-treated patients with schizophrenia, biperiden (an M₁ antagonist) treatment was associated with significant performance deficits in tests of verbal memory (Silver and Geraisy 1995). In this study, amantadine (a dopamine agonist and weak N-methyl-d-aspartate [NMDA] antagonist) had no effect on verbal memory. In schizophrenia patients treated with antipsychotic and anticholinergic (benztropine, trihexyphenidyl) medications, serum anticholinergic levels are inversely correlated with performance on tests of verbal memory (Tune et al. 1982).

Consequently, the potency of a drug’s anticholinergic effects may impair or limit its potential therapeutic effects on specific cognitive functions, including various forms of memory. For instance, some clinicians may be concerned that olanzapine and clozapine may impair memory. However, the evidence for this is weak. Although one early study (Goldberg et al. 1993) suggested that clozapine may impair memory, this finding was not supported by further studies. Nonetheless, it is interesting to note that in the studies reviewed above, atypical antipsychotics as a group do not have a strong ameliorative effect on measures of learning and memory. A possible explanation for the absence of cognitive worsening with drugs with anticholinergic properties is that, as reviewed below, the clinical impact of a drug’s anticholinergic effects on cognition is dependent on its effects at other neurotransmitter systems.

**Dopamine Receptors.** Drugs that affect dopamine receptors may also affect performance on various cognitive tasks. Acute administration of haloperidol has been shown to impair performance on tests of spatial working memory in monkeys (Sawaguchi and Goldman-Rakic 1994) and rats (Beatty and Rush 1983; Levin et al. 1987). Similarly, acute haloperidol administration to healthy humans results in impaired performance on the Wisconsin Card Sort test (Vitiello et al. 1997) and the Tower of Toronto (Peretti et al. 1997).

There is substantial evidence from animal studies that the effects of haloperidol may be related to effects on D₁ receptors. While the receptor affinity of haloperidol is highest for D₂ receptors, effects at D₁ receptors have potential clinical importance (table 5). In a series of studies with monkeys (Sawaguchi and Goldman-Rakic 1991, 1994), D₁-specific antagonists SCH 23390 and SCH 39166 locally applied to areas of the lateral prefrontal cortex induced deficits in performance on a spatial working memory task. Haloperidol had similar effects, while the selective D₂ antagonist sulpiride and the D₂/D₃ antagonist raclopride did not affect task performance (Sawaguchi and Goldman-Rakic 1994). It is interesting that the effects of the selective D₁ antagonist were dose dependent, with higher doses inducing greater performance deficits.

In vivo recording of single-cell activity in monkey prefrontal cortex during performance of a spatial working memory task provides evidence that very low doses of selective D₁ antagonists may in fact enhance working memory. Here, intracerebral administration of very low doses of the selective D₁ antagonist SCH 39166 enhanced neuronal activity in memory fields, whereas higher doses impaired neuronal activity in the same memory fields (Williams and Goldman-Rakic 1995). In these studies the partial D₁ agonist SKF 38393 selectively reversed the effects of SCH 39166, confirming that D₁ activity was involved in effects of SCH 39166 on the individual neurons. The authors conclude that there may be a range of D₁ receptor activity that optimizes the ability to perform tasks of spatial working memory. Supporting this notion are the results of studies of selective D₁ receptor agonists (A77636, SKF 81297) in monkeys. These D₁ agonists enhance performance at low doses and impair or have no effect on performance at high doses (Cai and Arnsten 1997).

Drugs that selectively affect D₂ receptors may also affect working memory functions. In monkeys, quinpirole, a selective D₂ agonist, improves performance on spatial working memory tasks at moderate doses but impairs task performance at very low doses (Arnsten et al. 1995). The authors speculate that impairments at low doses are due to effects at presynaptic D₂ autoreceptors, and the enhancements at higher doses are due to effects at postsynaptic D₂ receptors. This hypothesis is supported by the findings that low doses of raclopride, a D₂-specific antagonist, reversed quinpirole-induced deficits in performance, whereas SCH 23390 (a selective D₁ antagonist) had no effect. High doses of raclopride were needed to block enhanced performance occurring with high-dose quinpirole administration. Interestingly, high doses of SCH 23390 did reverse quinpirole-related improvements in task performance, suggesting that both D₁ and D₂ receptors potentially influence performance. One study in healthy humans similarly found that administration of the D₂ receptor agonist bromocriptine improved performance on a spatial working memory task (Luciana et al. 1992). These findings suggest that there may be a specific range of dopamine activity for optimal cognitive function. Furthermore, factors such as normal aging and individual variation affect baseline activity in the dopamine system. The impact of dopamine agonists and antagonists may
vary based on this baseline activity level (Goldman-Rakic and Selemon 1997).

As previously discussed, chronic treatment with conventional antipsychotics, all potent dopamine receptor antagonists, is generally thought to have little beneficial impact on cognitive functions (Medalia et al. 1988; Cassens et al. 1990). Patients with schizophrenia treated chronically with conventional antipsychotics have slowed performance on tests of motor function (Earle-Boyer et al. 1990; Sweeney et al. 1991) and impaired performance on tests of working memory and executive function (Gilbertson and van Kammen 1997). Performance on tests with distraction components may be improved (Marder et al. 1984; Harvey and Pedley 1989; Serper et al. 1994). It is important to note that most of the studies of the impact of conventional antipsychotics on cognition have involved doses that would now be considered too high. Very few studies have explored the impact of low-dose conventional treatment (e.g., 2–5 mg/day haloperidol) on cognitive deficits.

While the most relevant data come from human studies, a few studies in animals have examined chronic administration of D₂ antagonists. In rats, chronic haloperidol administration is associated with decreased speed of response (Levin et al. 1987). In one study, chronic treatment with fluphenazine decanoate (a nonselective D₂/D₁ antagonist) did not impair monkeys’ ability to learn a spatial memory task, but did impair their ability to modify their behavior based on contingencies (Levin and Gunne 1989). As discussed above, it is possible that schizophrenia patients treated with conventional antipsychotics may be impaired in their ability to learn the tasks that are repeatedly administered to them, while novel antipsychotics enable them to benefit from normal “practice effects” due to the reduced dopaminergic blockade associated with this class of medications.

**Cholinergic and Dopaminergic Interactions.** Administering a combination of drugs with high affinity for cholinergic and dopamine receptors may affect cognition differently than administration of either drug alone. In rats, the administration of either haloperidol (a D₂/D₁ antagonist) or SCH 23390 (a D₁ selective antagonist) with scopolamine eliminates the expected scopolamine-induced deficits in spatial working memory (choice accuracy in a radial-arm maze task) (Levin 1988b; McGurk et al. 1988). Raclopride, however, does not eliminate these scopolamine-induced deficits. These findings suggest that D₁ receptor blockade may be mediating the effects of the dopamine antagonist on scopolamine-induced impairments. It is of interest that SKF 38393 (a selective D₁ agonist), but not quinpirole, also prevents scopolamine-induced impairments in radial-arm maze tests in rats (Levin and Rose 1991). As haloperidol will also impair rats’ performance on radial-arm maze tests (Beatty and Rush 1983), these findings suggest that there may be an optimal balance of cholinergic-dopaminergic systems needed to perform tasks of spatial working memory, and that drugs that disrupt this balance may impair performance. Similar results were also found in healthy humans, where acute administration of haloperidol with scopolamine reversed scopolamine-related impairments in learning and memory (Vitiello et al. 1997). Thus, the potential anticholinergic effects of drugs like olanzapine and clozapine may be mitigated by their effects at dopamine receptors.

**Serotonin Receptors.** Some investigators (e.g., Green et al. 1997) have speculated that the cognitive improvement seen with the atypical antipsychotic risperidone may be the result of effects at serotonin receptors. Drugs that bind to serotonin receptors may facilitate or impair certain cognitive functions, depending on the location and subtype of the affected receptors (reviewed by Buhot 1997; Meneses and Hong 1997). For example, systemic administration of the selective 5-HT₁A agonist 8-OH-DPAT impairs spatial learning and retention in rats, as assessed by performance on water mazes (Carli et al. 1995; Kant et al. 1996) and a test of working memory (delayed non-matching-to-position) (Warburton et al. 1997). 8-OH-DPAT also impairs working memory in rats when directly infused into the dorsal hippocampus (Warburton et al. 1997). In contrast, direct infusion into the medial raphe nucleus results in working memory improvement. WAY-100635 (a 5-HT₁A antagonist) reversed the effects of 8-OH-DPAT on performance of the delayed non-matching-to-position test, but did not affect test performance independently (Fletcher et al. 1996). Thus, pre- and postsynaptic 5-HT₁A receptor stimulation may have differential effects on learning and memory in rats, with postsynaptic stimulation generally impairing and presynaptic stimulation enhancing test performance (Buhot 1997; Meneses and Hong 1997; Warburton et al. 1997). Effects may also depend on the specific brain region affected by the 5-HT₁A agonist (Warburton et al. 1997).

Other serotonin receptor subtypes may also be important to cognitive functioning. For example, the 5-HT₃ receptor antagonist ondansetron has been shown to enhance learning and memory in primates and rats (Barnes et al. 1990). In contrast, the 5-HT₁B receptor agonist CP 93129 impairs spatial reference memory in rats (Buhot et al. 1995).

Unlike conventional antipsychotics, many atypical antipsychotics have high 5-HT₂A/C receptor affinity. 5-HT₂A/C agonists (e.g., d,l-methylenedioxymethamphetamine, d,l-methyldioxymethamphetamine) consistently
enhance performance on associative learning tasks in animal studies (Harvey 1996; Buhot 1997). In contrast, 5-HT$_{2A/2C}$ receptor antagonists may impair (ritanserin, MDL-11939, pizotifen, cyproheptadine) or have no effect (ketanserin, mianserin, d-2-bromolysergic acid diethylamide, LY-53857) on conditioned learning (Harvey 1996; Buhot 1997). In other animal models of human cognitive function, however, the 5-HT$_{2A/2C}$ antagonists ketanserin and mianserin have been shown to impair more complex types of learning. For example, chronic administration of ketanserin to rats impaired their ability to learn a complex maze (Altman and Normile 1988). In contrast, some studies have shown enhancement of learning and memory with ketanserin, a selective 5-HT$_{2A/2C}$ antagonist. For example, acute administration of ketanserin and mianserin enhanced the ability of mice to perform previously learned aversive conditioned response tasks (Altman and Normile 1986). Generally, the effect of 5-HT$_{2A/2C}$ on learning is that agonists most consistently enhance performance and antagonists impair performance (Harvey 1996; Buhot 1997). However, there are conflicting results in the existing literature, leading others to opposite conclusions (Sirvio et al. 1994; Cassel and Jeltsch 1995). These conflicting study conclusions may stem from factors such as the use of drugs that are not selective (e.g., methysergide, a 5-HT$_3$ and 5-HT$_{2A/2C}$ agonist, and ritanserin, a 5-HT$_{1C}$ and 5-HT$_{2A/2C}$ antagonist), species differences in serotonin regulation of cognition, timing of drug administration, drug dose, and other methodological differences in study design. Further research is needed to clarify the circumstances and effects of 5-HT$_{2C/2A}$ receptor activity on cognition.

Some studies have investigated the cognitive effects of serotonergic drugs in humans. In one study, acute administration of the serotonin (5-HT$_{2C, 2A, 1D}$) antagonist metergoline to healthy controls did not affect their performance on an extensive cognitive battery (Vitiello et al. 1997).

The “atypical” clinical effects of the newer antipsychotics (risperidone, olanzapine, quetiapine) are thought to be related to their shared ability to antagonize 5-HT$_{2A/2C}$ receptors. While animal studies have generally shown that 5-HT$_{2A/2C}$ antagonists impair aspects of cognitive function, the above review also demonstrates that drugs similarly classified as 5-HT$_{2A/2C}$ receptor antagonists may interact with serotonin neuroreceptors to produce beneficial cognitive consequences.

Cholinergic and Serotonergic Receptor Interactions.

Some of the effects of serotonergic drugs on cognition may be mediated through serotonin's effects on cholinergic neurons (Decker and McGaugh 1991; Cassel and Jeltsch 1995). Impairments in cognitive function induced by anticholinergic drugs are exaggerated in animals with preexisting serotonin depletion (Cassel and Jeltsch 1995). In addition, drugs that interact with 5-HT receptors alter the detrimental effects of muscarinic cholinergic antagonists on learning. For example, WAY-100135 (a selective 5-HT$_{1A}$ serotonin antagonist), when administered alone, had no effect on spatial learning in rats. However, when it was administered with scopolamine, it minimized scopolamine's detrimental effects on spatial learning in rats (Carli et al. 1995). The 5-HT$_3$ receptor antagonist ondansetron reverses scopolamine-induced cognitive impairments in rats and primates (Barnes et al. 1990; Carli et al. 1995). The 5-HT$_{2A/2C}$ receptor antagonist methysergide had no independent effect on continuous non-matching-to-sample test performance in rats, but when coadministered with scopolamine led to exaggerated impairments compared with scopolamine alone (Sakurai and Wenk 1990). In rats, methysergide coadministered with scopolamine caused more severe impairments in spatial learning than scopolamine alone (Riekkinen et al. 1992). In one study of healthy humans, however, coadministration of metergoline (a 5-HT$_{2C, 2A, 1D}$ antagonist) and scopolamine did not alter the scopolamine-induced impairments in learning, memory, and rate of information processing, and metergoline alone did not affect cognitive performances (Vitiello et al. 1997). Thus there is substantial evidence that serotonin neurons modulate function of cholinergic neurons, and that coadministration of a serotonin antagonist with a cholinergic antagonist may alter the neuronal response to the cholinergic antagonist. Moreover, when these properties are present in the same compound, the net effect of the drug on cognition can be presumed to reflect this combination. This is particularly relevant to atypical antipsychotics such as clozapine and olanzapine, both of which have high affinities for cholinergic and serotonergic neuroreceptors.

Alpha-adrenergic Receptors.

Drugs that are alpha$_2$ agonists (e.g., clonidine, guanfacine, UK-14304) have beneficial neurocognitive effects, including enhancement of performance on tests of working memory. These beneficial effects of compounds with alpha$_2$ agonist activity are greater when the working memory tasks include distraction by irrelevant stimuli (reviewed in Arnsten et al. 1996). Thus, findings from animal studies suggest that norepinephrine may play a modulating role in working memory by regulating distraction by irrelevant stimuli during task performance.

In various animal studies, alpha$_2$ agonists enhance performance tasks involving working memory (Arnsten and Goldman-Rakic 1985; Arnsten et al. 1988; Jackson and Buccafusco 1991; Arnsten and Contant 1992; Carlson et al. 1992). This is particularly true when norepinephrine
is decreased in the prefrontal cortex, either through experimental manipulations or secondary to normal aging. Deficits in spatial working memory in nonhuman primates can be corrected with administration of alpha_2_ agonists (Arnsten and Goldman-Rakic 1985; Arnsten and Contant 1992; Cai et al. 1993). One study in healthy humans similarly found that clonidine improved performance on tasks involving spatial working memory (Coull et al. 1995). In contrast, yohimbine, an alpha_2_ antagonist, has been shown to impair delayed response performance (a test of working memory) in monkeys (Arnsten and Contant 1992; Li and Mei 1994).

We were able to find one study of the effects of clonidine in patients with schizophrenia. In this study, patients demonstrated improvement on Trails B, verbal fluency, and the Stroop test following clonidine administration (Fields et al. 1988). These findings are thus consistent with animal and healthy human studies that find clonidine improves performance on tests sensitive to frontal lobe dysfunction. In addition, alpha_2_ agonists have been used with varying degrees of success in treating patients with non-Alzheimer’s dementias (Coull 1994). It is of interest that the cognitive-enhancing effects of clonidine are lost in animals with prefrontal cortical lesions. This suggests that enhancement of working memory functions requires an intact prefrontal cortex. A second implication is that drug effects may be different (in this case, eliminated) in an animal with a specific lesion. Thus, if schizophrenia involves a functional disruption of prefrontal cortical circuits, drugs that improve performance by affecting these circuits may not have a similar beneficial performance in patients with schizophrenia.

Evidence from animal studies suggests that each of the different clinical effects of alpha_2_ agonism (sedation, orthostatic hypotension, and neurocognitive effects) is attributable to the effects of activity at different receptor subtypes (Arnsten et al. 1996). Based on a series of investigations in animals, Arnsten and colleagues (1996) suggest that the cognitive effects of alpha_2_ agonists such as clonidine are mediated by postfunctional alpha_2A_ receptors, since drugs that affect alpha_2B_ and alpha_2C_ receptors do not affect performance on tests of cognition.

Many antipsychotics (e.g., risperidone, olanzapine, see table 5) act as antagonists on the alpha_2_ adrenergic receptor. The effects of various antipsychotics on the newly cloned alpha_2_ receptor A subtype have not yet been published. Results of animal studies and the few human studies available raise the possibility that drugs that are alpha_2_ antagonists may have a negative impact on working memory.

Conclusions

Atypical antipsychotic drugs, as opposed to conventional antipsychotics, improve cognitive function in patients with schizophrenia. However, the mechanisms of this improvement are far from clear. Multiple neurotransmitter systems and brain regions subserve the range of cognitive functions required in human behavior. Although much has been learned about the nature of these functions in terms of their neuropsychology and neuroanatomy, their pharmacology is only beginning to be elucidated. Consequently, in considering the pharmacology of cognitive pathology in schizophrenia, we must acknowledge that our understanding is quite limited. The rigorous and sophisticated characterization of cognitive pathology in schizophrenia has only recently begun. Moreover, even for diseases like Alzheimer’s, which have a predominant and well-defined profile of cognitive dysfunction and a known neurobiology, the available therapeutic strategies are very limited. Thus we must be cautious in estimating our capacities and expectations in schizophrenia.

The profile of pharmacological effects of antipsychotic drugs includes those that appear to impair specific cognitive functions and those that might reasonably be expected to improve aspects of cognition. For example, drugs that uniquely decrease muscarinic cholinergic, 5-HT_2A_/2C_ serotonergic, alpha_2A_ adrenergic, or D_1_/D_2_ dopamine activity, or that increase 5-HT_1A_ serotonergic activity, may worsen aspects of cognitive function. Drugs that increase muscarinic cholinergic, 5-HT_2A_/2C_ serotonergic, and alpha_2A_ adrenergic activity may improve cognitive function. Drugs that enhance D_1_ dopamine receptors below their “therapeutic window” are also candidates to improve cognition function. As demonstrated with investigations into the ways neurotransmitter systems interact when drugs affect them simultaneously (e.g., cholinergic-serotonergic or cholinergic-dopaminergic interactions), it may well be the balance between multiple systems, rather than the function of one system, that is most crucial to optimal cognitive function. Thus it is unlikely that the cognitive effects of a drug are predictable exclusively from receptor binding studies, and that they must be empirically determined in vivo. At best, the present studies may be used to generate hypotheses about the cognitive effects of drugs in humans. As we more completely identify receptor subtypes and understand their functional importance and interactions, we will better appreciate the clinical relevance of specific pharmacological profiles to cognitive function in patients with schizophrenia.
The published studies of the effects of atypical antipsychotics on cognition have focused primarily on clozapine and risperidone. Data assessing the impact of quetiapine and olanzapine on cognition have been presented in abstract form and should be available in published form in the near future. Clozapine, the prototype of the “atypical” antipsychotics, has high affinity for multiple neuroreceptors. With the exception of the M₄ subtype of the muscarinic receptors, where it acts as an agonist, clozapine antagonizes receptor function. Potential explanations for clozapine’s cognition-enhancing effects include its low-affinity antagonism of D₁, moderate-affinity antagonism of 5-HT₁₉, and high-affinity agonism of M₄ neuroreceptors. Clozapine is a 5-HT₂A/₂C antagonist. Animal studies generally indicate that antagonism at these receptors might be expected to impair cognition, although some studies find improvements in ability to learn and remember. Thus effects at 5-HT₂A/₂C remain possible but are less likely to explain clozapine’s cognition-enhancing effects. In contrast, risperidone does not affect 5-HT₃ or muscarinic cholinergic receptors. The combination of low-affinity antagonism of D₁ and high-affinity antagonism of 5-HT₂A/₂C is a possible explanation for risperidone’s cognition-enhancing effects.

The recent focus on the central role that neurocognitive impairments play in the day-to-day function of patients with schizophrenia underscores the importance of finding better treatments for these symptoms (Buchanan et al. 1994; Green 1996). While atypical antipsychotics appear to have distinct advantages, it is clear that residual cognitive impairments still remain. There are many promising yet unexplored avenues of research, including NMDA receptor agonists, selective D₁ receptor antagonists at low doses, muscarinic agonists, and adrenergic agonists, to name a few. However, the process of developing these treatments is still in the initial stages and has a long way to go.

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