Effects of antipsychotic drugs on memory and attention in schizophrenia

Junghee Lee MA and Sohee Park Ph.D.

Department of Psychology and the Center for Integrative and Cognitive Neuroscience

Vanderbilt University

111 21st Avenue South

Nashville TN 37240

615 322 3435 (phone)

615 343 8449 (fax)

Correspondence to Junghee Lee or Sohee Park

junghee.lee@vanderbilt.edu

sohee.park@vanderbilt.edu

Abstract

Neurocognitive deficits are cardinal features of schizophrenia and are important predictors of functional outcome. In this article, we focus on the effects of antipsychotic drug treatment on two key cognitive symptoms, that of attention and memory. A review
of the literature suggests that atypical antipsychotic drugs are more effective in ameliorating cognitive impairments than typical antipsychotic drugs, with each atypical antipsychotic drug having selective effects on attention and memory. In addition, we offer a brief survey of unconventional and novel treatments for neurocognitive symptoms.

Neurocognitive deficits including abnormalities of attention, memory, executive function, perception, motor functioning, and language processing are an essential feature of schizophrenia. The fundamental role of neurocognitive impairments in schizophrenia was already recognized and accurately portrayed at the turn of the 20th century. For example, based on clinical observation, Kraepelin described a broad range of impairments including deficits in “mental efficiency”, “train of thought”, and “association experiments”, functions that appear to be analogous to modern conceptualizations of attention, working memory, and executive functions, respectively. However, despite these early insights and the pervasive presence of neurocognitive deficit in schizophrenia, cognitive abnormalities tended to be overshadowed by more conspicuously psychotic clinical symptoms such as hallucinations and delusions.

More recently there has been a revival of interest in understanding cognitive aspects of schizophrenic symptoms because accumulating evidence indicate that they are at the core of the disorder. First of all, studies of neurocognitive deficits in schizophrenia, their relatives, and individuals at high risk for schizophrenia suggest that neurocognitive deficit may be a vulnerability factor in schizophrenia and may be a biobehavioral marker. Neurocognitive deficits in schizophrenia appear to be present at the onset of psychosis.
or even during premorbid phase⁴ and they are found in relatives of patients with schizophrenia or individuals at high-risk for schizophrenia⁵,⁶. Secondly, alleviating neuropsychiatric symptoms may hold the key to improved rehabilitation and social functioning. Neuropsychiatric deficits have been reported to be associated with the social functioning impairments of schizophrenia patients⁵,⁶. They consistently account for significant variance in measures of social and occupational disability⁷,⁸, and this association is stable over time⁹. Indeed, functional outcome has been found to correlate more closely with the extent of neuropsychiatric deficits than with the severity of positive or negative symptoms¹¹. Improvement in neuropsychiatric deficits leads to improved skill in social problem-solving, improved psychosocial skills, improved community (social and occupational) skills, and improved quality of life⁷. Among neuropsychiatric deficits, secondary memory, immediate verbal memory, sustained attention and semantic memory are most related to functional outcome⁶. Therefore, improvement in neuropsychiatric deficits via pharmacological or nonpharmacological treatment, or a combination thereof, may be of great importance for rehabilitation of schizophrenia patients. In this paper, we will highlight two key cognitive symptoms of schizophrenia, that of memory and attention and discuss the effects of antipsychotic drug treatment.

Pharmacological treatment can be divided into two kinds: typical and atypical antipsychotic drugs¹⁰,¹³,¹⁴. Typical antipsychotics such as haloperidol predominantly block dopamine (DA) receptors of the D2 type in mesolimbic areas and improve positive symptoms such as delusions and hallucinations. But the blockade of D2 receptors in subcortical areas, specifically, the striatum is a major factor in causing extrapyramidal symptoms (EPS) as well as tardive dyskinesia. Atypical antipsychotic drugs such as
clozapine, risperidone, and olanzapine can be defined as drugs that produce minimal extrapyramidal symptoms (EPS) at doses that produce effective antipsychotic action\textsuperscript{15}. Although all antipsychotic medication currently available shares the action of antagonizing D2 dopamine receptors, antipsychotic drugs vary substantially in their pharmacological properties\textsuperscript{13,14}. Typical neuroleptics are generally effective at ameliorating positive symptoms, but there is little compelling evidence that they exert a similar benefit on negative symptoms\textsuperscript{16} or neurocognitive deficits\textsuperscript{17}. After introducing atypical antipsychotic drugs, robust cognitive improvement has been identified in both respondent and chronic, treatment-resistant schizophrenia patients\textsuperscript{18-22}.

Among the neurocognitive deficits in schizophrenia, attention and memory seem to be particularly important in the progress of the illness and outcome. Attention abnormalities, which is considered to be the one of the primary cognitive deficit in schizophrenia\textsuperscript{23,24}, are present even before the onset of the illness\textsuperscript{25} and are most closely linked to global functional impairment and poor outcome in first-episode schizophrenia\textsuperscript{26}. For example, sustained attention, or vigilance, predicts social problem-solving and the acquisition of skills\textsuperscript{27}. Memory deficits were observed even in patients with less severe generalized deficit\textsuperscript{26}. Verbal memory seems to be related to a wide range of functional outcomes\textsuperscript{27} and verbal memory\textsuperscript{11,28-29} and working memory\textsuperscript{29} are the strongest predictors of poor community outcome and impairment in skill learning. Several studies\textsuperscript{12,30} have already reviewed the effect of typical and atypical antipsychotic drugs on general neurocognitive deficits. In this article we will limit our discussion to the treatment effects of pharmacological therapy on selected areas of neurocognitive deficits, that of attention
and memory in schizophrenia. In addition, some unconventional pharmacological treatments will be reviewed.

A comprehensive survey of attention and memory would require a weighty tome and therefore is beyond the scope of this article. Below, we present a practical summary of the conceptualization of attention and memory functions as they are used in neuropsychiatric literature. Attention can be divided into the following conceptual components: sustained attention, selective attention and inhibition, and divided attention. Sustained attention involves maintaining focused attention over a prolonged period of time in order to detect infrequent signals. The Continuous Performance Task (CPT) is often used to measure sustained attention. Selective attention and inhibition refer to the ability to focus attention on relevant information while ignoring simultaneously presented irrelevant information that could interfere with the work in progress. Visual search task and Stroop task are widely used to measure selective attention and inhibition. Divided attention can be described as the capacity to divide attentional resources between several simultaneous tasks when attention is required for the performance of both (all) tasks. Dual task paradigm is commonly used to assess divided attention.

There are many ways of conceptualizing and subdividing memory and a large variety of assessment methods exist\textsuperscript{31}. Secondary memory, immediate memory span, working memory, and semantic memory are most often assessed by neuropsychologists when they study schizophrenia patients. Secondary
memory refers to the ability to acquire and store information over a longer period of time (usually lasting for several minutes or longer). For example individuals are asked to learn and recall a list of words, passages of text or complex figures. Immediate memory span refers to the ability to hold a limited amount of information for a brief period of time (usually a few seconds). Digit span forward and visual span forward can measure immediate memory span. Immediate memory is different from working memory. Working memory requires individuals to store information “on-line” for a brief period of time while manipulating that information to guide behavior. There are several ways to measure working memory, but digit or visual backward span, delayed response task in auditory, spatial or visual modality, and n-back task are most commonly used. Semantic memory refers to the storage of knowledge relating to objects, people, or words, and can be measured by word fluency task.

**Pharmacological treatment on memory and attention**

Typical antipsychotic drugs have less impact on the neurocognitive deficits and negative symptoms compared with their effect on the treatment of positive symptoms in schizophrenia. Short-term administration of typical antipsychotic drug has been reported to impair sustained attention\textsuperscript{32,33} and immediate memory span\textsuperscript{17}, but these effects decrease with chronic treatment\textsuperscript{17,32,33}. Verbal memory can be improved by typical antipsychotic drugs\textsuperscript{34,35}. Although conventional antipsychotics may improve performance on a few selective tasks in some studies, there is no conclusive evidence of improved secondary memory,
semantic memory or attention in schizophrenia by typical antipsychotics

A recent report showed that neuropsychological impairment in schizophrenia patients taking typical neuroleptics appears to remain stable, regardless of baseline characteristics and changes in clinical state. In addition, extrapyramidal (EPS) and anticholinergic side effects of typical antipsychotic drugs can have detrimental effects on cognition.

Although inconsistent at first, robust cognitive improvements on cognitive function in schizophrenia patients taking clozapine have been identified in several studies. Improvement of semantic memory owing to clozapine treatment has been consistently reported. Clozapine treatment also led to an improvement in secondary verbal memory in some studies but not in other studies. Clozapine had a positive effect on secondary visual memory but some studies found no effect, and even deterioration. Clozapine did not improve verbal working memory. A recent study, however, reported an improvement in verbal working memory after 16 weeks of clozapine treatment in treatment-resistant schizophrenia. For immediate memory, Fujii et al. found no effect of clozapine, whereas others found improvement. While clozapine has beneficial effects on some aspect of memory, it seems to have no effect on attention. Clozapine was found to have no effect on divided attention, sustained attention, and inhibitory processing in treatment-resistant schizophrenia patient. It even impaired selective attention and inhibition in one study, although Gallatley and colleagues found improvement in sustained attention with auditory modality after 6 months of clozapine treatment.
Risperidone improved working memory in verbal modality and spatial modality. Working memory is mediated by the neural circuitry that includes the prefrontal cortex. Improvement of working memory after risperidone treatment is consistent with recent finding that functional activation of the right prefrontal cortex, supplementary motor area, and posterior parietal cortex was increased during working memory task after substituting risperidone for typical antipsychotic drug. In contrast to the beneficial effects observed in working memory, the effect of risperidone on secondary verbal memory and immediate memory is not conclusive. Risperidone showed no effect or improvement on immediate memory span. Lindenmayer et al. found that schizophrenia patients taking risperidone performed worse at 12 week compared with baseline, but Kern et al. found risperidone-treated schizophrenia patients showed greater improvement in secondary verbal memory than haloperidol-treated patients. Long-term treatment of risperidone improved performance of schizophrenia patients on attention, specifically selective attention and alertness, but 8 weeks of risperidone treatment showed no effect on sustained attention. Lindenmayer et al. also found no effect of risperidone on inhibitory processing as measured by the Stroop task.

Olanzapine, similar to clozapine, is beneficial to verbal memory. After 20 weeks of olanzapine treatment, improvement in verbal memory was found in treatment-refractory schizophrenia patients. Harvey et al. also found the effect of olanzapine on verbal learning and memory. Cuesta et al. showed that olanzapine treatment improved inhibitory processing in Stroop task than risperidone or typical antipsychotic drugs, but not semantic memory and visual memory.
In the case of Quetiapine, another atypical antipsychotic drug, results of two studies are currently available. Velligan et al. \textsuperscript{61} reported improvement in semantic memory, inhibitory processing and verbal memory after 24 weeks of quetiapine treatment. Purdon and colleagues\textsuperscript{42} also showed that quetiapine had beneficial effects on semantic memory and secondary verbal memory.

Various pharmacological properties of atypical antipsychotic drugs and the resulting selective effects of specific atypical antipsychotic drugs on neurocognitive deficits could have important clinical consequences\textsuperscript{13,14}. A few studies have been conducted to assess the comparative efficacy of atypical antipsychotic drugs on neurocognitive deficits in schizophrenia\textsuperscript{20,59,62}. Purdon et al.\textsuperscript{62} found that olanzapine produced a substantial gain in immediate recall (verbal and visual domain) greater than that observed with haloperidole or risperidone. In a recent study with a 14-week, double blind design\textsuperscript{20}, treatment with risperidone resulted in great improvement over time than did treatment with either clozapine or haloperidol in verbal learning memory domain. But in the domain of selective attention, olanzapine was much more effective on reducing the interference on the Stroop task than risperidone\textsuperscript{60}. Harvey et al.\textsuperscript{59} showed that although olanzapine and risperidone improved verbal learning and memory, only risperidone showed improvement on semantic memory. A recent review and meta-analysis\textsuperscript{63} compared the effect of several atypical antipsychotic drugs with one another. In this study quetiapine and clozapine exhibited greater improvements in semantic memory than risperidone and quetiapine, and olanzapine had a larger effect on inhibitory attention than both clozapine and risperidone. For secondary verbal memory there was no difference among the atypical antipsychotic drugs.
Unconventional and novel treatments

Although the atypical antipsychotic drugs are much more effective in reducing neurocognitive symptoms, they have not enabled most schizophrenia patients to return to normal functioning levels. It might be, therefore, necessary to assess the effect of other adjunctive treatments with atypical antipsychotic drugs in schizophrenia patients. Donepezil has been used as an adjunctive treatment to risperidone, in order to increase cholinergic activity at muscarinic and nicotinic receptors but it had no effect on cognition including selective attention, sustained attention, spatial working memory, and verbal memory in schizophrenia.\textsuperscript{64} Norepinephrine plays a significant role in working memory functions in the prefrontal cortex by its action at alpha-2a noradrenergic receptors. Guanfacine, alpha-2 noradrenergic agonists, has been effective in reversing working memory deficits in non-human primate\textsuperscript{65}. But in a study by Friedman et al.\textsuperscript{66}, guanfacine adjunctive treatment to neuroleptics on memory and attention of schizophrenia showed no effect in a 4-week treatment trial.

Much more controversial and intriguing is the adjunctive treatment involving the essential fatty acids. It is based on the membrane hypothesis of schizophrenia, proposed by Horrobin et al.\textsuperscript{67}. They suggest that abnormalities of metabolism that affect omega-3 polysaturated fatty acids (PUFAs) may be the core feature of schizophrenia. Evidence for anomalous fatty acids metabolism have been obtained from the frontal cortex\textsuperscript{68} as well as in the red blood cell membrane\textsuperscript{69}. An association between dietary omega-3 PUFAs intake and severity in schizophrenia\textsuperscript{70} has also been reported. These findings
provide a rationale for treating schizophrenia patients with omega-3 PUFAs. Su et al.\textsuperscript{71} reported that a pregnant schizophrenia patient showed remarkable improvements in both positive and negative symptoms of schizophrenia after taking omega-3 fatty acids. Preliminary reports for schizophrenia patients with a short-duration of illness have indicated symptom improvement when omega-3 fatty acids were added to patient’s usual medication\textsuperscript{72,73}, but a larger trial\textsuperscript{74} found no effect of omega-3 fatty acid supplementation for psychopathological symptoms and cognitive impairments. However, the patients enrolled in Fenton et al.’s study\textsuperscript{74} tended to be older and the every day diet of the subjects could not be controlled. In order to evaluate the efficacy of the omega-3 PUFAs treatment on neurocognitive deficits and other symptoms more clinical trials are needed.

Development of schizophrenia during the reproductive period in a majority of those affected suggests that this disorder may be related to a disturbance in the reproductive hormone system\textsuperscript{75}. It has been suggested that estrogen may act as a protective factor in women: the age of onset of schizophrenia is significantly older in women than in men, with a second peak of onset larger and later in women after 40-45 years of age\textsuperscript{76,77}. Indeed, estrogen adjunctive treatment has positive impact on psychotic symptoms in female schizophrenia patients\textsuperscript{78}. In normal subjects, there is evidence that estrogen level is related to cognition through the menstrual cycle, with high levels of estrogen at the mid-luteal point being associated with better verbal memory, but not with spatial ability\textsuperscript{79,80}. A recent study\textsuperscript{81} also showed that in schizophrenia patients, higher average estrogen levels are associated with better neuropsychological performance in many areas of cognition including attention and memory. Specifically, in this study, there was no difference between patients taking oral contraceptive or those on the
estrogen –replacement therapy, suggesting that higher levels of either endogenous or exogenous estrogen were beneficial in their relationship to cognitive function. Future studies about estrogen treatment effect on neurocognitive deficits in schizophrenia are necessary.

Other adjunctive pharmacological agents such as anti-anxiety drugs or antidepressant are extensively used in the treatment of patients with schizophrenia\textsuperscript{82}, but very few studies have examined the effects of these adjunctive pharmacological agents on neurocognitive deficits in relation to the clinical symptoms of schizophrenia.

**Discussion**

In summary, the studies of pharmacological treatment on neurocognitive deficits provide strong evidence that atypical antipsychotic drugs are more effective in ameliorating neurocognitive deficits than typical antipsychotic drugs. The effects of atypical antipsychotic drugs on neurocognitive deficits in schizophrenia are not secondary to these drugs' decreased propensity to induce EPS\textsuperscript{83}. Clozapine improves secondary memory and semantic memory, but the results of the effects of clozapine on working memory and attention are not conclusive. Risperidone has relatively consistent positive effects on working memory, whereas improvement in verbal learning and memory and attention was inconsistent. Olanzapine seems to improve verbal learning and memory and semantic memory, but not working memory or attention.
Most studies of the effect of antipsychotic drugs on neurocognitive deficits have mainly focused on general, global effects and did not specify which characteristics of schizophrenia or pharmacological treatment could be related to the treatment effect. Because several methodological factors relating to study design have been discussed in detail\textsuperscript{13,22,62,84}, we will briefly mention a few factors. Several studies reported sex differences in schizophrenia patients in terms of progress of the illness and neurocognitive deficits. Some studies found that male schizophrenia patients perform worse than female patients on measures of cognitive function\textsuperscript{85,86}, and others showed opposite findings\textsuperscript{83,87,88}, or no sex differences\textsuperscript{89}. It is possible that men and women with schizophrenia may respond differently to pharmacological treatment but most studies do not examine sex differences and the results of many studies are based on male patients. Sex differences in neurocognitive deficits in schizophrenia are not consistent and need to be further examined. Other factors such as premorbid adjustment, education and handedness are associated with neurocognitive deficits\textsuperscript{90}, but most studies about treatment effect of antipsychotic drugs did not specify these factors. It is necessary to investigate how these factors could affect treatment of antipsychotic drug in schizophrenia specifically.

Neurocognitive studies can bridge the gap between neurobiological mechanism and etiology of schizophrenia. Methods used in cognitive neuroscience such as brain imaging techniques combined with meticulously designed experiments can help clarify exactly what type of memory or attention function a particular pharmacological agent is facilitating or inhibiting. Functional neuroimaging studies\textsuperscript{91} typically show different patterns of activations in the brain between schizophrenia and normal controls during
attention or memory task but we need to probe further by asking what these patterns of differences mean. We also need to know more about the individual differences in recruiting specific neural circuits during a task in response to a pharmacological agent. By combining the modern cognitive neuropsychological techniques, neuropharmacology and clinical science, future research on the treatment effects of antipsychotic drugs on specific neurocognitive function will bring better understanding of schizophrenia and hopefully, brighter outcome for the patients.

Reference


63. Woodward ND, Purdon SE. (under review) Neuropsychological change to second generation antipsychotic treatment in schizophrenia: A review and meta-analysis.


