Effects of Antipsychotic Drugs on Memory and Attention in Schizophrenia

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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, those of attention and memory. A review of the relevant literature was conducted in order to evaluate the efficacy of typical and atypical antipsychotic drugs on the cognitive impairments exhibited by schizophrenic patients. Our review suggests that atypical antipsychotic drugs more effectively ameliorate cognitive impairments than do typical antipsychotic drugs, and that each atypical antipsychotic drug exerts selective effects on attention and memory. In addition, we offer a brief survey of unconventional and novel treatments for neurocognitive symptoms.

Key words: Schizophrenia, Antipsychotic treatment, Memory, Attention.

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Introduction

Neurocognitive deficits, including abnormalities in attention, memory, executive functions, perception, motor functioning, and language processing, are essential features of schizophrenia. The fundamental role played by neurocognitive impairments in schizophrenia had already been recognized and accurately portrayed by the turn of the 20th century. For example, on the basis of clinical observations, Kraepelin described a broad range of impairments, including deficits in "mental efficiency", "train of thought", and "association experiments", functions that appear analogous to modern conceptualizations of attention, working memory, and executive functions, respectively.[1] However, despite these early insights and the pervasive presence of neurocognitive deficits in schizophrenia, cognitive abnormalities tended to be overshadowed by more conspicuously psychotic clinical symptoms, such as hallucinations and delusions.

More recently, interest in understanding the cognitive aspects of schizophrenic symptoms has been renewed, as accumulating evidence suggests that these symptoms lie at the core of the disorder. First of all, studies of neurocognitive deficits in schizophrenics, their relatives, and individuals at high risk for schizophrenia suggest that neurocognitive deficits may constitute a vulnerability factor in schizophrenia, and may also be considered biobehavioral markers. Neurocognitive deficits in schizophrenia appear to be present at the onset of psychosis[2,3] or even during the premorbid phase,[4] and have also been detected in the relatives of schizophrenic individuals, or individuals at high risk for schizophrenia.[2,3] Secondly, the alleviation of neu-

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rocognitive symptoms may be the key to improved rehabilitation and social functioning. Neurocognitive deficits have been consistently associated with the social functioning impairments exhibited by schizophrenia patients.[5,6] They also consistently account for significant variance in measures of social and occupational disability,[7,8] and this association appears to remain stable over time.[9] Indeed, functional outcomes have been correlated more closely with the extent of neurocognitive deficits than with the severity of positive or negative symptoms.[11] Improvements in neurocognitive deficits lead to improved skills in social problem-solving, improved psychosocial skills, improved community (social and occupational) skills, and improved quality of life.[7] Among the relevant neurocognitive deficits, secondary memory, immediate verbal memory, sustained attention, and semantic memory are most profoundly related to functional outcomes.[6] Therefore, improvements in neurocognitive deficits effected by pharmacological or non pharmacological treatments, or a combination thereof, may prove to be of great importance in the rehabilitation of schizophrenia patients. In this paper, we will highlight two of the key cognitive symptoms of schizophrenia, those of memory and attention, and will also conduct a short discussion regarding the effects of antipsychotic drug treatment.

Pharmacological treatments for schizophrenia can be divided into two types: typical and atypical antipsychotic drugs.[10,13,14] Typical antipsychotic drugs, most notably haloperidol, predominantly block dopamine (DA) receptors of the D2 type in the mesolimbic regions, and tend to effect improvements in positive symptoms, such as delusions and hallucinations. However, the blockade of D2 receptors in subcortical areas, specifically the striatum, is a major factor in the induction of extrapyramidal symptoms (EPS), as well as tardive dyskinesia. Atypical antipsychotic drugs, including clozapine, risperidone, and olanzapine, can be defined as drugs that generate minimal extrapyramidal symptoms (EPS) at doses that yield effective antipsychotic action.[15] Although all of the currently available antipsychotic medications antagonize D2 dopamine receptors, antipsychotic drugs vary substantially with regard to their pharmacological properties.[13,14] Typical neuroleptics are generally effective in the amelioration of positive symptoms, but there is little compelling evidence to suggest that they exert similar benefits on negative symptoms[16] or neurocognitive deficits.[17] Robust cognitive improvements have been fairly consistently observed in both respondent and chronic, treatment-resistant schizophrenics after the initiation of atypical antipsychotic drug therapy.[18,19,20,21,22]

Among the neurocognitive deficits associated with schizophrenia, attention and memory appear to be particularly salient with regard to the progress of the illness, and its outcome. Attention abnormalities, which are considered to be one of the primary cognitive deficits in schizophrenia,[23,24] can be present even before the onset of the illness,[25] and have been linked most closely to global functional impairments and poor outcomes in cases of first-episode schizophrenia.[26] For example, sustained attention, or vigilance, is known to predict social problem-solving and skill acquisition.[27] Memory deficits have been observed even in patients with less severe generalized deficits.[26] Verbal memory seems to be related to a wide range of functional outcomes,[27] and verbal memory[11,28,29] and working memory[29] are the strongest predictors of poor community outcomes and impairments in skill learning. Several studies[12,30] have already reviewed the effects of typical and atypical antipsychotic drugs on general neurocognitive deficits. In this article, we have limited our discussion to the effects of pharmacological therapy on selected areas of neurocognitive deficits, namely those of attention and memory, in schizophrenia. In addition, we have reviewed some unconventional pharmacological treatments.

A comprehensive survey of attention and memory would require a weighty tome, and is, therefore, beyond the scope of this article. Below, we have pre-

sented a practical summary of the conceptualization of attention and memory functions as used in the neuropsychiatric literature. Attention can be divided into the following conceptual components: sustained attention, selective attention and inhibition, and divided attention. Sustained attention involves the maintenance of focused attention over a prolonged period of time, in order to detect infrequent signals. The Continuous Performance Task (CPT) is frequently 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. The Visual Search and Stroop tasks 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. The Dual task paradigm is commonly used to assess divided attention.

There are many ways in which memory can be conceptualized and subdivided, and a variety of assessment methods have already been established[31]. Secondary memory, immediate memory span, working memory, and semantic memory are most frequently assessed by neuropsychologists in studies of schizophrenia. Secondary memory refers to the ability to acquire and store information over a prolonged period of time (usually several minutes or longer). For example, individuals may be 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 be used to measure immediate memory span. Immediate memory differs 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 in which working memory can be measured, but digit or visual backward span, delayed response task in auditory, spatial or visual modality, and the n-back task are the most commonly used techniques. Semantic memory refers to the storage of knowledge concerning objects, people, or words, and can be measured via the word fluency task.

Effects of pharmacological treatments on memory and attention

Typical antipsychotic drugs have less impact on neurocognitive deficits and negative symptoms associated with schizophrenia, than on positive symptoms. The short-term administration of typical antipsychotic drugs has been reported to induce impairments in sustained attention[32,33] and immediate memory span,[17] but these effects decrease with chronic treatment.[17,32,33] Verbal memory can be improved by the administration of typical antipsychotic drugs.[34,35] Although conventional antipsychotic drugs have been shown, in a few studies, to improve performance on a few selective tasks, there has been no conclusive evidence of improved secondary memory, semantic memory or attention in schizophrenia as the result of treatment with typical antipsychotic drugs[27,33,36,37] A recent study reported that neuropsychological impairments in schizophrenia patients receiving typical neuroleptics appear to remain stable, regardless of baseline characteristics and changes in the patients' clinical states.[38] In addition, the extrapyramidal (EPS) and anticholinergic side effects of typical antipsychotic drugs may exert detrimental effects on cognition.[49]

Although the results were initially inconsistent, several studies have reportedly identified robust cognitive improvements in the cognitive functions of schizophrenics treated with clozapine. Improvements of semantic memory as the result of clozapine treatment have also been consistently reported.[19,21,36,39,40,41,43,44] Clozapine treatment also resulted in improvements in secondary verbal memory in some studies[18,21,43,44,45] but not in others.[36,39,40] Clozapine has been associated with

a positive effect on secondary visual memory[19,42,43] but some studies have not detected this effect,[41,45,46] and some have even reported deterioration.[47] Clozapine is not known to improve verbal working memory.[36,39,40] A recent study,[18] however, did report an improvement in verbal working memory after 16 weeks of clozapine treatment in a case of treatment-resistant schizophrenia. With regard to immediate memory, Fujii et al.[48] reported that clozapine had no effect, whereas other studies reported that it resulted in some improvement.[21,43,44,45] While clozapine clearly exerts beneficial effects on some aspects of memory, it appears to have no effect on attention. Clozapine has been determined to have no effect on divided attention,[48] sustained attention,[46] or inhibitory processing[45] in treatment-resistant schizophrenia patients. It was even reported in one study, to impair selective attention and inhibition,[19] although Gallatley et al.[50] detected improvements in sustained attention in auditory modality after 6 months of clozapine treatment.

Risperidone has been shown to improve working memory in verbal modality[37,51] and spatial modality.[52] Working memory is mediated by a constellation of neural circuitry including the prefrontal cortex.[53] The improvements observed in working memory after risperidone treatment are consistent with the recent finding that functional activation in the right prefrontal cortex, supplementary motor area, and posterior parietal cortex was increased during working memory tasks after risperidone had been substituted for a typical antipsychotic drug.[54] In contrast to the beneficial effects observed in the context of working memory, the effects of risperidone on secondary verbal memory and immediate memory remain somewhat controversial. Risperidone has no effect on immediate memory span.[51,37] Lindenmayer et al.[45] reported that schizophrenia patients receiving risperidone treatment performed worse at 12 weeks as compared with baseline values, but Kern et al.[55] reported that risperidone-treated schizophrenia patients exhibited greater improvement in secondary verbal memory than did haloperidol-treated patients. Long-term risperidone therapy improved the performance of schizophrenia patients on attention assessments, specifically those involving selective attention and alertness,[56] but 8 weeks of risperidone treatment was determined to have no effect on sustained attention.[57] Lindenmayer et al.[45] also detected no effects of risperidone on inhibitory processing, as measured by the Stroop task.

Olanzapine, which is similar to clozapine, exerts beneficial effects on verbal memory.[58,59] After 20 weeks of olanzapine treatment, improvements were detected in the verbal memory of treatment-refractory schizophrenia patients.[58] Harvey et al.[59] also reported that olanzapine exerted beneficial effects on verbal learning and memory. Cuesta et al.[60] showed that olanzapine treatment improved inhibitory processing on the Stroop task to a higher degree than did risperidone or typical antipsychotic drugs, but that it had no significant effects on semantic memory or visual memory.

In the case of quetiapine, another atypical antipsychotic drug, the results of two studies are currently available. Velligan et al.[61] reported improvements in semantic memory, inhibitory processing, and verbal memory after 24 weeks of quetiapine treatment. Purdon et al.[42] also determined that quetiapine exerted beneficial effects on semantic memory and secondary verbal memory.

The diverse pharmacological properties of atypical antipsychotic drugs, and the resulting selective effects of specific atypical antipsychotic drugs on neurocognitive deficits, may have important clinical consequences.[13,14] A few studies have been conducted in order to evaluate the comparative efficacy of atypical antipsychotic drugs on neurocognitive deficits in schizophrenic patients.[20,59,62] Purdon et al.[62] found that olanzapine produced a substantial gain in immediate recall (verbal and visual domains), greater than that observed in conjunction with haloperidol or risperidone treatments. In a recent 14-week, double blind study,[20]

risperidone treatment was determined to result in huge improvements in the verbal learning memory domain over time, and these improvements were substantially more profound than those associated with either clozapine or haloperidol treatments. However, in the selective attention domain, olanzapine was reported to be much more effective in reducing interference on the Stroop task than was risperidone.[60] Harvey et al.[59] demonstrated that, although olanzapine and risperidone improved verbal learning and memory, only risperidone resulted in improvements in semantic memory. A recent review and meta-analysis[63] compared the effects of several atypical antipsychotic drugs. In this study, quetiapine and clozapine resulted in more pronounced improvements in semantic memory than did risperidone and quetiapine, and olanzapine had a more profound effect on inhibitory attention than did either clozapine or risperidone. With regard to secondary verbal memory, no differences in efficacy were found among the atypical antipsychotic drugs.

Unconventional and novel treatments

Although the atypical antipsychotic drugs appear to be much more effective than the typical drugs in terms of the alleviation of neurocognitive symptoms, they do not effect a return to normal functioning levels in the majority of schizophrenics. It might, therefore, prove necessary to assess the effects of other adjunctive treatments with atypical antipsychotic drugs in the treatment of schizophrenia. Donepezil has been previously used as an adjunctive treatment to risperidone, in an attempt to increase cholinergic activity at the muscarinic and nicotinic receptors. However, this approach had no effects on cognition, including selective attention, sustained attention, spatial working memory, and verbal memory, in the tested cases of schizophrenia[64]. Norepinephrine plays a significant role in working memory functions in the prefrontal cortex, via its action at the alpha-2a noradrenergic receptors. Guanfacine, an alpha-2 noradrenergic agonist, has proven very effective in the reversal of working memory deficits in non-human primates.[65] However, in a 4-week treatment trial conducted by Friedman et al.,[66] guanfacine treatment adjunctive to neuroleptics resulted in no effects on memory and attention in schizophrenic patients.

A much more controversial and intriguing area, though, is an adjunctive treatment involving essential fatty acids. These treatments are predicated on the membrane hypothesis of schizophrenia, which was proposed by Horrobin et al.[67] It has been suggested that metabolic abnormalities affecting omega-3 polyunsaturated fatty acids (PUFAs) may constitute a core feature of schizophrenia. Evidence for anomalous fatty acid metabolism has been observed in the frontal cortex,[68] and also in the cell membranes of red blood cells.[69] Dietary omega-3 PUFA intake has also been associated with the severity of schizophrenia.[70] These findings provide a rationale for the treatment of schizophrenia with omega-3 PUFAs. Su et al.[71] reported that a pregnant schizophrenia patient exhibited marked improvements in both positive and negative schizophrenic symptoms after being treated with omega-3 fatty acids. Preliminary studies of schizophrenia patients with short-duration illness have indicated some improvements in symptoms when omega-3 fatty acids were added to the patients' usual medications,[72,73] but a larger trial[74] found that omega-3 fatty acid supplementation had no effects with regard to both psychopathological symptoms and cognitive impairments. However, the patients enrolled in Fenton et al.'s study[74] tended to be older, and the daily diets of the subjects could not be controlled. In order to accurately evaluate the efficacy of omega-3 PUFAs treatment on neurocognitive deficits and other symptoms, more clinical trials will clearly be necessary.

The development of schizophrenia during the reproductive period in a majority of affected patients suggests that this disorder may be somehow related to a

disturbance in the reproductive hormone system.[75] It has been suggested that estrogen may function as a protective factor in women: the age of onset of schizophrenia is significantly older in women than in men, with a larger and later second peak of onset observed in women after 40-45 years of age.[76,77] Indeed, estrogen adjunctive treatment has been shown to have a positive impact on psychotic symptoms in female schizophrenia patients.[78] In normal subjects, some evidence suggests that estrogen levels are related to cognition throughout the menstrual cycle, with high levels of estrogen at the mid-luteal point being associated with better verbal memory, but not spatial ability.[79,80] A recent study[81] also indicated that, in schizophrenia patients, higher than average estrogen levels are associated with better neuropsychological performance in many areas of cognition, including the areas of attention and memory. Specifically, in this study, no difference was found to exist between patients taking oral contraceptives or those on estrogen–replacement therapy. This suggests that higher levels of either endogenous or exogenous estrogen exerted beneficial effects on cognitive functioning. Future studies regarding the effects of estrogen treatment on neurocognitive deficits in schizophrenia are also clearly warranted.

Other adjunctive pharmacological agents, including anti-anxiety drugs and antidepressants, have been used extensively in the treatment of patients suffering from schizophrenia.[82] but only a 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, studies of the effects of pharmacological treatment on neurocognitive deficits have provided strong evidence that atypical antipsychotic drugs ameliorate neurocognitive deficits more effectively than do typical antipsychotic drugs. The effects of atypical antipsychotic drugs on neurocognitive deficits in schizophrenia do not appear to be secondary to these drugs' decreased propensity to induce EPS.[83] Clozapine has been determined to improve both secondary and semantic memory, but results of studies on the effects of clozapine on working memory and attention have not been conclusive. Risperidone has relatively consistent positive effects on working memory, whereas its beneficial effects on verbal learning and memory and attention have been relatively inconsistent. Olanzapine seems to improve verbal learning and memory and semantic memory, but has no effects on working memory or attention.

Most studies regarding the effects of antipsychotic drugs on neurocognitive deficits have focused primarily on general, global effects, and have not been specific as to which particular characteristics of schizophrenia or pharmacological treatment might be related to the effects of treatment. Because several methodological factors relating to study design have been discussed in detail,[13,22,62,84] we will briefly mention a few factors here. Several studies have reported sex differences in schizophrenia patients with regard to the progress of the illness, and also in terms of neurocognitive deficits. Some studies have determined that male schizophrenia patients tend to perform worse than female patients on measures of cognitive function,[85,86] and others have reported opposite findings,[83,87,88] while others still have detected no such sex differences.[89] It is clearly possible that schizophrenic men and women may respond differently to pharmacological treatment, but the majority of the currently available studies have not examined sex differences, and the results of many studies are based solely on male patients. Sex differences in the neurocognitive deficits associated with schizophrenia are not consistent, and will require further investigation before any definitive conclusions can be drawn. Other factors, including premorbid adjustment, education, and handedness have been previously associated with neurocognitive deficits,[90] but the majority of studies regarding the effects of antipsychotic drug treatment

did not deal with these factors. It will be necessary, in the future, to specifically determine the extent to which these factors might influence the effects of antipsychotic drugs in the treatment of schizophrenia.

Neurocognitive studies can bridge the gap between neurobiological mechanisms and the etiology of schizophrenia. The methods employed in cognitive neuroscience, including brain imaging techniques, combined with meticulously designed experiments, may help to clarify exactly what type of memory or attention function a particular pharmacological agent is facilitating or inhibiting. Functional neuroimaging studies[91] typically reveal differences in the activation patterns in the brains of schizophrenics and normal controls during attention or memory tasks. However, it is necessary to probe further, by asking what these patterns of differences might mean. It is also clearly necessary to gather more information about the individual differences in the recruitment of specific neural circuits during tasks as the result of treatment with different pharmacological agents. By combining cognitive neuropsychological, neuropharmacological and clinical approaches, future research into the effects of antipsychotic drug treatments on specific neurocognitive functions will result in a better understanding of schizophrenia and a better outcome for patients who suffer from schizophrenia.

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