
Treatment of cognitive deficits in first-episode psychosis

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Cognitive dysfunction is a core and enduring feature of schizophrenia. Deficits in cognition are the most consistent findings in the schizophrenia literature. Since Kraepelin's [1] first clinical accounts it has been recognised that cognitive deficits are a prominent feature of schizophrenia. It is well established that schizophrenic patients exhibit significant pervasive cognitive impairments when compared with healthy controls. Furthermore, it would appear that a vast array of cognitive domains are affected by the disease (for a review *see* [2]).

Nature of cognitive impairment in first-episode psychosis

Patients in their first episode of psychosis present with neurocognitive impairment by the time they come to the attention of the mental health services. Studies examining neurocognition in first-episode psychosis have found patients to perform significantly worse than normal healthy controls on many cognitive functions, including memory, attention and concentration, executive function, language skills, psychomotor speed, spatial abilities and general cortical function [3–8]. Furthermore, the overall performance deficit can be up to 1.5 standard deviations below that of a normal control population [9]. This is clinically significant and meaningful, as 1 standard deviation in IQ below normal controls would be a difference of 15 IQ points. This could make the difference between being able to complete a college degree or not in a young person afflicted with the illness.

Some studies have suggested that there is a diffuse, non-localized impairment even at the first presentation of symptoms, and that left hemisphere functioning is significantly more impaired than right hemisphere function [4]. However, others argue that first-episode patients demonstrate selective deficits relating to the pathophysiology of the disease [7,10,11]. Saykin *et al.* [7] examined neuroleptic-naïve patients with first-episode psychosis and found that these patients showed a generalized impairment of approximately 2 standard deviations, relative to healthy controls, as well as a pronounced deficit in verbal memory and learning. These findings were replicated by Censits *et al.* [8]. Hutton *et al.* [10] found that patients were particularly impaired on specific aspects of executive function (the ability to think ahead and to organise responses) and also demonstrated poor verbal memory. It is possible that memory deficits are central to the cognitive pathology of schizophrenia, but that they share vari-

ance with most of the other cognitive domains. Such a notion would support – and would be supported by – neuroimaging findings of decreased volumes in the temporal and hippocampal regions, the areas often associated with memory processes.

Is there evidence of progressive cognitive decline?

The majority of studies have employed a cross-sectional design comparing patients with first-episode psychosis, patients with chronic schizophrenia and, occasionally, normal control individuals [3–8,10,12]. Hoff *et al.* [4] found that patients with first-episode or chronic schizophrenia showed significant impairments compared with the control group, while there were no significant differences between the two groups. Hoff *et al.* suggested that this could be interpreted as evidence against the notion of cognitive decline. Other studies, however, have shown that patients with chronic schizophrenia displayed greater impairment on certain cognitive tests than patients with first-episode schizophrenia [6,7].

These results suggest that there may be progressive decline on some functions, while others remain preserved. The areas in which greater impairment was displayed were primarily measures of executive/frontal function. It may well be argued that patients with chronic schizophrenia represent a subgroup of patients who show significant frontal pathology, but it is impossible to say that all schizophrenic patients will decline in this way. Bilder *et al.* [3] also found that patients with chronic schizophrenia showed impairments only on certain measures. More specifically, their sample showed significant impairments on measures of performance IQ from the Wechsler Adult Intelligence Scale-Revised (WAIS-R), but not on verbal IQ or full-scale IQ. Bilder suggests that the performance scale is more sensitive to deterioration; hence, this explains why the deterioration appears to be specific rather than generalized. Using a deterioration index and matching the two patient and control groups for pre-morbid IQ, they found that controls had the lowest score on the deterioration index, while patients with first-episode schizophrenia yielded intermediate scores and the group with chronic schizophrenia showed the highest score. However, it is not clear whether it follows that patients with first-episode schizophrenia will deteriorate further, or whether each group represents a subgroup.

There are many confounds associated with using a cross-sectional study design. Patients with chronic disease may represent a subgroup of schizophrenics with particularly profound neuropsychological deficits. Many patients, particularly those with good premorbid histories (good social support, short prodromal period, etc.), often go on to become well integrated into the community. These individuals are often those who displayed milder cognitive impairment [13]. Furthermore, it seems somewhat fruitless to compare a sample of patients with first-episode schizophrenia with a group who have received long-term neuroleptic treatment, particularly when

such treatments have previously been reported to have both beneficial and detrimental effects on cognitive functioning.

A way of overcoming such confounds is to employ a longitudinal study design. As yet, few studies have pursued this line of investigation, although the results from those that have are generally consistent. Sweeney *et al.* [5] assessed both chronic and first-episode groups at baseline, and then performed a reassessment after an interval of one year. No evidence of deterioration was detected; on the contrary, certain measures showed signs of improvement. Similarly, Hoff *et al.* [4] detected small, but significant improvements on measures of executive function, concentration/psychomotor speed and global scales (which was taken as an average of the six functional scales) when they reassessed patients with first-episode schizophrenia two years after the baseline assessment. A study performed in the same year by Bilder *et al.* [14] planned to examine patients at baseline (six months into the treatment), 18 months and 36 months. To date, data are available only for the first two assessments. However, the picture is consistent with the previous findings: there was generally high stability of neuropsychological function over the 12-month interval, with significant improvements in memory, motor and attention functions. However, Bilder *et al.* [14] also reported non-significant declines in some measures of language and a significant decline in digit span. It is possible that digit-span performance is a measure that can distinguish between those who will go on to suffer from recurring episodes and those who will remain in remission.

Gold *et al.* [15] performed a longitudinal study of cognitive function and its relationship with clinical symptoms in patients with first-episode and recent-onset schizophrenia. Overall there was no cognitive deterioration during five years of follow-up. Significant improvements were noted in cognitive performance, as well as in mean clinical status and medication dose. Specifically, there was improvement in the time to completion of the Circle A letter-cancellation task, free recall on the logical memory test and the number of categories correctly completed in the Wisconsin Card Sorting Test. IQ measures showed high stability over this period. Verbal IQ and full-scale IQ were significantly correlated with negative symptoms, and improvement in these measures was correlated with improvement in negative symptoms. This study did not control for medication dose or agent, and these parameters were allowed to fluctuate freely during the course of the study. Most of the treatment was with typical antipsychotics. The study supports the view that negative symptoms are associated with poor long-term cognitive outcome and may be closely related to the primary cognitive deficit.

In another study, with a cross-sectional and longitudinal design, Addington and Addington [16] compared cognitive functioning in a group of first-episode schizophrenia patients with that in patients who had experienced multiple episodes of schizophrenia. All the first-episode patients were part of a programme that offered optimal care as early as possible in the illness, and 90% of these patients were taking

second-generation antipsychotics. Again there were several significant associations between cognitive deficits and negative symptoms, which were apparent in both groups. The findings of this study suggest that first-episode patients have cognitive deficits that are similar to those of longer-term patients.

In order to establish whether or not cognitive improvement was a result of clinical improvement, Hoff *et al.* [4] performed paired t-tests on the clinical psychopathology scales employed in their investigation (Schedule for Assessment of Negative Symptoms [SANS] and Schedule for Assessment of Positive Symptoms [SAPS]) at times 1 and 2. Although there was a significant reduction in positive symptoms that may have accounted for the observed cognitive improvement, correlations between neuropsychological difference scores and clinical change scores were not significant. This suggests that changes in clinical state did not account for changes in cognitive function.

These longitudinal studies have shown that cognitive dysfunction is a core and enduring feature of schizophrenia. While there is little evidence of deterioration in the short term, there seems to be a cohort of patients who may be on a deteriorating course with poor outcome. Thus, cognitive dysfunction is a stable feature of the illness and is evident in remitted patients and is not due to symptom severity. The life course of the illness is shown diagrammatically in Figure 3.1. Cognitive impairment is being recognised as a central feature of the illness and not some epiphenomenon of other aspects of the illness or its treatment.

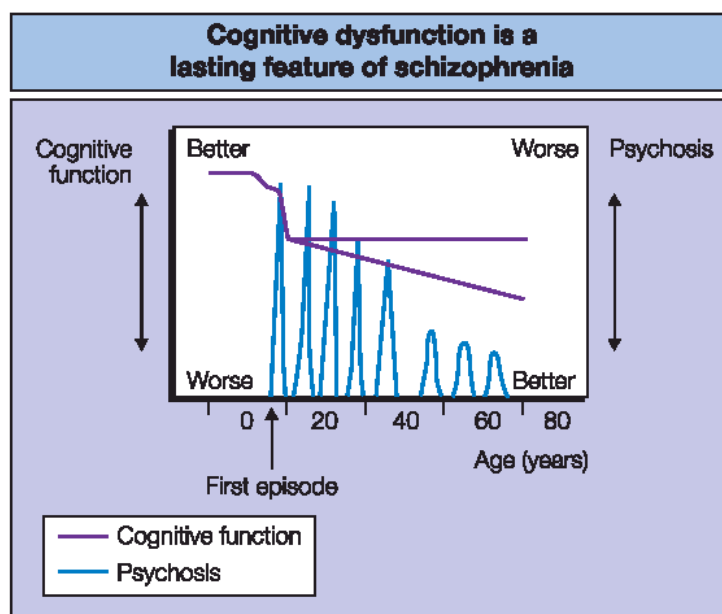


Figure 3.1

Is there cognitive enhancement with atypical neuroleptics?

Atypical antipsychotics have revolutionized the way in which psychosis is treated. Although all antipsychotic medications currently available share the pharmacological property of antagonising D₂ dopamine receptors, antipsychotic drugs vary substantially in their pharmacological profiles, each affecting a variety of neuroreceptors in the central nervous system. This variation in pharmacological properties could result in important clinical consequences, including selective effects of a specific antipsychotic drug on cognition.

The neurotransmitter systems affected by antipsychotic medications include (but are not limited to) cholinergic, adrenergic, serotonergic, dopaminergic and glutamatergic types. There are several reasons why the atypical antipsychotics would be expected to enhance cognition. Alteration of adrenergic, serotonergic or histaminergic functioning may increase attentional or memory performance. Studies in primates have suggested that manipulations of these neurotransmitters improve cognitive functioning in various ways [17]. In addition, the reduced need to co-prescribe anticholinergic drugs to counter neurological adverse effects is beneficial. It is possible that these drugs may target regions of the brain responsible for psychosis more specifically, while sparing those that are responsible for extrapyramidal side effects. This fact may also be responsible for their cognitive enhancement properties. Indeed, it has been shown that patients who have been switched from typical neuroleptics to one of the newer antipsychotics show improvement of blood flow to the frontal and parietal lobes [18].

Drugs that increase muscarinic cholinergic, 5-HT_{2A/2C} serotonergic and alpha_{2A}-adrenergic activity may improve cognitive function. Drugs that enhance glutamatergic function, especially at the NMDA glycine site, or drugs that enhance D₁ dopamine receptors below their 'therapeutic window' are also candidates to improve cognition function. As demonstrated with investigations of how neurotransmitter systems interact when drugs affect them simultaneously (eg, 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 at present, and must be determined empirically *in vivo*. Animal studies of cognitive function suggest that the effect of drugs will be altered if there are central nervous system impairments in particular neurotransmitter systems. For example, the effects of alpha-adrenergic agonists depend on an intact prefrontal cortex. Thus, results of studies conducted with healthy human subjects may not be applicable to patients with brain diseases, such as schizophrenia.

A number of preliminary studies examining the cognitive effects of atypical neuroleptics have been performed, with a variety of encouraging findings. Several previously published articles have suggested that atypical neuroleptics are superior to typical drugs for cognitive enhancement, and has been reviewed in detail by Keefe

and Gold (*see* Chapter 2). There are published reports that show general cognitive enhancement with atypical antipsychotics, including olanzapine, risperidone and clozapine [19,20].

Recent work suggests that patients in the first episode of psychosis may have greater cognitive improvements on olanzapine than low doses (5 mg) of haloperidol [21]. In this study, while patients on haloperidol and olanzapine improved, the olanzapine-related improvements were significantly larger. An empirically derived composite score improved 0.45 standard deviations with olanzapine compared with 0.26 with haloperidol. Olanzapine particularly improved vigilance and information processing speed, which may be very important for functional outcomes [13]. Finally, while the haloperidol patients in this study showed magnetic resonance imaging changes consistent with grey matter volume loss in the frontal cortex, patients treated with olanzapine patients had no such changes. Furthermore, the absence of vigilance improvement in the patients treated with haloperidol was correlated with reduction of volume in the frontal cortex [22].

It is important to note that the cognitive functions that improve with atypical antipsychotics are those that have been more strongly associated with outcome (eg, verbal memory, working memory and executive function) [13,23]. The effects of cognitive enhancement in studies can be seen within about six weeks of starting treatment with an atypical antipsychotic. One might speculate that a drug that enhances cognitive functioning will improve the capacity of patients to respond to psychosocial rehabilitation. In other words, the newer drugs may help patients to recover lost skills, or learn new ones in a rehabilitation setting. Thus, cognitive enhancement could help the ability to benefit from psychosocial treatment, especially interventions based on learning such as social skills training.

Special treatment strategies and neuroprotection

Longitudinal studies suggest the most devastating clinical progression in patients with schizophrenia occurs within the first five years from the time of onset [24]. Episodes of psychosis in the early stages of illness may reflect an active pathophysiological process that can produce enduring cognitive and functional impairment in patients and reduce their capacity to respond to treatment [25,26]. Wyatt [27] has suggested that early intervention with neuroleptic medication may alter outcome in schizophrenia. This is of considerable importance as it is possible that some types of neurodegenerative processes may be interrupted by prompt intervention with neuroleptics. It is also possible that early intervention would reduce cognitive impairment as well as improve outcome. As in other areas of medicine, selecting appropriate treatments should be based on a rational assessment of benefits compared with risks. Given the increased appreciation of neurocognitive

deficits as targets of treatment in schizophrenia, weighing the cognitive risk/benefit ratio should be an essential part of any treatment strategy. In this context, it must be appreciated that typical antipsychotics have no cognition-enhancing effects, and there is burgeoning evidence about the cognitive effects of newer antipsychotic treatments [20]. It is also possible that relapse may be accompanied by frank neurotoxicity. This model of the 'neurodegenerative' effects of psychosis in patients with schizophrenia suggests that the most debilitating effects of psychosis can be best limited by early, effective intervention [28].

Furthermore, as atypical neuroleptics appear to improve positive symptoms, negative symptoms and cognitive deficits even in short-term studies, it is possible that this 'neurodegenerative' process may be reversed by atypical neuroleptics [28]. Thus, intervention with atypical neuroleptics in the early stages of schizophrenia may promote cognitive and functional abilities later on in the illness. In addition, it is plausible that early intervention could have the potential to reverse some of the disability associated with the illness before it has secondary effects on the patient.

From rational research to clinical reality

There is now the recognition that neurocognitive functions should be acknowledged as treatment targets and considered along with the other symptoms of schizophrenia as important measures of treatment response and outcome. As cognitive impairment is correlated with the majority of the disability seen in chronic schizophrenia, treatment of this condition appears to have the potential to reduce this disability. Also, as the current group of atypical neuroleptics has shown preliminary promise in this area, they may serve to improve the typically poor outcome seen in schizophrenia. The issue is complex, but the preliminary data are promising and for the first time suggest that medication treatment for schizophrenia may improve the adaptive outcome of patients with this illness and increase quality of life in a way that far exceeds the improvements seen with typical neuroleptic medication.

Premorbid ability is the best predictor of long-term outcome, and provides us with an index of what a clinician should expect in terms of optimal treatment response. Knowledge of cognitive impairments may help guide other treatment decisions and expectations. It is accepted that there is pathophysiological and clinical heterogeneity in schizophrenia. Neurocognitive assessments may ultimately provide indexes of the degree to which distinctive neural systems are principally compromised, and/or which ones are still operating with sufficient integrity to mediate effective treatment. The realisation has come that neurocognitive deficits should be treatment targets in their own right in patients with first-episode psychosis. We now need to move from rational research to clinical reality, and identify specific strategies that directly enhance cognitive function early in the first episode of psychosis. This should

enhance compliance with medication, and enable the young patient to lead a better quality of life and to reintegrate into society. It may also serve to significantly alter the long-term outcome of the patient's disorder, perhaps even decreasing the likelihood of relapse and increasing the possibility of satisfying relationships, functional independence and employability.

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