The Impact of Antipsychotics on Cognitive Functioning in Schizophrenia

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Cognitive deficits, which play a crucial role in the pathogenesis and prognosis of schizophrenia, can lead to noncompliance and poor outcomes. New treatment options need to be tested that may offer surplus effects on neurocognition.

There is broad consensus that cognitive deficits play a crucial role for both the pathogenesis and prognosis of schizophrenic psychoses. Cognitive disturbances often precede the first psychotic episode (Cannon et al., 2000) and persist over the different stages of the illness (Goldberg et al., 1993). It is important to note, however, that not all patients display neurocognitive disturbances and that contrary to early descriptions of the disorder (Kraepelin, 1893), recent cross-sectional and longitudinal studies suggest that schizophrenia is a neurodevelopmental disorder rather than a neurodegenerative one (Moritz et al., 2002a; Rund, 1998).

A more recent tradition of research has shed light on the impact of neurocognitive disturbances on outcome and treatment-related variables. Meta-analysis research conducted indicated that cognitive deficits, especially impairments in the domains of memory and vigilance, are significant predictors of functional outcome (e.g., community outcome, social problem solving and skill acquisition) (Green, 1996; Green et al., 2000). In addition, neurocognitive functioning is related to insight (Rossell et al., 2003) and coping skills (Wilder-Willis et al., 2002). Further, there is increasing evidence that neurocognitive dysfunction may severely compromise medication compliance (Donohoe et al., 2001).

At least two factors may underlie this relationship. First, it is well-known that several psychotropic agents—especially anticholinergic medication (Nishiyama et al., 1998) and benzodiazepines (Rammayer et al., 2000; Tonne et al., 1995)—decrease neurocognitive functioning in some patients. Should such side effects remain undetected by clinicians and not be adequately dealt with, patients are likely to discontinue drug intake, deciding the side effects outweigh the benefit of drug treatment. Secondly, noncompliance can result from forgetting (Fenton et al., 1997) due to primary or induced (prospective) memory problems, which are frequently observed in psychiatric disorders (Moritz et al., in press).

Neurocognitive Functioning

Because of its impact on psychopathology, functional outcome and treatment-related variables, the amelioration of neurocognitive deficits is increasingly considered a target domain of antipsychotic treatment. The majority of studies conducted to date have shown that typical antipsychotics have a negligible impact on most neurocognitive functions. However, verbal fluency (e.g., verbal production of animals, nouns that begin with a certain letter) and spatial processing (e.g., block design test) are sometimes decreased under conventional medication (Moritz, 2002).

Some of the results indicating stable cognitive functioning with conventional medications may in fact obscure real cognitive decline since patients' overall health state generally normalizes over the course of clinical trials and improved psychopathology in turn is often accompanied by modest neurocognitive improvement. (See Moritz et al. [2003] for a method to verify real memory change in patients taking antipsychotics--Ed.) Moreover, familiarity with the assessment procedures and practice effects also predicts some increase in achievement even without real change.

In addition, the induction of extrapyramidal side effects due to the administration of conventional D₂ antagonists often necessitates prescription of anticholinergic medication, which, as outlined, has negative effects on learning and memory. Taken together, the conventional "treatment package" (D₂ antagonists and anti-Parkinson agents) potentially harms the already decreased cognitive capacity of patients with schizophrenia.

With the possible exception of clozapine (Clozaril), for which divergent findings have been collected with respect to memory, studies investigating the efficacy of atypical antipsychotic agents have mostly found enhancing effects on neurocognition (Keefe et al., 1999; Potvin et al., 2003). Although there is evidence that atypical antipsychotics directly exert beneficial effects on neurocognitive...
functioning, some of the positive effects of atypical antipsychotics on neurocognition stem from a more pronounced remission of negative symptoms relative to conventional agents. The positive impact of atypical antipsychotics on neurocognitive functioning embraces the domains of memory (short- and long-term), selective attention, executive functioning and verbal fluency (Bilder et al., 2002; Stip et al., 2003b). As spatial processing rarely has been assessed, no solid conclusions can yet be drawn regarding this domain (Moritz, 2002).

**Subjective Cognitive Deficits**

In recent years, studies employing standard neurocognitive tests have been complemented by research on subjective cognitive complaints in patients. The assessment of subjective cognitive well-being is by no means redundant to objective testing since subjective and objective testing are often poorly correlated (Moritz et al., in press) and may therefore measure different aspects of cognitive functioning. The assessment of subjective cognitive deficits offers a means to circumvent simple practice effects that plague studies that have objective neurocognitive tests but no control groups.

In two studies, subjective cognitive deficits predicted later symptomatic outcome in first-episode patients, further highlighting the importance of subjective complaints (Moritz et al., 2000b, 2002b, 2002c). In addition, Naber (1995) found that well-being at discharge as assessed by the Subjective Well-Being Under Neuroleptic Treatments questionnaire (SWN), which also incorporates a mental functioning scale, predicted compliance at follow-up.

In one of the first studies that investigated subjective cognitive deficits, patients with schizophrenia reported fewer subjective cognitive complaints after treatment with clozapine in comparison to haloperidol (Haldol) (Morgner, 1992). Differences were largest for the subscales of motor functioning and loss of automation on the Frankfurt Complaint Questionnaire (FCQ) (Stllwold, 1991). The FCQ was originally designed to cover basic schizophrenia symptoms but is increasingly utilized to tap general subjective cognitive problems. A study by Cuesta et al. (1996) found that the FCQ is related to objective cognitive functioning.

Daniel et al. (1996) found that patients treated with clozapine and risperidone (Risperdal) reported fewer complaints in the domains of memory, alertness and attention. Naber (1995) compared patients treated with clozapine with a sample treated with a variety of conventional agents. He observed that clozapine led to an improved well-being along different dimensions including cognitive functioning. More recently, Naber et al. (2001) demonstrated that olanzapine (Zyprexa) led to greater improvement of well-being regarding mental functioning, social integration, physical functioning and the SWN total score in comparison to risperidone and clozapine. However, the naturalistic design and small sample size render the results preliminary and call for a replication.

Some recent studies have investigated the impact of antipsychotic dosage on cognition. In line with a study by Spohn et al. (1985), which employed standard neurocognitive tests, Moritz et al. (2000a) found that nine out of the 10 FCQ subscales were significantly correlated with conventional antipsychotic dosage before and after correction for psychopathology (r=0.38 to r=0.54; i.e., higher antipsychotic dosage was accompanied with greater subjective cognitive deficits). The FCQ total score was significantly related to extrapyramidal symptoms (r=0.35) as assessed with the Simpson-Angus Scale (SAS).

In a subsequent study, higher doses of conventional antipsychotics were again associated with decreased subjective cognitive well-being as assessed with the mental functioning subscale of the SWN (Moritz et al., 2002c). Interestingly, high doses of clozapine, risperidone and olanzapine did not show aversive effects on neurocognition. When replicated, this may indicate that higher doses of atypical antipsychotics are better tolerated by patients, with respect to neurocognitive functioning.

**Conclusion**

In view of the presumed linkage of cognitive dysfunction with the pathogenesis of schizophrenia and its prognostic importance on a variety of outcome variables, cognitive disturbances must be taken more seriously by clinicians. Cognitive deficits should by no means be regarded as tolerable side effects of psychopharmacological intervention, as they may endanger medication compliance and often reduce the already compromised cognitive resources of patients, thereby enhancing the patients' vulnerability to stress and renewed psychosis.

It is increasingly obvious that atypical antipsychotics are superior to conventional antipsychotics on a number of treatment domains including negative symptoms, quality of life and neurocognition (Naber et al., 2002). Whereas studies conducted on subjective cognitive impairment are less frequent, results are compatible with results obtained from standard tests. Valid scales are needed that fulfill basic psychometric properties and allow for a more fine-grained analysis of subjective cognitive functioning (see Stip et al. [2003a] for a new scale).

For future research, new treatment options need to be tested that may offer surplus effects on...
neurocognition. For example, the additional prescription of dopamine agonists is an interesting avenue to pursue (Friedman et al., 1999). Moreover, cognitive rehabilitation programs need to be incorporated into the routine therapy of schizophrenia, as there is evidence that many patients benefit from such interventions (Kurtz et al., 2001).

References:


31. Spohn HE, Coyne L, Lacoursiere R et al. (1985), Relation of neuroleptic dose and tardive dyskinesia to attention, information-processing, and psychophysiology in medicated schizophrenics. Arch Gen Psychiatry 42(9):849-859.


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