Treatment Response and Compliance Are Rarely Absolute in Schizophrenia

BY CARL SHERMAN
Contributing Writer

New York — In schizophrenia, black-and-white thinking fails to capture the reality of treatment response and compliance. An appreciation of the wide middle ground can help clinicians understand relapse issues and the relative efficacy of antipsychotics, Jean-Pierre Lindenmayer, M.D., said at a meeting on psychopharmacology sponsored by New York University.

Even in ostensibly successful antipsychotic treatment, “it is rare for a patient to respond in all domains of pathology or function,” which include, but are not limited to, affective symptoms, schizotypal symptoms, and cognitive deficits as well as positive and negative syndromes. “Partial response is the rule,” said Dr. Lindenmayer, clinical director of the Manhattan Psychiatric Center, New York.

Although positive symptoms can be largely controlled by both conventional and atypical antipsychotics, cognitive deficits often remain troublesome. “They may be another core area in schizophrenia,” he said.

Such deficits are independent of positive and negative symptoms and more highly correlated with work capacity, social adaptation, and community residency than either. They are not iatrogenic but are present early in the disease.

Second-generation antipsychotics appear to have a more positive effect than older drugs on cognitive symptoms, particularly executive functions, and on verbal memory and learning. Augmentation strategies have been disappointing. The best data are for ACE inhibitors, for which “the news is not too good,” Dr. Lindenmayer said.

A large study involving atoxine for this application is currently underway, he said.

Psychosocial approaches, such as computer-assisted neurocognitive training, may be just as effective as any drug treatment currently available for this aspect of schizophrenia, he said.

In treatment for cognitive symptoms should be the center of development of new drugs, but it’s not,” Dr. Lindenmayer said.

Evidence-Based Psychiatric Medicine

Cognitive Side Effects of Anticholinergics

The Problem
You have a patient diagnosed with schizophrenia who does well with a typical antipsychotic. He experiences extrapyramidal symptoms, and treatment with an anticholinergic is indicated. You are concerned about potential cognitive side effects.

The Question
What evidence exists regarding cognitive side effects of anticholinergics? Is there evidence to show that these cognitive side effects limit a major life function?

The Analysis
Our Medline search combined “anticholinergic, cholinergic antagonist, trihexyphenidyl, or benzatropine” and “cognitive, cognition, or memory.”

The Evidence
Memory can be divided into three categories: declarative memory (DM), nondeclarative memory (NDM), and working memory (WM). Declarative memory consists of recollection of words, scenes, faces, stories, events, and personal experience. Nondeclarative memory does not require conscious storage or retrieval of information and is needed for forming motor or cognitive skills. Working memory is similar to short-term memory (“Textbook of Neuropsychiatry” [Washington: American Psychiatric Press, 1997]).

In healthy volunteers, several single- or double-dose studies using scopamine, iboprenal, or trihexyphenidyl have demonstrated a decrease in DM, a decrease in DM and NDM, or a decrease in DM and NDM but not WM. One multidose study showed that benzotropine 4 mg/day given for 3 days decreased DM in healthy volunteers, and another showed that benzotropine 4 mg/day or trihexyphenidyl 8 mg/day given for 4 days decreased DM, with the effect more pronounced in the elderly.

In one long-term study of healthy volunteers, 20 cognitively intact patients (mean age 47 years) were given trihexyphenidyl 15-74 mg/day for ideopathic dystonia in this placebo-controlled trial (Clin. Neuropharmacol. 1991;14:627-77). After 2-4 months of treatment, no significant change to DM or NDM was found, with two exceptions: Logical verbal information presented at normal speed on a single exposure was reduced in the anticholinergic group, and speed of information processing was reduced.

In the elderly, several single-dose studies using scopamine, orphenadrine, trihexyphenidyl, or diphenhydramine have shown a decrease in DM, and two studies using trihexyphenidyl 4-8 mg/day for 4 days found similar results.

In healthy volunteers, trihexyphenidyl 6 mg/day for 2 weeks in patients with early Parkinson’s disease ascribed minor cognitive changes to the disease. However, adherence rates for typical and atypical antipsychotics were comparable after 1 year, Dr. Lindenmayer said (Am. J. Psychiatry 2002;159:103-8).

Depot formulations of older agents have been shown to reduce relapse rate, presumably through enhanced compliance, Dr. Lindenmayer observed, and data suggest this applies to depot risperidone as well.

Small studies of patients with depression and anorexia have shown a trend to increased spatial working memory and motor performance with risperidone compared to placebo.

The Conclusion
In healthy volunteers and the elderly, several single- or brief multidose studies have shown consistent evidence that anticholinergics decrease DM and NDM. In a long-term study giving high- to very-high-dose trihexyphenidyl to cognitively healthy volunteers produced minimal cognitive side effects, which were overcome by either repeated exposure to the material or by increasing the time to commit the material to memory. Studies examining anticholinergic cognitive side effects on patients with Parkinson’s disease have demonstrated that exposure to anticholinergics for a period of 2 weeks to more than a decade decreases DM.

In patients with schizophrenia, single or brief multidose studies have demonstrated that anticholinergics decrease DM and NDM. An inverse relationship between anticholinergic load and DM (or spatial working memory) has consistently been demonstrated. (The duration of anticholinergic exposure was not reported, with the exception of one 1-year study on elderly patients with schizophrenia.) Thus, we can conclude with some level of confidence that brief or long-term anticholinergic treatment of elderly patients with schizophrenia decreases DM. We can also conclude that single dose or brief multidose exposure of young patients with schizophrenia decreases DM.

We were unable to locate long-term studies on young patients with schizophrenia, so we cannot conclude whether long-term anticholinergic treatment of young patients with schizophrenia affects DM, NDM, working memory, or socioeconomic functioning. This is especially interesting given the findings of the above-cited longer-term study examining cognitive side effects of high- to very-high-dose trihexyphenidyl on cognitively healthy young adults.

Dr. LIAHANNSON is a forensic psychiatrist affiliated with Atascadero (Calif.) State Hospital. Dr. GUTTMACHER is associate professor of psychiatry at the State University of New York at Rochester (N.Y.) Psychiatric Center. They can be reached at cpnews@elsevier.com.