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 excitement, affective 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.

An appreciation of the wide middle ground can help clinicians understand relapse issues and the relative efficacy of antipsychotics.

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 atomoxetine for this application is currently underway, he said.

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

"Treatment for cognitive symptoms should be the center of development of new drugs, but it's not," Dr. Lindenmayer said.

Although second-generation agents appear more effective than their predecessors for negative and affective symptoms, these symptoms are still likely to remain after psychotic phenomena are under control.

Antidepressant augmentation may help, and there are some "encouraging data" for glutaminergic agents such as glycine and cycloserine, he said.

Atypical antipsychotics also appear to be more effective than conventional agents in preventing relapse.

A metaanalysis of studies including more than 1,700 patients found significantly fewer relapses in the course of a year with second-generation drugs (15%) than conventional drugs (23%) (Am. J. Psychiatry 2003;160:1209-22).

Difficulties in maintenance remain, however, and probably relate to continuing compliance problems.

It is well established that relapse rates are substantially higher with intermittent than with continuous antipsychotic therapy, and many patients are essentially opting for the former, Dr. Lindenmayer said at the conference.

"Both complete noncompliance and satisfactory compliance are rare," he said. "We see patients regularly and assume they are taking the antipsychotic, but most are partially compliant" and follow prescribed regimens erratically.

Although second-generation antipsychotics were expected to substantially ameliorate compliance problems, their advantage in this regard appears to diminish over the long run.

In one study of pharmacy refill records of outpatient veterans, investigators found that medication adherence rates were significantly higher with the newer atypical antipsychotics after 6 months.

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. ■

EVIDENCE-BASED PSYCHIATRIC MEDICINE

Cognitive Side Effects of Anticholinergics

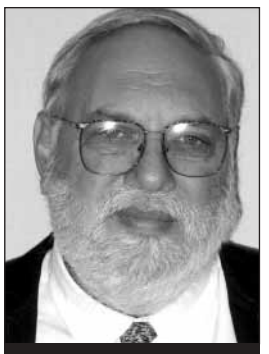
The Problem

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?

BY JAN LEARD-HANSSON, M.D.



BY LAURENCE GUTTMACHER, M.D.

The Analysis

Our Medline search combined "anticholinergic, cholinergic antagonist, trihexyphenidyl, or benztropine" 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 performing 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 scopolamine, biperiden, 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 benztropine 4 mg/day given for 3.5 days decreased DM in healthy volunteers, and another showed that benztropine 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 idiopathic dystonia in this placebo-controlled trial (Clin. Neuropharmacol. 1991;14:62-77). 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 scopolamine, 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.

One study using trihexyphenidyl 6 mg/day for 2 weeks in patients with early Parkinson's disease ascribed minor cognitive changes to the anticholinergic. Three studies using trihexyphenidyl 4-6 mg/day or benztropine 2 mg/day for 1 month to 13 years found decreases in DM. In one study of trihexyphenidyl 2-10 mg/day or benztropine 2-6 mg/day, there were no memory changes in the Parkinson's patients.

In schizophrenia patients, one or two doses of benztropine decreases DM, as does trihexyphenidyl 15 mg/day for 4 days. Anticholinergic load has been shown inversely proportional to DM in schizophrenic patients "with no change for at least 1 month in their current medication regimen" (Am. J. Psychiatry 2004;161:116-24). Discontinuing biperiden 2-6 mg/day that had been given for 1 year or longer in elderly patients with schizophrenia improved DM. One uncontrolled study showed that trihexyphenidyl 7 mg/day given for 6 months reduced scores on the Mini-Mental State Examination and Cambridge Cognitive Examination in a group of elderly patients with schizophrenia (mean age 64 years).

The Conclusion

In healthy volunteers and the elderly, several single or brief multidose studies have most consistently demonstrated that anticholinergics decrease DM and NDM. In one long-term study, giving high- to very-high-dose trihexyphenidyl to cognitively healthy volunteers produced minimal cognitive side effects, which were overcome with 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. Also, 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 sociooccupational 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 volunteers.

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