ABSTRACT

This article summarizes findings from recent clinical investigations of the long-term effectiveness of antipsychotic therapies. Because schizophrenia is a lifelong illness, long-term clinical data, collected over a matter of weeks and not years, has limited application to clinical reality. However, it does provide some insights into drug efficacy over time, an important consideration in the prevention of relapse. Combined data from several studies demonstrate that the atypical agents are highly effective in preventing or increasing a patient’s time to relapse, and significantly more effective as compared with the conventional agent haloperidol. Results from long-term studies of the newest antipsychotic, aripiprazole, are summarized with an emphasis on data surrounding cognitive function. Problems with cognition and verbal expression profoundly affect the nursing treatment plan and must be addressed in order to enhance recovery and to prevent relapse. Recommendations for assessing cognitive function and nursing interventions to help patients overcome such limitations are also provided.

160-mg daily doses of ziprasidone (36%) versus placebo (77%). This dose-adjusted study suggests that ziprasidone efficacy is not dose related; clinicians’ inclination to increase medication dose to achieve greater efficacy in stabilized patients is not supported by the medical evidence surrounding ziprasidone dosing.

Combined, these studies demonstrate that the atypical agents are highly effective in preventing or increasing patient’s time to relapse, and significantly more effective as compared with the conventional agent haloperidol. The atypical agents are not interchangeable, however; each has a unique pharmacologic and side-effect profile. A more detailed description of these characteristics is provided in the article by Dr McEnany (see page 135).

The newest addition to the atypical drug class is aripiprazole, which has been evaluated in long-term clinical trials extending to 26 weeks and 52 weeks. In a 26-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter study, Pigott et al compared 15-mg, fixed dose, once-daily dose of aripiprazole with placebo in 310 patients with chronic stable schizophrenia as defined by the Diagnostic and Statistical Manual of Mental Disorders-IV. Of the 155 patients in each treatment group, 50 patients (34%) taking aripiprazole experienced relapse (relative risk, 0.59; \( P < .001 \)) as compared with 85 patients (57%) taking placebo. In a 52-week, randomized, double-blind, multicenter study, Kasper et al investigated the efficacy and safety of aripiprazole versus haloperidol in 1294 patients. Aripiprazole demonstrated comparable efficacy to haloperidol across all symptoms measures, including significantly greater improvements in PANSS negative subscale scores and Montgomery Asberg Depression Rating Scale total score (\( P < .05 \)). The time to discontinuation due to any reason and due to adverse events or lack of efficacy were significantly greater with aripiprazole as compared with haloperidol (\( P = .0001 \) for both).

These findings suggest that fewer adverse effects are associated with aripiprazole, resulting in increased adherence to the medication regimen. At the same time, efficacy is shown to be sustained long term over the course of 52 weeks, with significant improvements in both positive and negative symptoms. Perhaps more importantly, a statistically significant and marked separation occurred between the haloperidol and aripiprazole study arms with regard to control of negative symptoms (Figure 1). As shown in clinical practice, the conventional antipsychotics have not worked adequately to relieve negative symptoms of psychosis, and negative symptoms are more difficult and take longer to treat. The atypical agents represent an opportunity to treat negative symptoms effectively, allowing for improved psychosocial functioning in patients.

**Efficacy Versus Effectiveness**

Studies of long-term efficacy influence daily decisions in clinical practices. But the gap existing between the outcomes demonstrated in clinical trials and those experienced in the real world of clinical care must be acknowledged. In the research setting assessments are precise, and patient samples are selected using rigorous inclusion/exclusion criteria. But the clinical world does not mirror the research setting. Dosing is highly variable, and concomitant medication use is likely. Clinicians are faced with the paradigm of clinical trial

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**Figure 1. Aripiprazole 52-Week Study: Mean Change from Baseline in PANSS Negative Score**

![Graph showing mean change in PANSS negative score over weeks](image_url)

- **Aripiprazole 30 mg** (\( n = 853 \); baseline = 24.7)
- **Haloperidol 10 mg** (\( n = 430 \); baseline = 24.7)

\( *P < .05 \); LOCF analysis.

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* \( P < .05 \) between treatment groups; last observation carried forward.
Baseline scores: aripiprazole, 24.7 \( (n = 853) \); haloperidol, 24.7 \( (n = 430) \). 
PANSS = Positive and Negative Syndrome Scale; LOCF = last observation carried forward.
efficacy data as compared with the real-world experience of drug effectiveness. Research on real-world effectiveness is key to understanding the appropriate approach to antipsychotic therapy, and more research is needed in this area.

Cognition involves perception, awareness, and judgment needed for the brain to process information effectively. This cognitive process is impaired in people with schizophrenia due to problems with the brain’s neurotransmitters, which prevent organization of sensory input into appropriate behavioral responses. Problems with attention, memory, learning, interpretation, and organization of sensory input result in impaired behavioral responses. Psychiatric nurses must frequently assess symptoms of cognitive dysfunction, such as impaired memory, distractibility, speech problems, and delusions (see Sidebar) and may rely on the Mini-Mental Status Examination (MMSE) tool. However, the Neurobehavioral Cognitive Status Examination (NCSE; see Appendix) assesses a broader range of cognitive function than the MMSE, is brief enough to be administered in clinical settings, and has been shown to be more sensitive (86%) than the MMSE (3%) when traditional cutoff criteria for impairment were used (raw score <23 on the MMSE and 1 or more impaired scales on the NCSE). The NCSE uses independent tests to evaluate function in 5 major cognitive ability areas: language, constructions, memory, calculations, and reasoning. The examination separately assesses level of consciousness, orientation, and attention. While the NCSE quickly identifies intact areas of functioning, it also provides more detailed assessment in areas of dysfunction.

The value of assessing cognitive function in nursing cannot be overstressed, as these symptoms profoundly affect community functioning and the ability of patients to lead lives they feel are of value (Figure 2). Patients want to return to work and have a sense of purpose, but neurocognitive symptoms prevent patients from realizing these fundamental needs and are significant in terms of long-term functioning.

Some research indicates that the newer antipsychotic agents have somewhat beneficial cognitive effects as compared with standard (US) doses of conventional agents; other research contradicts these findings, reporting mixed results regarding the cognitive effects of the newer antipsychotic agents.

Why is the research not more definitive? Part of the problem is the lack of a uniform standard for measuring outcomes for cognitive improvement—the same problem that once confounded researchers studying Alzheimer’s disease. Other factors that cloud research findings include variations in concomitant medications, side effects, and dosing, making it difficult to compare patients across all these spectrums. Finally, inaccurate diagnosis is a persistent problem, as many
of the negative symptoms of schizophrenia also appear in bipolar disorder and other forms of mania; psychosis, one of the major symptoms of schizophrenia, affects up to 80% of manic patients. Nurses who work with veterans of war are especially aware that many patients in this population who suffered from hallucinations and other symptoms of post-traumatic stress syndrome may have received an inaccurate diagnosis of schizophrenia.

Recent studies have attempted to modify study design to overcome issues that have skewed reporting in previous clinical trials. Cornblatt and colleagues compared aripiprazole 30 mg daily with olanzapine 10 mg and 15 mg daily in a 26-week open-label study of patients with schizophrenia or schizoaffective disorder (n = 255). Patients were taking a stable dose of either risperidone or quetiapine for at least 1 month prior to enrollment and had not been hospitalized for at least 2 months. Although there was no statistical difference between the aripiprazole and olanzapine groups in symptoms, as evidenced by PANSS scores, there were observed differences in cognition. Over 8 weeks, the best improvement and most significant results were found in patients’ general overall cognitive function, with little difference between the antipsychotic agents.

Verbal learning assessment both within clinical practice and clinical trial analyses is very important. Verbal learning involves the ability to acquire, store, and retrieve verbal information for more than a few minutes. Naturally, this ability affects many areas, such as the information nurses give patients regarding medications and the likelihood of patients following those instructions. Verbal learning affects important activities required in daily living as well as the success of treatment plans. Remembering information from a rehabilitation program, class, vocational setting, and clinic visit are all essential to patient outcome. Thus, patients’ verbal learning abilities profoundly affect the clinician’s ability to care for them, making assessment of neurocognition and subcomponents of cognition essential to clinical practice. Clinicians now have access to potent new therapies, and continuing research into the possibilities of new antipsychotic agents targeting glutamate receptors will likely yield additional therapeutic gains. Only if these functions are adequately assessed, however, can the clinician identify the gains and the lapses patients are experiencing in their everyday lives.
CLINICAL IMPLICATIONS

Problems with cognition and verbal expression profoundly affect the nursing treatment plan and must be addressed in order to enhance recovery and to prevent relapse. Recommendations for assessing cognitive function and nursing interventions to help patients overcome such limitations can be found in the Sidebars.

REFERENCES


NURSING INTERVENTIONS TO PREVENT RELAPSE

- Identify symptoms that signal relapse
- Identify symptom triggers
- Select symptom management techniques
- Identify coping strategies for symptom triggers
- Identify support system for future relapse
- Document action plan in writing and file with key support people
- Facilitate integration into family and community