The child of a mother age 28 years and father age 52 years, the patient was born at term and had normal APGAR (Appearance [color], Pulse [heartbeat], Grimace [reflex], Activity [muscle tone], and Respiration [breathing]) scores. During the pregnancy his mother had not experienced any infections or other medical difficulties. The patient was noted to have developmental delays and did not walk until age 2 years. His first word was at age 1 year, and he did not speak in sentences until age 2 1/2 years. Although he spent his earlier school years in special education classes, much academic support enabled him to graduate high school. Socially withdrawn and able only to maintain 1 or 2 friendships, he enjoyed playing primarily by himself and was noted at times to be “lost in his own world.” The patient was age 16 years when his father died and felt very upset about this loss, as his father had been a major support for him. At this time the patient began to experience intermittent auditory hallucinations and was noted to become more withdrawn. There was no family history of schizophrenia or other psychiatric disorder.

CLINICAL COURSE

While in the hospital, the patient was treated with haloperidol 10 mg twice daily, which resulted in significant improvement in his symptoms. After experiencing parkinsonian symptoms, including stiffness and shuffling gait, he was started on benztropine 1 mg twice daily with effective relief of these side effects. His psychotic symptoms improved considerably, and he was able to return to his apartment. Although the auditory hallucinations continued, they were much less intense, and the patient was able to keep them from interfering with his daily activities. He continued to think that people were talking about him behind his back when he walked down the street, but despite this concern, he was able to go outside.

At the age of 25 years the patient experienced an increase in his symptoms and again developed a fear that people were peering into his apartment. He barricaded himself indoors and made calls to his family saying that if people did not stop bothering him, he would have to retaliate. He was again hospitalized and treated with risperidone 10 mg daily. His symptoms having improved to his baseline level, he was able to be discharged after a 2-week stay. Because he continued to have parkinsonian symptoms on risperidone, the benztropine was continued. As an outpatient, the patient was able to have his medication decreased slowly to 5 mg daily, and the benztropine was stopped. The voices and ideas of reference continued but were intermittent. The patient was able to socialize more,
felt that his thinking was clearer, and could concentrate for longer periods of time. His affect, which had been very restricted on haloperidol, was much wider in range. He developed galactorrhea and some decrease in sexual interest. Although very embarrassed by these symptoms, he was reluctant to switch medications because he felt that the risperidone was helping him and was fearful that other agents would do him harm.

After the patient spent several years on risperidone, his mother became ill and had to be hospitalized briefly. Because she was his major support and he had refused more comprehensive community services, he became increasingly anxious and developed problems sleeping and increased auditory hallucinations. Olanzapine 5 mg was added to his regimen and helped with sleep, but the psychotic symptoms did not improve. Risperidone was tapered, and olanzapine was increased to 30 mg at bedtime. The patient became less anxious and slept well; the auditory hallucinations diminished, and he was able to return to his baseline level of function. However, his weight began to increase, and over the ensuing 6 months he gained 25 pounds. Although there was no family history of diabetes, his fasting glucose was also noted to increase from 100 to 138 mg/dL.

Because of the ongoing symptoms despite several adequate medication trials, the patient was switched to clozapine. Olanzapine was tapered, and clozapine was gradually increased to a dose of 400 mg over a period of 2 months. Although the dose could not be increased further because of fatigue and increased salivation, the patient experienced significant improvement in his symptoms. After 6 months on the medication he was much less paranoid and his auditory hallucinations diminished significantly and were heard only on occasion. His motivation increased, and he began more actively to initiate social contacts. Throughout the trial his weekly white blood cell counts remained stable, but he gained 25 additional pounds and his fasting glucose rose to 175 mg/dL. Because of the ongoing side effects, quetiapine was added to the clozapine and titrated up to 300 mg. The clozapine dose was reduced to 275 mg with no decrease in clinical efficacy. The quetiapine could not be increased further because of an increase in fatigue. On the combined regimen, the patient’s appetite decreased; he lost 20 pounds, and his fasting glucose decreased to 140 mg/dL.

**DISCUSSION**

This patient has a history of chronic schizophrenia that has been partially responsive to multiple medication trials of adequate duration and dose. His various positive symptoms included derogatory auditory hallucinations and multiple paranoid delusions. He also manifested multiple negative symptoms, including social withdrawal, difficulty socializing and making friends, and low motivation and interest. Although there was no family history of schizophrenia or birth difficulties, his father was 52 years old when the patient was born, and there is an association between advanced paternal age and schizophrenia. Along with social withdrawal and isolation, the presence of developmental delays is frequently seen in individuals similar to this patient who later develop the illness.

Haloperidol primarily improved the patient’s positive symptoms. Parkinsonian motor symptoms of stiffness and shuffling gait were relieved by the addition of benztropine. This agent may produce multiple anticholinergic side effects, including dry mouth, blurred vision, and constipation and may cause cognitive difficulties because cholinergic transmission is a central neurotransmitter involved in learning and memory.

In an individual already burdened with cognitive impairment, this may produce further decline.

The switch to the atypical agent risperidone resulted in overall improvement. At the relatively high 10-mg dose of risperidone, benztropine was still required and was later stopped after the risperidone was decreased to 5 mg. Compared to the other atypical agents, risperidone is associated with increased extrapyramidal side effects that may be present even at lower doses. The galactorrhea and diminished sexual interest experienced by the patient are symptoms related to prolactin increases that are also associated with risperidone. Compared to the other atypical agents, risperidone is associated with the highest incidence of prolactin increase, a side effect that may be alleviated by switching medications.

Several of the patient’s negative symptoms improved after the switch from haloperidol to risperidone. He began to socialize more and experienced increased clarity of thinking, in addition to a fuller range of affect. Several but not all studies have shown improvement in negative symptoms on atypical compared to typical agents. The improvement in restricted affect noted with the switch to risperidone may have been amelioration of a primary negative symptom or secondary to decreased extrapyramidal symptoms on the lower dose of risperidone. Haloperidol also may result in cognitive slowing and social withdrawal that can mimic negative symptoms. In this
case, they were present premorbidly and clearly improved with the switch to an atypical agent.

The addition of 5 mg of olanzapine to risperidone was helpful in controlling sleep. Atypical neuroleptics are frequently used in combination, an effective clinical strategy if applied judiciously. In this case, the sedating properties of olanzapine were clinically helpful. When olanzapine was increased to 30 mg and the risperidone was stopped, a weight gain of 25 pounds occurred, as did hyperglycemia. With respect to these side effects, olanzapine and clozapine impose the highest burden. Quetiapine and risperidone have intermediate effects on weight and glucose metabolism, whereas ziprasidone and aripiprazole exert the least effect on these parameters.10-11

As the only atypical agent approved for the treatment of treatment-resistant schizophrenia,12 clozapine was helpful monotherapy in this patient, as positive and negative symptoms improved. Serious side effects, such as agranulocytosis, require close monitoring and limit the general use of the medication, the health risks of which are increased by the high rate of weight gain and tendency to induce glucose regulation. Augmentation with quetiapine, a medication less likely to cause these difficulties, allowed for reduction of the clozapine dose and moderation of the weight gain and glucose elevation.13 However, the values did not return to pretreatment levels.

Although significant partial treatment success was achieved with these atypical agents, aripiprazole or ziprasidone should also be considered as adjunctive or first-line agents for several reasons.14 Both of the drugs possess unique neurochemical profiles that result in differing clinical and side-effect profiles. Some but not all studies have shown improvement compared to other atypical agents in positive and negative symptoms.

REFERENCES