Medical Complications and Selectivity of Therapeutic Response to Atypical Antipsychotic Drugs

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Although conventional antipsychotic drugs are clearly a boon to the treatment of psychotic illnesses, their limitations are well-known. As many as two-thirds of patients with schizophrenia will have only a partial symptom response and will be left to cope with residual symptoms. The advent of clozapine offered new hope for many such treatment-resistant patients because of its superior clinical efficacy compared with conventional antipsychotics. Numerous studies have demonstrated that clozapine offers some treatment-resistant patients remarkable improvement in positive symptoms such as hallucinations and delusions (1). In addition, patients who are unable to tolerate drug-induced extrapyramidal side effects, such as parkinsonism and akathisia, or who develop tardive dyskinesia respond very well and do not experience extrapyramidal side effects with clozapine (1–3). Negative symptoms, including decreased experience and expression of emotions, poor motivation and initiation of activities, and decreased social drive, may also improve with clozapine treatment (1). Improvement in negative symptoms may represent resolution of secondary negative symptoms, as with the apathy and akinesia resulting from antipsychotic-induced parkinsonism, or with increased social drive resulting from improved psychosis. The extent to which clozapine improves negative symptoms primary to schizophrenia remains controversial (4, 5).

The basis for the superior efficacy of clozapine is unknown. Clozapine has a remarkably broad pharmacological profile, with affinity for multiple neuroreceptor subtypes in the central nervous system (6). There is tremendous interest in understanding the pharmacological properties that confer clozapine's unique clinical profile and superior efficacy. At the same time clozapine's novel multireceptor antagonist profile is a "double-edged sword," in that it also produces an array of unpleasant and potentially life-threatening adverse effects (7, 8).

In the wake of clozapine have come numerous putative atypical antipsychotic drugs. Risperidone, olanzapine, and, most recently, quetiapine have been approved by the Food and Drug Administration (FDA) and are currently in clinical use. Others, including sertindole and ziprasidone, are expected to follow suit. At present there is little information on the comparative efficacy and safety of the atypical antipsychotics. Pending results of head-to-head comparisons in controlled clinical trials, reports of individual patients undergoing sequential treatment may be informative. Here we present the case of a patient that typifies clozapine's superior clinical efficacy, lack of extrapyramidal side effects, troublesome and potentially life-threatening adverse effects, and comparative effects to typical antipsychotics and to a putative atypical compound, sertindole.

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CASE PRESENTATION

Initial History

Mr. A was a 36-year-old single white man with schizophrenia who presented 10 years earlier, at age 26, with a 5-month history of auditory and visual hallucinations, delusions (bizarre and grandiose themes, thought insertion, thought control, thought broadcasting), disorganized behavior, and loose associations. At the point of initial hospitalization his symptoms were severe; he was preoccupied with his delusional beliefs, auditory hallucinations occurred almost constantly and were difficult for him to ignore, and the cognitive and behavioral disorganization made function outside of a hospital impossible. Before the onset of psychotic symptoms, he had a 2-year history of declining ability to work and care for himself.

Mr. A had good psychosocial function before the onset of illness. He graduated from high school, completed several community college courses, and lived independently, supporting himself through employment. He had friends and dated regularly.

Following hospital admission a medical workup, including computerized tomography of the head, EEG, and laboratory studies including CBC, urinalysis, electrolytes, creatine, liver enzymes, thyrotropin, T_4, vitamins B_{12} and folate, VDRL, and toxicology screen, failed to demonstrate a neuromedical cause for his symptoms.

Mr. A received a series of trials with typical antipsychotics and subsequent adjunctive mood stabilizers, with uniformly unsatisfactory results due to both poor clinical response and adverse effects. The initial pharmacotherapy included fluphenazine, 10 mg/day, and benztropine, 2 mg b.i.d. Lithium carbonate, 300 mg t.i.d. (blood level=0.9 meq/liter), was added at week 4 of treatment to target agitated behavior and aggressive outbursts. He was discharged after 2 months with a partial symptom response. Residual symptoms included mild thought disorganization, rare auditory hallucinations (lasting 1–2 hours, several times a week), continued belief in previous well-organized delusions (but no active ideas of reference, thought broadcasting, or other new delusions), and moderate extrapyramidal side effects.

Despite Mr. A's regular attendance at a day treatment program and adherence to the prescribed pharmacotherapy, his symptoms waxed and waned after discharge and significantly impaired his function. A trial of a second antipsychotic medication, haloperidol, 10 mg/day, was attempted with the

hope of better symptom response. Psychosis persisted, and he continued to experience poorly tolerated extrapyramidal side effects (akathisia, feeling like a "zombie," and parkinsonian syndrome) that were only partially controlled with benztropine, 2 mg t.i.d. After a few months he became intermittently compliant with antipsychotic medication, finally stopping all medications after 6 months because of poor symptom response, motor stiffness, and "feeling like a zombie all the time." He also quit day treatment. Over the next 5 months he became increasingly preoccupied with his well-organized delusional beliefs and experienced frequent ideas of reference and suspiciousness. The frequency and intensity of auditory hallucinations increased, as did the severity of his cognitive and behavioral disorganization. He required rehospitalization. He received haloperidol, 10 mg/day, augmented with valproic acid, 250 t.i.d. (blood level=81 μg/ml). Level of preoccupation with delusions, frequency of hallucinations, and disorganization improved minimally, and on discharge he immediately stopped all medications again because of poor symptom response and poorly tolerated adverse effects. Three weeks after he was discharged Mr. A's psychotic symptoms worsened and he required rehospitalization, whereupon he was given a trial of thiothixene, 10 mg b.i.d., for 4 weeks, with no change in psychotic symptoms and poorly tolerated extrapyramidal side effects.

The patient's lack of insight into the nature of his psychiatric illness, disorganization, and poor tolerance of adverse effects of antipsychotic medication contributed to his ambivalence about taking antipsychotic medication. Because of inconsistent compliance and poor response, a trial of a parenteral medication (fluphenazine decanoate, 12.5 mg administered intramuscularly, every 3 weeks) was given. He was discharged after a 10-week hospitalization and continued with fluphenazine decanoate at the same dose for the next 18 months. He had a partial reduction in his severity of psychosis, with continued belief in well-organized delusions, hallucinations that occurred for 1–2 hours several times each week, and mild disorganization. Throughout his treatment he experienced poorly tolerated extrapyramidal side effects despite treatment with an anticholinergic agent (benztropine). After 18 months of outpatient treatment he again stopped pharmacotherapy. Over the next 7 months the intensity of his psychotic symptoms worsened, again requiring hospitalization. At this time, 4 years after his initial treatment contact, clozapine treatment was considered.

Comment

Mr. A had an unusually poor response to conventional antipsychotic medications even in his initial antipsychotic treatment trial. This is in contrast to the majority of patients, who will have total or near total resolution of positive symptoms with the first antipsychotic treatment trial (9). Longer duration of untreated psychotic and prodromal symptoms is a strong predictor of poor initial treatment response (10). First-episode studies in the United States suggest that average duration of untreated psychosis before first treatment contact is from 1 to 2 years; thus, Mr. A's 8-month tenure as an untreated patient is not unusually long. While poor premorbid function is also associated with poor treatment response, Mr. A had good premorbid function. Two factors associated with poor treatment response that the patient had included male gender and susceptibility to extrapyramidal side effects.

Inconsistent compliance with medication may lead to poor treatment response. Studies suggest that repeated exacerbations of psychotic symptoms are associated with more severe and treatment-nonresponsive symptoms (11). This ultimately may have contributed to Mr. A's declining clinical course. Patients may be ambivalent about or unwilling to take medications because they perceive that the medications offer little benefit and that the adverse effects outweigh any benefits, or they may have difficulty complying with the medication regimen because of poor organizational abilities. As is true for many patients with schizophrenia, Mr. A had limited insight that he had a mental illness, and he did not perceive any benefit from the various medications beyond an idea that the medications "helped [him] keep out of the hospital." In addition, he suffered unpleasant extrapyramidal side effects, including a dysphoric response to the medication (12) (feeling like a zombie), that he was unwilling to tolerate long-term. Finally, Mr. A was disorganized secondary to schizophrenia, and it was difficult for him to remember to consistently take medications.

The strategies used to deal with poor symptom response in this patient included adjunctive treatment with mood stabilizers. In addition, medications from several different classes were tried, at therapeutic doses. Decanoate injections were also employed in the hope of maintaining consistent medication use in this poorly organized patient, who was also ambivalent about chronic antipsychotic treatment. While blood levels were not determined, the presence of significant extrapyramidal side effects argues against rapid metabolism of medications and resultant low blood levels as a reason for his poor treatment response. It is important to note that Mr. A responded poorly to all treatments administered, but his sensitivity to and intolerance of adverse effects limited the doses that he received.

Initial Clozapine Trial

A clozapine trial was indicated because of Mr. A's poor clinical response and poorly tolerated extrapyramidal side effects. A complete medical history, review of systems, and physical examination revealed no significant current or past medical problems. Family history was significant only for cancer in one brother; there was no family history of cardiovascular disease. The initial clozapine dose was 25 mg/day, and it was increased gradually over 14 days to a total of 200 mg daily, divided every 8 hours (25 mg/50 mg/125 mg). He showed a marked clinical response, with significant improvement in organization, and dramatic reduction in the severity of delusions (belief in past well-organized delusional system but no active delusions) and hallucinations (rare transient auditory hallucinations) by the second week of treatment. For the first time in the past 4 years of treatment of his illness, Mr. A actively participated in unit activities and was well-groomed and appropriately dressed without staff prompting.

Mr. A experienced serious adverse effects to clozapine. These included significant sedation that worsened with dose increases, eventually leading to increased sleep from his usual 8 hours per day to more than 12 hours per day, and complaints of daytime drowsiness. He had a low-grade fever on days 15 and 16 of treatment (to 39°C). He experienced tachycardia (heart rate to 124 bpm) and hypotension (systolic blood pressure=80 mm Hg, diastolic=60 mm Hg), beginning with low doses of clozapine (50 mg/day) and occurring at dose increases. On day 16 of the clozapine trial, at a daily dose of 200 mg, he complained of an episode of chest pain. Later that evening he complained of a second episode of chest pain, pain radiating down his left arm, and syncope. ECG revealed sinus tachycardia (heart rate of 113 bpm), and T wave inversions in leads I, II, and V4–V6. Laboratory study results confirmed a subendocardial myocardial infarction, with an elevated total creatine kinase level (221 U/liter, normal=61–200 U/liter) and creatine kinase-myocardial band (24.7 ng/ml, normal=<3.5 ng/ml). Clozapine was discontinued, Mr. A's clinical condition was stabilized, and he was transferred to cardiac intensive care. Stress thallium studies revealed a fixed anterior apical defect. Cardiac catheterization and angioplasty studies revealed mild anterior wall hypokinesia and no focal hemodynamically significant lesions. He had normal ventricular function, with an ejection fraction of 77%. Coronary arteriography revealed normal coronary arteries. Lipid profile revealed a cholesterol level of 150 mg/dl. At the time he had a normal body weight for his height (150 lb., 5 feet 7 inches) and had no other serious medical illnesses. Thus, he

had no apparent risk factors for myocardial infarction except for clozapine treatment.

Comment

Mr. A had a very good clinical response to his brief trial of clozapine, with improvement in hallucinations, delusions, organization, and ability to function. Several well-designed studies have shown that up to 60% of treatment-resistant patients will have significant clinical improvement with clozapine (1, 3, 7), making clozapine an appropriate treatment for patients with incomplete symptom resolution with other antipsychotic medications.

Mr. A experienced common troublesome side effects, as well as a less common life-threatening side effect, associated with clozapine treatment (8). Sedation, probably due to histamine and noradrenergic receptor blockade, occurs in up to 70% of clozapine-treated patients. Low-grade fever may occur in 10% of patients during initial stages of treatment.

Cardiovascular adverse effects occur in one-third of clozapine-treated patients, usually are mild, and may resolve over time. The adverse effects include sinus tachycardia and hypotension induced by anticholinergic and antiadrenergic effects. In one of 3,000 clozapine-treated patients, sinus tachycardia may be severe and lead to respiratory or cardiac arrest (13). In addition, the strong α-adrenergic antagonism that occurs with clozapine treatment may cause orthostatic hypotension, reflex tachycardia, and syncope if it is severe. Clozapine must be initiated at low doses and titrated as tolerated, primarily because of the cardiovascular effects. The myocardial infarction that Mr. A suffered was most likely secondary to the cardiovascular effects of clozapine. Mr. A was a young man with an enviable lipid profile and with no risk factors for cardiovascular disease. Cardiac catheterization revealed no significant atherosclerotic coronary artery disease.

Because of the potential cardiovascular adverse effects of clozapine, patients should be evaluated for preexisting cardiovascular disease before initiating treatment. Screening evaluation should routinely include personal and family medical history, review of systems, and physical examination, including orthostatic blood pressure. In patients with identified cardiovascular disease risk factors (e.g., personal or family history of heart disease, hypertension, diabetes, smoking; family history of cardiovascular disease; age greater than 45 years) a pretreatment ECG may be warranted. Careful monitoring is needed for patients with preexisting cardiovascular disease, and severe heart disease is a relative contraindication to clozapine treatment.

Return to Typical Antipsychotics

As Mr. A was medically stabilized he experienced worsening of symptoms, to the severity that he had experienced before clozapine treatment. He was treated with haloperidol, 10 mg/day, which was again poorly tolerated because of extrapyramidal side effects (motor stiffness, emotional dulling, decreased facial expressions, feeling like a zombie, a perioral "rabbit" tremor, and akathisia) that minimally responded to benztropine, 1 mg t.i.d., and clonazepam, 1 mg t.i.d. Psychosocial treatment included weekly supportive individual and group psychotherapy, integrated with case management services. The focus of these therapies was maintaining medication compliance and improving his quality of life (e.g., housing, recreational activities, social skills). While the severity of symptoms decreased with haloperidol, Mr. A continued to believe in his well-organized delusions, experience auditory hallucinations several times a week, and need considerable structure in a group home setting to maintain activities of daily living.

Comment

Four years after the onset of illness, Mr. A accepted treatment on an outpatient basis, becoming consistently compliant with therapy. Treatment with haloperidol resulted in partial improvement in psychosis; continued symptoms, including negative symptoms secondary to extrapyramidal side effects, hindered his ability to function. Gradually declining psychosocial function required increasing levels of outpatient support in order to maintain Mr. A in the community. Adverse effects of haloperidol, while accepted by the patient, interfered with his quality of life. A similar illness course is all too common for patients with schizophrenia, with disabling residual symptoms and medication adverse effects both contributing to poor functioning and impaired quality of life.

Trial With Sertindole

Sertindole (14), a putative atypical antipsychotic drug with predominantly dopamine 2 (D_2) and serotonin (5-HT_2) receptor affinity, which is currently under review by the FDA for the treatment of psychosis, became available to Mr. A as part of an open-label phase II safety study. After providing written informed consent, Mr. A began a trial of sertindole. The initial dose was titrated to 16 mg/day, with clinically significant improvement in thought process organization, delusions, and hallucinations. He tolerated the sertindole well. Motor stiffness, feeling like a zombie, apathy, blunted affect, tremor, and akathisia resolved over the next 4 months. Mr. A denied any side effects with sertindole. However, he became intermittently noncompliant with medication as an outpatient and developed increasing thought process disorganization and began again to act on delusional ideas. Eventually he was admitted to the hospital for 2 weeks. The sertindole was increased to 24 mg/day, which was tolerated without adverse effects, and his thought process disorganization and delusions improved. After discharge he again became intermittently noncompliant with treatment, primarily because of poor insight into illness, and outpatient therapy focused on maintaining consistent medication compliance. Seven months into the sertindole trial, Mr. A informed his case manager that he had "forgotten" to take his medication for the week and, not wanting to disappoint his therapist by coming to his appointment with his weekly medication box full, took all of the sertindole for that week (168 mg) before coming to the clinic. He received emergency treatment for overdose, with ECG monitoring, emesis, and charcoal lavage. No pill fragments were recovered. He experienced no adverse events from the sertindole overdose. Serial ECGs revealed a minimally and asymptomatically prolonged corrected QT interval (504 msec, upper limit of normal=500 msec). Mr. A was transferred from the emergency room to the inpatient psychiatric unit for further management.

Comment

The new generation of antipsychotics, dubbed "atypical" primarily because of clinical efficacy at doses that do not cause extrapyramidal side effects, offer promise to many patients with chronic psychotic disorder. Sertindole has a high affinity for D_2, 5-HT_{2A}, 5-HT_{2C}, and α-adrenergic (α1 and α2) receptors. In a multicenter clinical trial (14), both positive and negative symptoms significantly improved with sertindole treatment (dose of 20–24 mg/day), compared with placebo treatment. Sertindole's efficacy was equal to that of haloperidol (8 and 16 mg/day). Clinical adverse effects of sertindole include nasal congestion, decreased ejaculatory volume, orthostatic hypotension, and reflex tachycardia (requiring dose titration). ECG studies revealed a small but statistically significant increase in the corrected QT interval with sertindole treatment, not associated with clinical symptoms (e.g., ar-

rhythmias). Extrapyramidal side effects were not seen in sertindole-treated patients. Sertindole thus joins risperidone and olanzapine as an effective treatment for psychosis with low risk of extrapyramidal side effects and related secondary negative symptoms and with minimal side effects.

Mr. A was a good candidate for sertindole treatment because of his marked intolerance for the side effects of the typical agents, especially extrapyramidal side effects. A consulting cardiologist judged the subendocardial myocardial infarction that he experienced while taking clozapine to not be a contraindication for sertindole, given his negligible cardiac damage. He tolerated sertindole overdose without medical complications. Significantly prolonged QT interval is a risk factor for a ventricular tachyarrhythmia—torsade de pointes; Mr. A did not develop arrhythmias with his overdose.

It is not known whether sertindole will offer improved efficacy for positive symptoms compared to conventional agents. With sertindole, Mr. A had a partial response with positive symptoms and marked improvement in negative symptoms. He did not have the deficit syndrome; thus, the improvement in negative symptoms was presumably due to a resolution of secondary negative symptoms that had resulted from extrapyramidal side effects. Residual motor stiffness and tremor from his previous treatment gradually resolved over a 4-month period.

Return to Clozapine

Because of the overdose, it was determined that Mr. A was no longer a candidate for the sertindole study. Mr. A's past excellent pharmacological treatment response warranted reconsideration of a clozapine trial. The decision for a second trial of clozapine, in the face of a life-threatening adverse event during the first trial, was carefully made. Pretreatment cardiac consultation advised that the patient's cardiovascular status was stable, with no residual effects from the previous myocardial infarction; he had no cardiovascular contraindications to clozapine. The risks and benefits of clozapine treatment were carefully reviewed with the patient and his close family members, including the risk of a myocardial infarction or other serious, life-threatening adverse outcomes. Also discussed were measures to be taken to minimize risks of adverse effects, particularly the need for inpatient monitoring of his vital signs, ECG, and clinical condition. Clozapine titration was slow—with a maximum increase of 12.5 mg/day. If he experienced tachycardia or orthostatic changes, the clozapine dose was held until these resolved. He tolerated clozapine well, without any cardiovascular adverse effects. The dose was titrated to 300 mg/day, divided into three daily doses. Positive symptoms began to lessen by the second week of treatment. Mr. A showed gradual symptom reduction and functional improvement over the next year and a half of clozapine treatment. Hallucinations completely resolved by the fourth month of treatment. By month 8 he no longer was acting on delusional ideas. Probing revealed that he continued to believe that past delusional events had occurred but no longer considered these beliefs relevant to his current life. While his organizational ability, including ability to manage personal affairs, was impaired, it continued to show gradual improvement 2 years into the clozapine trial.

On discharge from the hospital, Mr. A lived in a group home setting, with careful medication monitoring. He continued to participate in weekly rehabilitative and supportive therapies. In these therapies he was encouraged to take gradual steps toward independence, resulting in improved psychosocial function. Mr. A's functional improvement was considerable, and he was able to work part-time, maintain friendships, and have good relationships with family. He now lives independently in an apartment.

Initial side effects of clozapine treatment included sedation, which resolved by week 8 of treatment, and weight gain of 40 lb. He complained of hypersalivation. In addition, Mr. A suffered a troublesome and unusual probable adverse effect of clozapine—parotid gland enlargement. By month 6 of clozapine treatment Mr. A began to complain that his cheeks were swollen and tender. He reported that the "swelling came and went." Physical examinations revealed intermittent, diffuse, bilateral enlargement of the submandibular parotid glands, which lasted for several weeks at a time. No focal masses were palpated. He was afebrile, and white blood cell counts were consistently normal. Determination of amylase levels was ordered during a time of symptomatic enlargement, but when blood was drawn the swelling was resolved, and results were normal (60 U/liter). The intermittent swelling occurred during months 3 to 12 of clozapine treatment.

Comment

A second clozapine trial, despite a previous life-threatening adverse event, was clinically indicated after careful weighing of the potential benefits (symptomatic improvement, lack of extrapyramidal side effects), risks (adverse effects including myocardial infarction), and measures to minimize risks (slow titration and careful patient monitoring). Mr. A has had an excellent symptom response to the second trial of clozapine, with symptomatic improvement in the first few weeks of treatment and continued improvement over the next year. His response to clozapine is not unusual. Most patients who respond to clozapine will show some symptom reduction within 6 months of therapy, and maximal response may take 12–18 months to occur (1–3). Individual and group therapies were essential in helping Mr. A achieve the improvements in psychosocial function that the reduction in symptom severity allowed.

Hypersalivation may occur in one-third of clozapine-treated patients (7). This is despite the significant anticholinergic effects that most patients experience with clozapine treatment. A balance of the parasympathetic and sympathetic nervous system regulates salivary gland secretion. Parasympathetic stimulation by means of cholinergic receptors results in increased secretions, whereas sympathetic stimulation, by means of adrenergic receptors, results in decreased secretions. Two possible mechanisms for clozapine-induced hypersalivation have been proposed. Clozapine has a high affinity for all five of the known muscarinic (M) cholinergic receptor subtypes, with antagonism of the M1–M3 and M5 receptor subtypes, which explains the common occurrence of anticholinergic adverse effects in treated patients. Recent reports show that clozapine is an M4 receptor agonist (15), possibly leading to cholinergic stimulation of the salivary gland. Clozapine also has potent adrenergic antagonist activity, and antagonism of salivary gland α-adrenergic receptors may increase salivation (16). Both α-adrenergic and cholinergic agonists have been used to treat clozapine-induced hypersalivation, with limited success.

Benign, transient salivary gland enlargement coincident with clozapine treatment has been described (17). The possible mechanism may be the formation of minuscule calculi due to increased saliva production; these calculi transiently block the release of saliva, causing a backup and swelling of the gland.

CONCLUSIONS

Mr. A experienced an all too common course of schizophrenia, with only a partial improvement in psychotic symptoms, and poor tolerance of typical antipsychotic medication side effects. Atypical drugs offered him (as they have many patients) the prospect of effective and tolerable treatment. As Mr. A's case illustrates, however, these medications are not without their own side effects, which

vary with their related but differential pharmacological properties. As with their adverse effects, the therapeutic efficacy of the atypical drugs may vary. We are just developing a comparative experience with the new atypical antipsychotics that have been developed in the wake of clozapine (6). Indeed, what we are finding is that these compounds, although referred to uniformly as atypical, are far from uniform and have distinctive properties. Mr. A's responses to clozapine and sertindole differed in several important ways. Adverse effect profiles, here the ultimate determinant of the sequence of treatment in his case, differed substantially. In addition, the magnitude of the therapeutic response differed; Mr. A improved more with clozapine. In addition to the substantial reductions in psychosis and secondary negative symptoms that both drugs achieved, Mr. A's lack of insight improved with clozapine. This last feature proved to be decisive, since it was his lack of insight, leading to noncompliance and overdose, that was Mr. A's undoing with sertindole. Indeed, this may be revealing of a pattern of efficacy in which clozapine is the most potent (as well as toxic) of the atypical drugs. However, verification of this hypothesis will require extensive comparative trials of the new atypical antipsychotics and their prototype, clozapine.

As with Mr. A, clozapine offers hope for dramatic symptom improvement, albeit at a potentially high cost. Decisions to use clozapine are based on careful weighing of potential risks, including life-threatening adverse effects (cardiovascular effects, agranulocytosis, seizures), and potential benefits. A clozapine trial should be considered for all patients who have incomplete symptom response with trials of two other antipsychotics. As with Mr. A, many patients will reap substantial clinical rewards from clozapine. Slow titration and careful monitoring will minimize risks to most patients.

The explosion of drug development, in large part sparked by the recognition of clozapine's unique clinical and pharmacological properties, holds hope for the future of the treatment of schizophrenia. Eventually, the specific pharmacological properties that give clozapine its superior efficacy will likely be understood, leading to the development of safer and more effective medications for the treatment of schizophrenia. In the meantime we must learn the comparative differences between clozapine and the new putative atypical compounds in order to use them most judiciously with our patients.

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