Novel Antipsychotic Agents and Their Implications for Forensic Psychiatry

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Recent developments in psychopharmacology have lead to the introduction of several novel antipsychotic agents into clinical practice. As these agents become more commonly encountered, it is essential that forensic psychiatrists have a working knowledge of their efficacy as well as the advantages of their use. This article reviews current literature regarding the clinical efficacy and mechanisms of action of clozapine, risperidone, olanzapine, quetiapine, sertindole, and ziprasidone, with a discussion of their use in forensic psychiatry. Specifically, studies show certain advantages of the novel agents in the treatment of violent patients. Use of these medications may also reduce the risk of civil litigation. The novel antipsychotic agents offer the potential of improved patient care within forensic settings by both expediting judicial processing while providing long-term cost savings. Forensic patients represent an underserved population but must have equal access to new medications as they become available. Familiarity with these issues and the medications themselves will facilitate their use in forensic settings.

Since the time chlorpromazine was first introduced into clinical practice with the work of Delay and Deniker[1] in the early 1950s, traditional neuroleptics have been considered an effective treatment for both the acute and chronic psychoses. However, the traditional antipsychotics have an array of side effects, including akathisia and tardive dyskinesia, which are clinically challenging to manage and may even be associated with potential liability. This is especially highlighted by the fact

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that other safer and possibly more effective options now exist. Given the introduction of this new line of atypical antipsychotics (Table 1), clinicians are faced with a growing number of options for treating patients. It is our contention that in the field of forensic psychiatry there are especially important reasons to be familiar with these new medications and to understand the medicolegal aspects that clinicians face when selecting among the variety of available agents.

Prevalence rates of significant psychiatric disorders among prisoners have been estimated to range from 8 to 19 percent, although many of these inmates receive little mental health care.[2] It has been es-

Table 1
Representative Antipsychotic Agents

Name	FDA Approval (yr)
Clozapine	Yes (1990)
Risperidone	Yes (1993)
Olanzapine	Yes (1996)
Quetiapine	Yes (1997)
Sertindole	Limited availability in Europe
Ziprasidone	Pending

Table 2
Forensic Psychiatric Aspects of the Novel Antipsychotic Agents

1. Treatment of aggression
2. Potential avoidance of malpractice
   Decreased risk of tardive dyskinesia
   Potential of decreased suicide risk
3. Expedited judicial processing
   More rapid competency restoration
   Earlier return to the community with improved symptoms
4. Avoidance of constitutional violations by providing forensic patients with equal access to new treatments
5. Potential for cost savings to state hospitals and judicial systems

timated that the prevalence of psychoses among jail inmates ranges from one to seven percent.[3] An association between serious mental illness and violence has been widely discussed in the literature.[4-6] Persons diagnosed with schizophrenia, especially when poorly treated, have been shown to have an increased incidence of fighting with others, hitting a partner or a child, or using a weapon within a one-year period.[7]

The economic impact of high rates of recidivism, treatment resistance, and medication noncompliance is enormous. For example, schizophrenia alone accounts for 25 percent of hospital bed days and 40 percent of long-term care days in the United States compared with the entire general medical population.[8] Furthermore, it has been suggested that forensic patients with psychotic illnesses may be a subgroup of patients who are more refractory to conventional agents.[9] The risk of dangerous behavior as a result of poorly treated psychotic symptoms highlights the need for improved treatments as a necessity for individuals and society.

The purpose of this article is to profile several of the novel antipsychotic agents and to outline their importance with re-

spect to forensic psychiatry, such as with refractory and potentially violent patients, with those patients involved in the criminal judicial system, and in the context of malpractice issues absent their use (Table 2). In addition, pharmacoeconomic studies are highlighted that reveal overall cost savings with the use of novel antipsychotics. Given the availability of these agents and their potential advantages, this article considers the rights of forensic patients to have access to these promising new medications.

Review of the Novel Antipsychotic Agents

Clozapine Clozapine, initially developed in the 1960s, gained increasing popularity as an effective antipsychotic with no risk of extrapyramidal side effects. In 1975, however, 13 patients on this medication developed agranulocytosis, and 8 of these died.[10] Despite these events, clozapine continued to be used in rare cases with noted success in the treatment of psychosis. The long-term morbidity asso-

ciated with treatment resistance, in tandem with clozapine's reputation of superior efficacy with a unique side effect profile, lead to a multicenter trial of clozapine for only treatment-resistant schizophrenia. This seminal study showed superior response with clozapine (30%) compared with chlorpromazine (4%) in treatment-refractory patients.[11] Other studies corroborated the finding of increased efficacy compared with traditional agents.[12–14] The importance of this development cannot be overestimated. For the first time in 40 years, since the chlorpromazine-like agents had been introduced into clinical practice, there was a drug with greater efficacy and a completely different side effect profile. Based on these promising findings, clozapine became the first atypical antipsychotic agent approved by the Federal Drug Administration (FDA) for use in the United States.

The term atypical derived from the fact that unlike the traditional antipsychotics, clozapine improves psychosis without the risk of extrapyramidal side effects or elevations in prolactin in humans.[15] Although the exact mechanism of action remains unclear, clozapine has effects on a wide range of neurotransmitter systems. Most notably, it has been found to be a relatively weak D2 antagonist (unlike traditional antipsychotics), has high affinity for the D4 receptor, and is a strong antagonist at 5-HT2 receptors.[16] Studies have also that clozapine has effects on noradrenergic transmission as well,[17] which has been hypothesized to be relevant to its superior efficacy.[18]

Since its introduction into clinical use in the United States, clozapine has continued to show promise in the treatment of refractory patients, with rates of response consistent with early studies. Furthermore, the use of clozapine has been associated with improved quality of life, reduction of negative symptoms (possibly secondary to reduction in extrapyramidal symptoms), and mild cognitive improvement. Its use has also broadened as it has been effective in the management of new onset schizophrenia, as well as in treating certain cases of illnesses other than schizophrenia that are commonly seen in forensic populations, including schizoaffective disorder, refractory bipolar disorder, borderline personality disorders, and delusional disorder.

Although it has become a mainstay of treatment, clozapine is limited as a first-line agent. The risk of agranulocytosis, with an incidence of almost one percent[19] necessitates frequent blood monitoring. For many years it was required that patients on this medication in the United States be monitored weekly throughout their treatment. The regulations have recently been amended such that following six months of treatment, a complete blood cell count need only be done every two weeks. However, other side effects complicate its use; these include orthostatic hypotension, tachycardia, sialorrhea, sedation, elevated temperature, weight gain, and a dose-dependent risk of seizures with an increased risk associated with doses of 600 mg/day and higher.[20]

Risperidone The excitement of the response to clozapine inspired further research and lead to the development of several novel antipsychotic agents. The

first of these to gain FDA approval, in 1993, was risperidone. Although it is a novel agent, it is not always considered "atypical" because of its dose-dependent tendency to cause extrapyramidal side effects. However, it has a unique biochemical profile compared with typical neuroleptics and is an effective medication for the treatment of positive psychotic symptoms with some efficacy against negative symptoms.[21]

Like clozapine, risperidone has a complex profile of neurotransmitter action. It has high D2 blocking properties as well as high 5-HT2 blockade.[22] Risperidone is not associated with agranulocytosis and is, in general, well tolerated. Side effects most frequently reported include agitation, insomnia, headache, nausea, and sedation. Doses between 4 and 8 mg appear best tolerated, and doses above 10 mg appear to be associated with extrapyramidal side effects similar to those seen with haloperidol.[23] It has been recommended that risperidone be initiated at low doses, as even doses of two mg and six mg have been associated with dystonic reactions, although less often than is seen with haloperidol.[24] One advantage of risperidone is its availability in liquid form, which became available in 1996. The liquid form may prove helpful in patients suspected of noncompliance or in elderly patients with swallowing difficulties.

Olanzapine This medication, which became available in the United States in the fall of 1996, has become a significant alternative to traditional antipsychotic agents. It is a thienobenzodiazepine with a biochemical profile somewhat in between that of clozapine and risperidone.

Its affinity for D2 and 5-HT2a receptors is higher than that of clozapine but lower than that of risperidone, with affinity for adrenergic sites, along with a high affinity for the M1 muscarinic and H1 histaminergic receptors.[25]

Studies have shown olanzapine at starting doses of 10 mg per day to be more effective than placebo and as effective as haloperidol (10 to 20 mg/day) in ameliorating both positive and negative symptoms in chronic schizophrenic patients.[26, 27] In a large, multicenter trial examining almost 2,000 patients diagnosed with schizophrenia, schizoaffective, and schizophreniform disorder across Europe and North America, olanzapine was associated with overall greater clinical improvement than haloperidol.[28] Although the patients studied were not specifically considered treatment-resistant, the majority had experienced a chronic course of disease. Importantly, for this group of chronically ill patients for whom noncompliance with conventional antipsychotics is often a problem, this study showed that a greater percentage of patients stayed on olanzapine (66.5%) than on haloperidol (46.8%). The higher study completion rates for the olanzapine-treated group was related to overall fewer side effects and greater efficacy for positive, negative, and depressive symptoms.[28] In addition, this medication has the advantage of a long half-life (29 to 55 hours),[29] allowing once daily dosing, as well as being well-tolerated,[30] so that doses may be initiated in the therapeutic range.

With regard to side effects, olanzapine is felt to be a safe, well-tolerated medica-

tion. It is more commonly associated with increased appetite, weight gain, and dry mouth than haloperidol.[27, 28] A careful review of the safety profile of olanzapine also shows it to be associated with transient mild elevations in prolactin level (to a lesser degree than haloperidol), as well as early transient increases in hepatic transminase. There were no clinical symptoms associated with the changes in hepatic enzyme levels. Furthermore, in the international collaborative study, there were no cases of agranulocytosis. Extrapyramidal symptoms were noted to improve with olanzapine, and the incidence of new extrapyramidal symptoms was similar to what is seen with placebo.[26, 27] In addition, rates of treatment-emergent tardive dyskinesia were significantly lower with olanzapine (1%) than with haloperidol (5%).[31]

Quetiapine (ICI-204,636; Seroquel)
Quetiapine, in both clinical and preclinical studies, has shown promise as a novel atypical antipsychotic agent. This drug is the most recent to receive FDA approval, which was granted in the fall of 1997. Preclinical studies have shown quetiapine, a dibenzothiazepine, to have a biochemical profile similar to clozapine. For example, both have low D2 affinity and are more potent 5HT2 antagonists compared with traditional neuroleptics.[32, 33]

Recent literature suggests that quetiapine is more effective than placebo and with comparable efficacy to traditional neuroleptics in the treatment of schizophrenia.[33] For example, in a major multicenter double-blind, placebo-controlled trial of 286 patients diagnosed with schizophrenia, at doses of more than 250 mg daily, quetiapine was shown to be an effective treatment for positive symptoms found in acute exacerbations of schizophrenia.[34] There was less consistency in the treatment response of negative symptoms. Quetiapine showed similar efficacy to haloperidol and superior efficacy to placebo at doses between 150 and 750 mg/day in the treatment of positive symptoms and negative symptoms (at 300 mg/day).[35] In a six-week multicenter double-blind study of schizophrenic patients with acute exacerbations at doses of between 75 and 750 mg/day, quetiapine lead to greater reductions in activation and negative symptoms and slightly greater reduction in total BPRS scores and positive symptom scores than placebo.[36] In another study of 345 inpatients with schizophrenia that compared quetiapine, placebo, and chlorpromazine, quetiapine was effective in treating schizophrenic symptoms, was well-tolerated, and did not differ from placebo in its effect on plasma prolactin level.[37]

These studies show a side effect profile of quetiapine that appears quite favorable compared with conventional antipsychotic medications.[33–36] Although the drug is generally well-tolerated, its use was associated with headache constipation, dyspepsia, and some dizziness, as well as agitation and sedation, in these studies. The incidence of extrapyramidal symptoms appears to be lower than that seen with traditional agents. Laboratory analyses revealed generally asymptomatic transient increases in alanine aminotransferase as well as a dose-dependent decrease in total T4 and free T4 concentrations, neither of which caused clin-

ical symptoms. Hematologic parameters showed no association of quetiapine with agranulocytosis. Also, there were no clinically significant electrocardiogram changes. Future studies will further delineate its efficacy in treating positive and negative symptoms as well as its clinical safety profile.

Sertindole Although it was removed from further FDA testing, sertindole represented the development of an alternative atypical antipsychotic and the need to attend to liability issues in drug development. Similar to risperidone, sertindole has high 5-HT2 and α-1 affinity, a midrange affinity for D2 receptors, and no affinity for muscarinic receptors.[38] Clinical trials of sertindole showed that there is a dose-related amelioration of positive and negative symptoms in schizophrenic patients. Furthermore, it appeared to be an effective antipsychotic agent that was well-tolerated, with doses as high as 20 mg/day showing no increased incidence of extrapyramidal side effects compared with placebo,[39] and was comparable in its antipsychotic efficacy to traditional agents.[40, 41] In a large study examining 497 schizophrenic patients, sertindole at 20 mg/day demonstrated more effect against negative symptoms than placebo.[41]

Side effects most commonly reported in studies[39–42] included insomnia, headache, nasal congestion, and dry mouth, as well as decreased ejaculatory volume with no change in libido. In addition, cardiovascular side effects associated with sertindole include prolongation of QT and Qt$_c$ intervals, tachycardia, and orthostatic hypotension. It was concern

over the effect of sertindole on cardiac conduction that caused the FDA to require more restricted labeling of this medication. Sertindole was withdrawn from marketing in the United States because of this restriction.[43] Sertindole has also been taken off the market in several European countries due to similar concerns.

Ziprasidone Currently under investigation, this medication has been shown to have an *in vitro* 5-HT2a to D2 receptor affinity ratio that is higher than the clinically available novel antipsychotic agents. In addition, it appears to have a high affinity for other subtypes of the 5-HT receptor, including 1A, 1D, and 2C.[44] Because of its high 5-HT2 and D2 blocking properties, it has been compared with risperidone, although its additional high potencies at 5-HT2 receptor subtypes may have added benefit by reducing the likelihood of extrapyramidal effects.[45]

In two studies of the use of ziprasidone in the treatment of acute exacerbations of schizophrenia reviewed by Kerwin and Taylor,[45] ziprasidone was found to be as effective as haloperidol with regard to overall symptom improvement and more effective than placebo, with some evidence of efficacy in the treatment of negative symptoms. The effective doses used in these studies were between 120 and 160 mg/day. This drug has a short half-life, but there is some potential for its use in a parenteral form. Kerwin and Taylor's review highlighted the most common side effects associated with ziprasidone, which are somnolence, headache, and constipation. There was no evidence of a significant effect on hepatic enzymes, plasma prolactin levels, or blood

Table 3
Psychopharmacologic Agents Used in the Treatment of Aggression

Drug Class	Advantages	Disadvantages
Benzodiazepines	Intramuscular availability, fast onset, safe	Potential for paradoxical disinhibition and tolerance
Beta-blockers	Effective for long-term use, generally well-tolerated	Side effects may limit use at high doses; contraindicated with certain medical conditions
Selective serotonin reuptake inhibitors	Clinically safe and well-tolerated, demonstrated efficacy in decreasing violent impulsivity	May cause insomnia and agitation, which can worsen aggression
Mood stabilizers	Anticonvulsants especially effective in patients with EEG abnormalities; effective in aggression associated with mania	Require blood monitoring to follow blood levels
Traditional neuroleptics	Long-acting and acute intramuscular forms available; · rapid onset	Risk of significant side effects including tardive dyskinesia; extrapyramidal side effects may worsen aggression; low-potency agents more difficult to tolerate
Novel antipsychotic agents	Well-tolerated; good safety profile; decreased risk of tardive dyskinesia and extrapyramidal symptoms	Not indicated for acute episodes; long-acting and intramuscular forms not yet available

pressure. Furthermore, extrapyramidal symptoms were infrequent. Given its promising biochemical and clinical profile, ziprasidone is certain to be evaluated additionally in future studies.

Atypical Antipsychotic Agents in Forensic Populations: Putative Use in the Treatment of Aggression

Aggression within forensic populations is often the most difficult symptom to treat. Currently there are a number of classes of agents that have been used in the treatment of aggressive symptomatology, all with advantages and disadvantages (Table 3). It is our contention that the novel antipsychotic agents offer spe-

cific advantages for antiaggression that are worth reviewing for the forensic psychiatrist who may be likely to come across patients with a history of violence and aggression.

When traditional antipsychotic agents are used to treat aggression, patients are exposed to a number of potential side effects, including akathisia.[46] This subjective sense of motor restlessness has itself been associated with aggression in some cases.[47] Because of the difficulty in diagnosing akathisia, clinicians may confuse this side effect with agitation and treat it with even more antipsychotic medication, thus exacerbating the problem. The complicated side effect profile of traditional neuroleptics, as well as our

increased understanding of causes of aggression, have lead to a specific evaluation of the novel antipsychotics as emerging options for the treatment of aggression.

It has been widely reported in the literature that aggression is associated with decreased serotonin. Animal studies have shown an association between decreased brain serotonin and aggressive behavior.[48] In humans, studies have identified decreased levels of serotonin metabolites such as 5-HIAA in impulsive offenders who have attempted suicide,[49] in violent offenders and fire setters,[50] and in recidivistic violent offender groups.[51] In addition, Coccaro et al. [52] identified altered serotonergic function in a study of aggressive persons diagnosed with personality disorders.

Because the novel antipsychotics have antagonistic effects at serotonin receptors, it has been suggested that these medications may have specific antiaggressive effects.[53, 54] It may seem paradoxical that lower central serotonin levels are also associated with increased aggression and serotonin antagonism is associated with decreased aggression. However, clinical studies finding that agents that increase serotonin also cause amelioration of aggression[55, 56] point to the complexity of the neurotransmitter systems involved.

Indeed, several studies examining clozapine have demonstrated specific antiaggressive effects. The use of clozapine was associated with decreased time in seclusion and restraint,[54, 57-60] decreased aggression and hostility,[54, 61-63] and successful transition to less restrictive levels

of movement (Refs. 57, 60, and 61; for a further review of these studies, see Ref. 65).

Of the new agents, clozapine has been the most widely studied and has been used in the United States for the longest period of time. However, there have been recent reports examining the effects of risperidone on aggression in both adults and adolescents.[64-67] In a U.S.-Canadian multicenter study comparing risperidone and haloperidol, risperidone was shown to decrease hostility as measured on a subscale of the Positive and Negative Syndrome Scale (PANSS).[64] In a second study, risperidone and haloperidol were found to be equally effective in reducing time in seclusion and restraint.[65]

With regard to the other novel antipsychotic agents, preliminary data examining olanzapine have shown it to be effective in reducing agitation and hostility.[29] Additionally, a recent case series found at least one patient with a decrease in violent thoughts after treatment with sertindole.[68]

The implications of these findings are enormous. Decreased time in seclusion and restraint is correlated with reduced staffing time and ultimately reduced cost. There is also the advantage of improved safety for staff working with these difficult patients. Of course, patients themselves benefit with decreased time in restraint and medications that are easier to tolerate.

The novel antipsychotic agents, however, are not yet a panacea. There remains the problem of treatment-resistant aggressive symptoms. Also, there is the need to develop medications that are available in long-acting forms, as well as medications

that can be used in acute situations in both oral and intramuscular forms. Nonetheless, the potential benefits already identified with the novel antipsychotic agents will drive future studies to continue to examine the efficacy of the atypical agents on the treatment of aggression and further elucidate the mechanism of action involved.

Liability Issues for Traditional and Atypical Antipsychotic Agents

Obtaining appropriate informed consent, recognizing untoward side effects, and responding appropriately to complications as they emerge defines, in part, reasonable medical care. However, despite a clinician's best efforts, there are a broad range of liability factors associated with potential side effects of psychotropic medications. The risk of liability with regard to tardive dyskinesia, for example, has been discussed widely in the literature.[69, 70] Neuroleptic malignant syndrome presents a potentially fatal consequence associated more commonly with the traditional neuroleptics.[71] On the other hand, given the already increased risk of suicide among schizophrenic patients,[72] there is also the potential for greater liability associated with misdiagnosis and inadequate treatment of psychotic symptoms. Therefore, clinicians are faced with a careful weighing of the risks and benefits of treatment options before prescribing specific medications to patients.

Atypical antipsychotic agents are not without their own risk for complications and, therefore, civil suits. Pre-marketing concerns regarding potential liability and FDA labeling of sertindole exemplify the inherent medicolegal concerns associated with new medications. The possibility of seizures or a potentially fatal agranulocytosis associated with clozapine, as well as possible yet unknown side effects with the less-tried agents, will necessitate a prudent decision-making process when considering all available treatments.

However, as newer antipsychotic agents are developed with fewer significant side effects, clinicians may be at decreased risk of liability with the use of the novel agents. The newer agents have clearly been linked to a lower risk of tardive dyskinesia. In fact, clozapine has been reported to lower the severity of tardive dyskinesia in some patients.[73] Clozapine has also been found to decrease the rate of suicide among schizophrenic patients by one-fourth.[74] While early reports are promising, future studies will determine whether the other novel antipsychotics will offer similar benefits. The potential improvements in quality of life as well as the decreased morbidity and mortality associated with the newer agents create a sound argument that failure to initiate a trial with a novel agent could fall below the current standard of care in the court's eyes.

Cost Considerations for the Novel Antipsychotic Agents

With expanding pressures to minimize costs, there is an increasing trend for chronic public hospitals, local boards, and correctional institutions to limit the use of novel antipsychotic agents, given the

higher cost of the medications themselves. However, this trend does not take into account the findings that total costs (bed days, morbidity, and mortality) are actually reduced with the use of the novel agents.[75, 76] This issue was highlighted in a report of a forensic inpatient who was denied conditional release because concern over increased cost limited the patient's access to clozapine treatment.[77] These circumstances can be avoided if forensic specialists are aware of current data that show overall cost savings with the newer medications (Table 4).

Right to Treatment of Forensic Patients

In the celebrated case of *Osheroff v. Chestnut Lodge*,[87] damages for negligence were sought after a Chestnut Lodge psychiatrist failed to offer biologic treatment for a patient (Osheroff) with a case of severe depression. Instead, the patient was treated for seven months with psychotherapy, which proved ineffective. After protestations from his family, Osheroff was discharged from Chestnut Lodge and was admitted to a second psychiatric hospital where he received a combination of neuroleptic and antidepressant therapy to which he responded after approximately three weeks. The case was settled out of court. This well-publicized lawsuit sparked a heated debate among psychiatric professionals regarding the rights of psychiatric patients to receive psychopharmacologic versus psychotherapeutic treatments.[87–90]

The case also highlighted the need for psychiatrists to appropriately assess and diagnose patients, as well as to discuss with patients their illnesses and possible treatments.[87] Furthermore, although much of the debate centered on defining appropriate patient care, the case demonstrated the importance of utilizing proven means of treating patients. Inherent in doing so is the need to maintain an awareness of options that have demonstrated efficacy through methodologically sound investigations.

Current literature supporting the efficacy of the novel antipsychotic agents implies that the use of these medications will have profound effects at the interface of the judicial and mental health systems. For example, an insanity aquittee with a psychotic illness may not have access to novel medications (because of cost or because of limited awareness on the part of the treating psychiatrist of their efficacy or availability), resulting in inadequately treated symptoms. Therefore, release into the community could be delayed if the very institution to which the person is confined does not provide potentially more effective treatment.

Also, because one measure for newer medications is a greater tolerability along with decreased side effects, there is the hope that their use will lead to improved compliance.[91] The courts are not unfamiliar with the issue of medication refusal. In *Riggins v. Nevada*,[92] for example, the courts related lengthy commentary on the potential "zombie"-like side effects of antipsychotic medication and the potential of these side effects for compromising the defendant's behavior at trial in their consideration of medication refusal of a pretrial defendant. If the new agents lead to improved compliance, long legal battles

Table 4
Representative Pharmacoeconomic Studies of Novel Antipsychotics

Authors	Sample Group	Medications Evaluated	Design	Results/Comments
Meltzer *et al.*, 1993 (78)	Neuroleptic-96 patients resistant schizophrenia	Conventional neuroleptics versus clozapine	Two-year observation before and after clozapine treatment	22% decrease in cost for patients with further decreases noted with continued clozapine compliance
Reid *et al.*, 1994 (79)	311 state hospital patients with chronic schizophrenia	Clozapine versus traditional neuroleptics	Comparison of bed days before and 1.5 to 2.5 years after starting clozapine	Reduction of bed days from 132 to 201 days per year, with greater reductions seen with longer follow-up
Gury *et al.*, 1995 (80)	14 clozapine-treated patients in France	Clozapine treatment versus conventional neuroleptics	Comparison of one-year clozapine treatment with year before clozapine treatment	10% overall cost reduction with clozapine treatment
Rosenheck *et al.*, 1997 (81)	423 refractory schizophrenics at 15 Veterans Affairs medical centers	Clozapine versus haloperidol	Randomized one-year, double-blind comparative study	Clozapine patients had fewer mean days of hospitalization, required more outpatient services. Also, clozapine patients had fewer side effects. Similar overall costs despite cost of clozapine itself.
Addington *et al.*, 1993 (82)	27 patients with chronic schizophrenia	Risperidone compared with conventional neuroleptics	Retrospective analysis of hospital bed day utilization one year prior to and one year after risperidone treatment	20% reduction in hospital bed day use after introduction of risperidone

(Continues)

**Table 4
Continued**

Authors	Sample Group	Medications Evaluated	Design	Results/Comments
Guest et al., 1996 (83)	31 patients with chronic schizophrenia in the United Kingdom	Risperidone compared with treatment with traditional antipsychotics agents; two patients had trials of clozapine	Resource utilization data comparing one year before and two years after risperidone treatment	Significant cost savings with greater cost savings seen with longer treatment; cost savings largely due to decreased hospitalization; decreased side effects also noted
Viale et al., 1997 (84)	139 patients with treatment-refractory schizophrenia or schizoaffective disorder	Risperidone compared with conventional neuroleptics	Inpatient and ambulatory services and outpatient medications measured before and after initiation of risperidone over a 28-month period	Following initiation of risperidone, reduction of 26% days in inpatient facilities and 57% reduction in days in residential treatment; shift of use of resource to lower-cost services; overall comparable total health care costs
Chouinard and Albright, 1997 (85)	130 patients with chronic schizophrenia	Risperidone and haloperidol	Analysis of data from the Canadian multicenter risperidone trial to examine quality of life and cost effectiveness of risperidone	Risperidone-treated patients showed improved quality of life measures as well as overall cost benefits
Glazer and Johnstone, 1997 (86)	817 schizophrenic patients	Olanzapine and haloperidol	Cost comparisons of a randomized double-blind study	Total health care costs were reduced after the first six weeks and one year

paid for by taxpayer dollars may be avoided.

By the same token, given the potential for a greater response with newer medications, especially for patients who have otherwise been found treatment-resistant, the novel antipsychotic agents could have a profound role in both expediting community release and community commitment and even in making competency

restoration possible in what might have previously been considered an unrestorable patient. These advantages to the legal system and society would be in addition to the potential positive impact on individual forensic patients who are offered the chance to try the newer medications.

Limitations on the use of these medications in forensic populations, for any reason, flies in the face of constitutional rights, as a patient caught in the judicial system may not be afforded the same opportunity to receive treatments widely available to civil patients. As more psychotropic medications become available, forensic patients should be allowed trials with the new agents. Forensic psychiatrists, acting as treating clinicians or expert witnesses, must therefore maintain an increased awareness of current treatment options.

Conclusion

Novel antipsychotics such as clozapine, risperidone, olanzapine, quetiapine, and ziprasidone offer promise for patients with psychotic disorders including schizophrenia, with decreased risk for debilitating neurological side effects such as tardive dyskinesia. Forensic clinicians need to have an awareness of the newer agents and an understanding of their efficacy in relation to treatment resistance and violence, as these are problems often seen in forensic settings. Studies have shown specific efficacy of the novel antipsychotic agents in the treatment of violence and aggression.

Use of the new medications may reduce the risk of civil liability by decreas-

ing the risk of suicide and debilitating side effects such as tardive dyskinesia. Furthermore, they may expedite the judicial processing of forensic patients through more effective treatment, while providing long-term cost savings. Finally, forensic patients are at risk of differential treatment if they are not afforded the same opportunity as nonforensic patients to be prescribed these medications.

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