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Abstract

Although antipsychotic drugs have a high therapeutic index (ratio of clinical benefit to adverse effects), they are associated with a range of adverse effects in most patients. The majority of these side effects are tolerable, readily managed, and not life threatening. The most troublesome side effects are neurological. Two new antipsychotics (clozapine and risperidone) have recently been introduced and are the first of a new generation of compounds that may further improve the therapeutic index of routine antipsychotic drug administration. Clozapine clearly has a reduced risk of drug-induced parkinsonism, akathisia, and tardive dyskinesia, while producing an increased risk of agranulocytosis, seizures, and weight gain. Risperidone at low doses produces relatively few parkinsonian side effects, but it can cause tardive dyskinesia (though relative risk remains to be established). Risperidone has not been associated with blood dyscrasias or increased risk of seizures, but weight gain can be a problem for some patients. Neuroleptic malignant syndrome has been reported with both drugs, but relative risk has not been established.

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Antipsychotic drugs overall have a high therapeutic index, that is, the ratio of clinical benefit to adverse effects. Although these drugs do produce some adverse effects in most patients, the majority are tolerable, readily managed, and not life threatening. The most frequent and troublesome adverse effects have generally been neurological—drug-induced parkinsonism, dystonic reactions, akathisia, tardive dyskinesia

(TD), tardive dystonia, and neuroleptic malignant syndrome (NMS). An important feature of the “new generation” of antipsychotic drugs (those recently marketed and those in late stages of development) is their reduced propensity to cause neurological adverse effects.

This article focuses on medical complications associated with clozapine and risperidone. We will focus only on adverse effects that are clinically significant in terms of relative frequency and/or potential seriousness. We will not discuss the therapeutic properties of these drugs, as those have been discussed elsewhere, though in clinical practice potential risks must be considered in the context of potential benefits.

Extrapyramidal Side Effects (EPS)

The low propensity of clozapine to cause EPS has been borne out by many double-blind studies as well as by routine clinical use (Casey 1989). Kane et al. (1988) found significantly lower EPS ratings among clozapine-treated patients at the end of 6 weeks of treatment, even when compared with treatment with chlorpromazine and benztropine. A recent comparison by Gerlach and Peacock (1994) of 100 patients treated with clozapine and 100 patients treated with conventional antipsychotics found tremor in 3 percent and rigidity in none of the patients treated with clozapine, whereas the rates were 11 and 19 percent, respectively, among patients with conventional antipsychotics. Overall, 33 percent of the clozapine

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group showed some signs of parkinsonism compared with 61 percent of the control group. In a study by Kurz et al. (1995), the cumulative incidence rates of various EPS were recorded during the initial 12 weeks of treatment with clozapine ($n = 92$) and haloperidol ($n = 59$). Excluding patients who showed the signs at baseline, the cumulative incidence rates for tremor were 24.4 percent in the clozapine group and 39.3 percent in the haloperidol group; for bradykinesia, 21.8 and 47.7 percent, respectively; and for akathisia, 5.6 and 31.7 percent, respectively.

Some reports (Claghorn et al. 1987; Cohen et al. 1991) suggested that the prevalence rate of akathisia in patients on clozapine may be comparable to that in patients on conventional antipsychotics; however, this may be a carryover effect from the previous treatment, since the rate of akathisia shows a declining pattern during extended treatment with clozapine (Safferman et al. 1993). In patients who have been on clozapine for at least 3 months, the rate of akathisia was 9 percent in 22 patients, while this side effect was observed in 23 percent of 26 patients on conventional antipsychotics (Miller et al. 1996). These findings are consistent with those of Chengappa et al. (1994), who observed a rate of akathisia of 7 percent among 29 patients treated with clozapine. Regarding acute dystonia, there is only one case report with clozapine treatment (Kastrup et al. 1994), in contrast to rates of up to one-third with conventional antipsychotics.

Risperidone's propensity to cause EPS appears to be dose dependent. The European (Peuskens 1995) and U.S. multicenter (Marder and Meibach 1994) studies reported that at doses of 16 mg, the increase from baseline in severity of parkinsonism was com-

parable to the change observed in patients on haloperidol 20 mg, while doses below 12 mg the change increased linearly with dose but remained lower than the observed changes in the haloperidol group. In the Canadian multicenter study (Chouinard et al. 1993), 10 mg of risperidone produced a change in parkinsonism score comparable to the haloperidol group, while the EPS change at 16 mg was not different from placebo. However, in all three studies the rate of patients requiring antiparkinsonism medication rose linearly with increasing doses of risperidone. The European multicenter study found that at all doses the change in akathisia was significantly smaller than that observed for haloperidol. While these data suggest that risperidone has a lower propensity than haloperidol to cause EPS, only the European multicenter study used a dose of haloperidol (10 mg) that was within the range of the different risperidone doses. Both North American studies used 20 mg of haloperidol as the comparator. In three studies with similar doses of risperidone and haloperidol, the overall severity of EPS was not found to be significantly different (Claus et al. 1992; Ceskova and Svestka 1993; Min et al. 1993). However, the use of anticholinergic medication was lower in the risperidone group in the two studies (Claus et al. 1992; Ceskova and Svestka 1993) that provided data. Ceskova and Svestka (1993) also found that risperidone was less likely to cause akathisia.

In conclusion, these data suggest that risperidone shows a linear relationship between dose and occurrence of EPS. Its propensity to cause EPS at doses of 6 mg is probably lower than that of comparable doses of haloperidol, but the available data are less convincing in this regard.

Some patients can clearly show EPS at doses as low as 3 mg. The available data suggest that the propensity to cause akathisia may be less at any given dose compared with haloperidol.

TD

The syndrome of abnormal involuntary movements referred to as TD has been, in many ways, the most serious adverse effect of conventional neuroleptics, though it is rarely immediately life threatening. Given its frequency, its potential for persistence, and the existence of rare cases in which severe disability and suffering can result, the risk of TD has at times been suggested to outweigh the benefits of antipsychotic drugs. Most experts and consensus reports (American Psychiatric Association 1992) have concluded that, when indicated and appropriately used, the benefits of these drugs clearly outweigh the risks. At the same time, TD has been the focus of enormous research efforts and has provided a major impetus to new drug development.

One of the most impressive aspects of clozapine's novel clinical profile is its qualitatively reduced propensity to produce acute EPS such as dystonia and pseudoparkinsonism. There are problems in determining the incidence of TD, particularly with clozapine, that should be acknowledged at the outset. A subset of individuals with schizophrenia may have involuntary movements that were present before the introduction of antipsychotic medications or that may have developed over time without medication treatment. It has been suggested that this is more likely to be the case in patients with poorer prognosis, and these patients are the most likely to be treated with clozapine. In

addition, since clozapine has rarely been used as a first-line drug, clozapine-treated patients have, as a rule, received varying degrees of prior treatment with conventional antipsychotic drugs. Therefore, if patients develop TD after being switched to clozapine, it is difficult to establish it as the causative agent.

With this as background, it is remarkable that only a handful of cases of putative TD have been described in association with clozapine (Kane et al. 1993; Dave 1994). This low incidence suggests that, if TD is associated with clozapine, it is seen significantly less frequently than it is with conventional antipsychotic drug treatment. In fact, clozapine has been shown to be an effective treatment for patients with severe TD or tardive dystonia (Van Putten et al. 1990; Lieberman et al. 1991; Lamberti and Bellnier 1993; Tamminga et al. 1994). The critical question is whether or not the improvement in movement disorders seen after clozapine treatment is a "masking" or a true amelioration. In trials that have attempted to address this issue, it appears to be the latter (Tamminga et al. 1994).

Risperidone's propensity to produce EPS was systematically studied in clinical trials. It is clear that risperidone does cause EPS in a dose-related fashion. At doses of 16 mg/day, risperidone produces EPS at a rate comparable to that of haloperidol at 10 mg/day, but lower than that of haloperidol at 20 mg/day. At doses of 4 or 6 mg/day, risperidone produced significantly fewer EPS than haloperidol at 10 or 20 mg and was not distinguishable from placebo in trials that used placebo controls (Chouinard et al. 1993; Marder and Meibach 1994). The roughly 20 percent incidence of EPS among placebo-treated patients was probably caused by a carryover effect from

previous antipsychotics that the patients had been receiving.

The observation that risperidone at the higher doses does produce EPS (in contrast to clozapine, for which a dose-response relationship is not apparent) supports the possibility that TD may occur in some patients. Indeed a few case reports are now beginning to emerge involving patients who have been treated only or primarily with risperidone or had no evidence of TD before the introduction of risperidone (Addington et al. 1995; Woerner et al., in press).

Whether or not risperidone has reduced the propensity to cause TD compared with conventional antipsychotics remains to be seen, pending further experience with the drug.

Based on a post hoc analysis, Chouinard (1995) reported that patients who had TD upon entering a clinical trial that compared risperidone and haloperidol improved more on risperidone 6 mg/day than they did on haloperidol 20 mg/day. The significance of this finding remains to be seen as longer trials are conducted in patients with preexisting movement disorders.

NMS

We were able to identify seven case reports of NMS associated with clozapine treatment. The first one described a 76-year-old male patient in whom NMS developed after clozapine had been added to carbamazepine treatment. This patient had previously developed hyperthermia, akinesia, and increased creatine phosphokinase during treatment with bromperidol (Müller et al. 1988). Four cases have been reported in which NMS developed during clozapine monotherapy (Anderson and Powers 1991; Das Gupta and Young 1991; Miller et al. 1991; Reddig et al.

1992). In one of the cases, a history of NMS was present (Miller et al. 1991), while in another case previous treatment with fluoxetine may have played a role (Reddig et al. 1992). This case was later treated with clozapine at a lower dose without recurrence of NMS. An additional case report (Pope et al. 1986) described the development of NMS in a patient with a prior history of NMS when clozapine was added to lithium treatment. Finally, Nopoulos et al. (1990) reported on a case with classical signs of NMS, except for the lack of rigidity, during treatment with clozapine.

These reports demonstrate that NMS can occur during clozapine therapy and must be included in the differential diagnosis when a patient on clozapine presents with fever. A previous history of NMS is a likely risk factor. However, the low number of cases on clozapine monotherapy suggests that clozapine's propensity to cause NMS is substantially lower than it is for conventional antipsychotics.

Two reports have described the occurrence of NMS in association with risperidone treatment. Webster and Wijeratne (1994) described two geriatric patients who developed NMS shortly after initiating risperidone treatment. In one case, an 82-year-old had been treated with sulpiride for more than 10 years but then developed EPS and was switched to risperidone. After 5 days, NMS developed. In the second case, an 81-year-old woman was switched to risperidone treatment after EPS developed secondary to treatment with trifluoperazine and sulpiride. Within 12 hours of the first risperidone dose, signs of NMS developed. In both cases, the occurrence of EPS before the switch to risperidone suggests that the initial neuroleptics may

have been involved. Finally, Raitasuo et al. (1994) described a case of a 31-year-old man with a prior history of NMS with haloperidol treatment and an exceptional susceptibility to EPS who developed NMS after 15 days of risperidone titration up to 6 mg/day.

Given the propensity of risperidone to cause significant EPS at doses above 10 mg, it is likely that more cases of NMS will be observed with continuing use.

Hypotension

Because of its antagonism of norenergic receptors, clozapine can cause a significant decrease in systolic and diastolic blood pressure, leading to orthostatic hypotension that can result in dizziness and syncope. The reported incidence rates for this side effect range from as low as 1.2 percent (Povlsen et al. 1985) to 35 percent (Leppig et al. 1989). In most studies, the rates lie between 6 and 13 percent (Kane et al. 1988; Honigfeld and Patin 1990; Naber and Hippus 1990; Jalenques and Coudert 1992; Clozapine Study Group 1993). If one considers dizziness a symptom of postural hypotension, two more studies reported rates of 37 percent (Breier et al. 1994) and 50 percent (Lieberman et al. 1994).

Generally, this side effect occurs transiently at the beginning of treatment and disappears in most patients with continued treatment. Following the recommended titration of clozapine can minimize occurrence and severity. For the rare cases in which hypotension persists, elastic stockings and fludrocortisone have been recommended (Lieberman et al. 1989).

Risperidone also possesses antagonist properties at α -adrenergic receptors. It can therefore be expected to

and has been found to cause orthostatic hypotension in susceptible patients. Including reports of orthostatic dizziness, the rates range from 3 to 30 percent (Ceskova and Svestka 1993; Hoyberg et al. 1993; Marder and Meibach 1994; Peuskens 1995). In the European multicenter study (Peuskens 1995), the highest rate of orthostatic dizziness (30.4%) was observed at a dose of 16 mg of risperidone, while the rate for 10 mg of haloperidol was 23 percent. In the U.S. multicenter study, treatment with 16 mg of risperidone was also associated with the highest rate of dizziness (10.9%), whereas no patient on placebo and only 4.5 percent of the patients on haloperidol reported this side effect (Marder and Meibach 1994). In the Canadian multicenter study (Chouinard et al. 1993), 3 out of 92 patients on risperidone experienced transient hypotensive episodes (in 1 patient accompanied by syncope), whereas no such events were observed in the patients on haloperidol or placebo. No special measures were required for the treatment of these episodes. Compared with perphenazine, risperidone was found to be associated with hypotension in about twice as many cases (22% vs. 12%; Hoyberg et al. 1993).

These data suggest that transient hypotension at the beginning of risperidone treatment may occur in up to a third of all patients. For this reason, risperidone should be started at a low dose and titrated upward as tolerated.

Weight Gain

Treatment with conventional antipsychotics is often associated with weight gain—a side effect that can be quite bothersome to patients and can increase the long-term risk for cardio-

vascular morbidity and mortality (Doss 1979; Bernstein 1987; Brady 1989). Clozapine is no exception with regard to this side effect. Retrospective chart reviews (Povlsen et al. 1985; Gerlach et al. 1989; Leppig et al. 1989; Naber et al. 1989) suggest incidence rates of weight gain in patients taking clozapine that ranged from 1 percent in a short-term study (Naber et al. 1989) to 23 percent in a long-term study (Leppig et al. 1989). In a point-prevalence study (Schmauss et al. 1989), 69 percent of 27 patients treated with clozapine for 7 to 8 years were found to be overweight. Recently, more detailed studies (Leadbetter et al. 1992; Lamberti et al. 1992, 1993; Tuan-Ping et al. 1993; Umbricht et al. 1994; Hummer et al. 1995) suggest specifically that weight gain associated with clozapine treatment is substantial and significantly higher than that associated with conventional neuroleptic therapy. Most weight gain occurs during the first 6 to 12 months. While the amount can vary considerably among patients, the available data suggest that at least two-thirds of all patients will experience moderate to marked weight gain (Lamberti et al. 1992; Leadbetter et al. 1992; Umbricht et al. 1994). Two long-term studies (Lamberti et al. 1993; Umbricht et al. 1994) found that patients may continue to gain weight well into the second and third year of treatment. In one study (Umbricht et al. 1994) that evaluated 68 patients with a followup time ranging from 3 to 90 months, the cumulative proportions of patients becoming 10, 20, 30, and 40 percent overweight were 86, 54, 23, and 13 percent, respectively. These authors also found that being overweight at baseline did not prevent patients from gaining further weight, indicating an absence of a

ceiling effect. Unfortunately, no systematic research has been conducted to date to address the question of how to prevent and best treat this side effect. At least during the initial treatment phase, clozapine dose has not been found to be correlated with weight gain (Umbricht et al. 1994; Hummer et al. 1995).

Risperidone treatment has been reported to be associated with moderate weight gain in some studies although it has been less well studied than clozapine with regard to this side effect. In the European multicenter study (Peuskens 1995), which included 1,362 patients, a significant body-weight increase was observed at all risperidone dose levels (1, 4, 8, 12, and 16 mg/day). Weight increase was noted in 26 to 39 percent of the patients in the different treatment groups. It was also significantly higher at 8, 12, and 16 mg of risperidone than at 16 mg of haloperidol. Marder and Meibach (1994), reporting on the U.S. multicenter study, observed a significant correlation between risperidone dose and weight gain without providing more detailed data. In a double-blind study (Hoyberg et al. 1993) in which risperidone was compared to perphenazine, weight gain was observed in 52 percent of all patients treated with risperidone compared with 24 percent of those on perphenazine. However, other studies have found that risperidone treatment was not associated with weight gain (Ceskova and Svestka 1993; Min et al. 1993) or that weight change was modest and not different from weight change observed in haloperidol-treated patients (Claus et al. 1992).

Harmon et al. (1994), investigating weight gain associated with treatment with clozapine, risperidone, or haloperidol decanoate, found that patients treated with clozapine or

risperidone gained significantly more weight than patients on haloperidol decanoate. Maximum weight gain was associated with duration of treatment.

Overall, these data indicate that both clozapine and risperidone treatment are likely to produce weight increase in some patients. It seems that this side effect is more prominent for clozapine in terms of both the proportion of patients affected and the degree of weight gain observed. The available data also suggest that in the case of risperidone a correlation exists between dose and weight gain; this has not been demonstrated for clozapine.

Hematologic Adverse Effects

The fact that clozapine is associated with a higher incidence of agranulocytosis than conventional antipsychotic drugs has been the major factor limiting its use. Without this liability, clozapine might long ago have become the treatment of choice for schizophrenia (and other psychotic disorders). Recent results from the data base of the clozapine patient-monitoring systems in Britain, the United States, France, Canada, and Australia show the incidence of agranulocytosis to be less than 0.8 percent (Dev et al. 1994). Since the launch of clozapine in 1972, 688 cases of agranulocytosis (defined as a reduction in the absolute neutrophil count to below $500/\text{mm}^3$) have been reported. The median age of the patients was 40, the median daily dose of clozapine was 350 mg, and the median duration of clozapine therapy before the development of agranulocytosis was 60 days. Alvir et al. (1993) showed that older and female patients are at greater risk for developing agranulocytosis but

found no relationship with dose or other factors. The affected patients usually recovered within 4 to 21 days of stopping clozapine treatment.

Hematopoietic growth factors have been shown to be useful in facilitating recovery from clozapine-induced agranulocytosis (Geibig and Marks 1993; Oren et al. 1993). A retrospective review indicated that the time to recovery was almost halved in patients who received growth factors in comparison with patients who did not (Dev et al. 1994).

Seventy-nine patients died from complications of clozapine-associated agranulocytosis between 1972 and 1994; however, the percentage of fatalities has decreased steadily and significantly over the past 22 years (Dev and Krupp 1995).

Risperidone has not been associated to date with agranulocytosis or other blood dyscrasias.

Seizures

Although the relationship between schizophrenia and epilepsy remains a topic of some controversy, it is clear that antipsychotic medications do increase the incidence of epileptic seizures in patients with schizophrenia. Clozapine appears to have a higher risk than conventional antipsychotics of causing seizures. Devinsky et al. (1991) reviewed all of the reports of epileptic seizures in more than 7,000 patients exposed to clozapine during the 16-year period before Food and Drug Administration approval and subsequently during the first 6 months after marketing (Devinsky and Pacia 1994).

Among the 1,718 patients treated with clozapine in the United States between 1972 and 1988, 2.9 percent had generalized tonic-clonic seizures while receiving clozapine. A life-table

analysis of these data revealed a cumulative risk of 10 percent after 3.8 years of clozapine treatment.

These investigators also reported an increased risk of seizures with higher doses of clozapine—4.4 percent at 600 mg/day or higher; 2.7 percent at doses between 300 and 599 mg, and 1.0 percent at doses below 300 mg. Rapid dosage escalation also was believed to increase seizure risk. Among the 41 patients who experienced seizures, 31 remained on clozapine either at a lower dose or with anticonvulsant therapy.

In their review of 5,629 patients exposed to clozapine in the first 6 months after marketing, Devinsky and Pacia (1994) found 71 patients who experienced tonic-clonic seizures, yielding an incidence of 1.3 percent. In this cohort, no dose-dependent increase in risk for seizures was apparent. The authors reported that 29 of 37 patients maintained on clozapine were able to continue therapy without a recurrence of seizures following a reduction in dosage, a rechallenge with more gradual dosage titration, or the addition of anticonvulsants.

Myoclonic seizures without loss of consciousness or with progression to generalized tonic-clonic seizures have also been observed with clozapine treatment (Devinsky and Pacia 1994). As these authors pointed out, myoclonic seizures are often underreported and may be more common than realized. Episodes of unexplained falling or so-called "drop attacks" have been reported with clozapine, which may also be the result of myoclonic seizures (Berman et al. 1992). Malow et al. (1993) reported that myoclonic seizures resolved with dosage reduction or the addition of valproic acid in three of five patients.

The mechanism responsible for

clozapine's epileptogenicity remains unclear, though regional brain specificity and/or noradrenergic activity have been postulated as contributing factors.

In contrast to clozapine, risperidone has not been associated with increased seizure liability.

Withdrawal Effects

Although experience with most psychoactive drugs suggests that gradual discontinuation is preferable to abrupt withdrawal, it has been suggested that the latter is particularly problematic with clozapine. Several reports of rapid return of psychotic symptoms following abrupt discontinuation of clozapine have appeared in the literature (Borison et al. 1988; Palia and Clarke 1993; de Leon et al. 1994; Musser et al. 1994). Clearly these observations underscore the need for slow withdrawal whenever possible; however, the issue of clozapine's special risk in this regard is far from clear. Given that clozapine is indicated in treatment-refractory or treatment-intolerant patients, the appropriate control group for a study of withdrawal effects would be a similar population that experienced a comparable degree of improvement with a comparative agent. Otherwise it is difficult to separate the particular vulnerability or sensitivity to abrupt withdrawal that this patient population might manifest from that associated with clozapine withdrawal specifically. Clearly in cases of agranulocytosis, NMS, or seizures, the importance of abrupt discontinuation outweighs the potential risks.

Risperidone has not been associated to date with an unusual incidence or array of withdrawal effects, though gradual withdrawal still remains preferable.

Conclusion

Both clozapine and risperidone are useful additions to our therapeutic armamentarium. With the exception of the risk of agranulocytosis with clozapine, these drugs produce adverse effects that are rarely life threatening and are usually manageable. As more new-generation antipsychotic drugs are developed, it is hoped that the benefit-to-risk ratio will improve even further.

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