Movement Disorders Associated With Neuroleptic Treatment

William C. Wirshing, M.D.

Neuroleptic-induced movement disorders, or extrapyramidal side effects (EPS), can be classified into acute and tardive syndromes. Among the former are parkinsonism, dystonia, and akathisia. Conventional neuroleptics that have traditionally been used to treat psychiatric disorders are often associated with EPS. The newer atypical antipsychotics provide a more promising treatment strategy for psychiatric disorders and have a lower potential for producing EPS than conventional neuroleptics.

(J Clin Psychiatry 2001;62[suppl 21]:15–18)

While conventional neuroleptic drugs are among the most efficacious of all compounds in the entire psychiatric armamentarium, this benefit has come at a sometimes tragically high cost—extrapyramidal side effects (EPS), or neuroleptic-induced movement disorders. EPS can be conveniently classified into acute and tardive syndromes.[1–5] Among the former are parkinsonism, dystonia, and akathisia. The first of these, parkinsonism, was recognized soon after the introduction of the conventional neuroleptics in the early 1950s. Subsequently, and particularly following the advent of the high-potency compounds in the mid-1950s, dystonia emerged as a side effect. Finally, akathisia, despite its common occurrence, was recognized only much later. Each of these side effects has distinct manifestations, clinical courses, and optimal treatments. Tardive syndromes are classified by phenomenology (chorea, dystonia, tics, etc.) and can, unlike their acute counterparts, be irreversible.

The advent of the atypical antipsychotics, such as risperidone, should have made the issue of EPS or movement disorders redundant. Indeed, using atypical compounds such as risperidone, it has been demonstrated that a psychotic person can be effectively treated at low doses without neurotoxicity. However, since none of these agents is completely devoid of neurotoxic liabilities and the conventional neuroleptics are still widely used, movement syndromes as side effects remain a serious clinical issue. This article reviews the phenomenology and treatment of both acute and tardive EPS and presents the rationale for switching antipsychotic medications when such EPS are detected in the elderly patient.

PARKINSONISM

Parkinsonism was the first motor syndrome to be recognized as a property of neuroleptics. It became apparent soon after the introduction of these drugs in France in the early 1950s.[6] Drug-induced parkinsonian side effects closely resemble the disease itself.[7] Bradykinesia and rigidity are predominant. There is also an impaired righting reflex, accompanied by seborrhea and sialorrhea (excessive salivation), and autonomic instability is sometimes observed. While it is generally stated that the drug-induced condition is associated less with tremor compared with the disease, some patients do suffer mainly from tremor. It usually begins in one or both upper extremities and, in severe cases, may involve the jaw, tongue, and lower extremities.

Parkinsonian signs and symptoms do not appear immediately after the onset of treatment. They tend to appear after 1.5 to 2 weeks of therapy with neuroleptics. This appearance is coincident with the onset of the drugs' antipsychotic effect. It was initially believed that these 2 phenomena were linked, hence the origin of the term *neuroleptic* to describe these compounds. This belief was incorrect, however, and it is now known that antipsychotic effects can be achieved without significant neurotoxicity.[8]

The occurrence of sialorrhea raises an interesting point regarding clozapine. It is well known that patients treated

From the Department of Psychiatry and Biobehavioral Science, University of California at Los Angeles School of Medicine, Los Angeles.

Presented at the symposium "Restoring Harmony—Adding Life to Years," which was held June 16–17, 2000, in Seville, Spain, and supported by an unrestricted educational grant by Janssen Cilag and Organon.

Financial disclosure: Dr. Wirshing has received grant/research support from Janssen, Knoll, Lilly, Pfizer, AstraZeneca, Hoechst Marion Roussel, Organon, Bristol-Myers Squibb, and Sanofi; has received honoraria from Janssen, Lilly, Pfizer, Hoechst Marion Roussel, and AstraZeneca; and is on the speaker/advisory board of Janssen, Lilly, Pfizer, Hoechst Marion Roussel, and AstraZeneca.

Reprint requests to: William C. Wirshing, M.D., Department of Psychiatry, VA Greater Los Angeles Healthcare System, 11301 Wilshire Blvd., Los Angeles, CA 90073.

with conventional neuroleptics, in the presence of a parkinsonian syndrome, frequently hypersalivate, leading to drooling. It is also known that the atypical antipsychotic clozapine, a compound that is essentially devoid of parkinsonian liability, causes significant drooling in about 30% to 35% of patients. This, however, is a different type of sialorrhea. The sialorrhea associated with parkinsonism is secondary to a decrease in swallowing rate. Clozapine-associated drooling tends to occur at night rather than during the day, because patients' salivary flow increases and they are unable to compensate by increasing the swallowing rate (as they do when awake).[9,10]

Anticholinergics have traditionally been used to treat parkinsonian symptoms, and they have been used prophylactically for many years.[11–15] These drugs tend not to be effective, however, or even to remedy the classic syndrome for which they were designed. In general, the best that can be achieved is partial remission, even with the maximum dosage of anticholinergic agent.[16] The ideal anticholinergic would have only central effects. While this ideal agent would still result in side effects such as confusion, it would avoid the peripheral manifestations of anticholinergic activity, including impaired visual accommodation, constipation, dry mouth, and tachycardia.[17,18] Compared with the other available anticholinergic drugs, biperiden has a slightly higher affinity for the muscarinic receptors that predominate in the central nervous system. This means that biperiden is associated with fewer peripheral effects, although it still has the potential to cause confusion.[12,19,20]

More promising treatment strategies for parkinsonism are to reduce the dose of the neuroleptic, change to a low-potency conventional neuroleptic, or switch to an atypical antipsychotic such as risperidone.

DYSTONIA

Dystonia manifests itself differently from drug-induced parkinsonism. Dystonia (sustained, uncontrollable muscular contractions, usually of the head and neck) occurs during the first few doses. Fifty percent of dystonias appear within 48 hours of the start of treatment and 90% within the first 4 days.[1] This syndrome was first identified in the mid-1950s, coincidental with the introduction of the high-potency neuroleptics.

Again unlike parkinsonism, dystonias decrease with age: in those aged over 65 years, the risk is reduced to about 3%. In contrast, children are particularly susceptible, and in young men, high-potency conventional neuroleptics will cause dystonias in about 20% to 40% of cases. Patients who present with repeated intermittent dystonias are at risk of developing tardive dystonia, one of the most functionally distressing and irreversible of the tardive syndromes. (Alternatively, recurrent acute tardive dystonias may be a sign of nonconcordance [noncompliance] with medication.)

Anticholinergic drugs are generally the standard treatment for dystonic reactions. Indeed, prophylactic therapy with these compounds is recommended for patients receiving conventional neuroleptics that are more potent than thiothixene—except in the elderly. Since the risk of dystonias is lower in the elderly, and the risk of serious side effects with anticholinergics is higher, these agents should not be used in older patients, even with high-potency conventional neuroleptics.

AKATHISIA

Akathisia, like dystonia, appears rapidly, tending to be coincident with maximum drug concentration (C_{max}). This can be problematic in terms of diagnosis—akathisia is frequently mistaken for agitation or a worsening of the psychosis. Is the patient agitated because he or she is frightened, is disturbed, and has been admitted to a strange environment? Or is the patient miserable because he or she is suffering from drug-related akathisia?

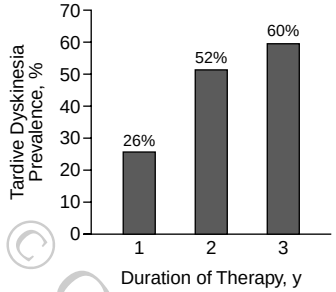
Akathisia has a subjective and an objective component. The subjective aspect is an intense sense of internal restlessness. The objective result is the attempt to deal with this sensation by pacing, marching in one place, wriggling ones legs, fidgeting, etc. It can be likened to nausea, i.e., each is one of the few human conditions that cannot be escaped by moving in any direction. Akathisia can cause extreme dysphoria and is a factor in patients' failing to comply with their medication regimens.

Up to 90% of young patients will experience this syndrome. It decreases with age, however, appearing in only about 15% of those aged over 65 years. Although the atypical agents represent a great advance in terms of their tolerability profiles, they are still associated with some risk of akathisia. This particular toxicity should, therefore, be carefully monitored in all patients.

Antiadrenergic agents, such as propranolol, 30 to 240 mg, can be a useful treatment and are generally the first-line therapy for akathisia.[21] This usefulness is probably not solely due to their β-blocking properties, but to the fact that β-blockers have cross-affinity with various serotonergic receptors. It is likely that the latter is the mechanism that mediates the antiakathisic properties of β-blockers. Caution is advised, however, when using this treatment strategy with elderly patients. If the patient's antipsychotic medication has akathisic liability and also causes α_1 blockade, the addition of β-blockade can result in a drop in peripheral vascular resistance and cardiac decompensation.

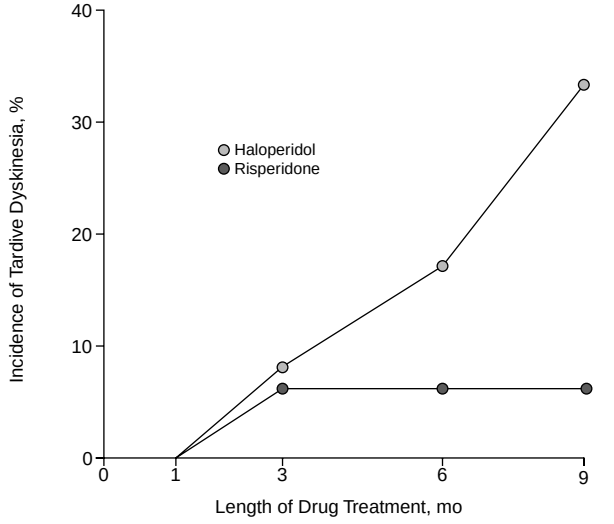
The judicious use of benzodiazepines can also sometimes be helpful in treating akathisia,[21] particularly in cases in which the diagnosis is unclear. Care should be taken, however, to avoid oversedation, particularly when the patient is receiving an antipsychotic with sedative properties. Anticholinergics should not be used, because

Figure 1. Risk of Tardive Dyskinesia in Elderly Patients Prescribed Conventional Neuroleptics (N = 266)[a]



[a]Reprinted, with permission, from Jeste et al.[23]

Figure 2. Risk of Tardive Dyskinesia in Patients Treated With Risperidone or Haloperidol (total N = 122)[a]



[a]Reprinted, with permission, from Jeste et al.[25]

they are even less beneficial for akathisia than for parkinsonism. A final alternative is to reduce the dose of the conventional neuroleptic or switch to an atypical antipsychotic with a low potential for akathisia.

TARDIVE DYSKINESIA

Tardive dyskinesia occurs with chronic exposure to conventional agents in about 3% to 5% of younger patients per year. The risk appears to be linear; it does not reach a plateau. The problem is much greater, however, in elderly patients.[22] The incidence of tardive dyskinesia rises significantly with age, and, after 2 years, more than half of patients treated with conventional neuroleptics will experience the syndrome (Figure 1).[23,24] After about 3 years, the risk of developing tardive dyskinesia appears to decrease, and the curve starts to flatten. Unfortunately, by that time about 60% of elderly patients will be suffering from this side effect. It should be noted that these data relate to de novo treatment; they do not come from patients treated for long periods (tens of years). Patients treated for behavioral and psychological symptoms of dementia (BPSD) for the first time with haloperidol will develop tardive dyskinesia at a rate of 25% to 50%/year. This wide range probably reflects a dose-related influence.

The introduction of the atypical antipsychotics has changed the picture: there are now sufficient data to indicate that the rate of tardive dyskinesia is 5- to 10-fold lower with risperidone compared with an equivalent dose of haloperidol.[22,25–27] For example, in a 1-year open-label study among 330 elderly patients,[22] risperidone therapy caused tardive dyskinesia in 2.6% of those who did not display tardive dyskinesia at baseline (N = 255). In a previous study by the same authors, the cumulative incidence of tardive dyskinesia among patients receiving risperidone was about one fifth of that observed for patients assigned to haloperidol (Figure 2).[25]

Risk factors for tardive dyskinesia include older age, female gender (in postmenopausal women, sex steroids may have a neuroprotective effect), nonschizophrenic diagnosis, and the presence of acute EPS. There has been some debate over whether intermittent dosing is a factor. Some years ago, it was theorized that the etiology of tardive dyskinesia was related to postsynaptic blockade producing a postsynaptic hypertrophy, either in number or in efficiency. Intermittent dosing was thus proposed as a way of avoiding tardive dyskinesia by preventing the hypothesized chronic pathologic reaction. In fact, intermittent dosing is associated with a higher rate of tardive dyskinesia. Frequent interruptions of long-term treatment do not reduce the incidence of persistent dyskinesia.[28] This is a weak effect, but nevertheless it is curious that it contradicts the theoretical basis of the etiology of tardive dyskinesia.

Most tardive dyskinesia is beyond the patient's awareness and does not affect function to a great degree, and so previously was not treated. Now, however, new treatment options are available. Clozapine, for example, can be useful, particularly for patients with tardive dystonias.[29,30] For choreic tardive dyskinesia, the most powerful suppressant appears to be risperidone—it is even more powerful than haloperidol.[31,32] In regional or segmental syndromes, such as torticollis or retrocollis, botulinum toxin can be injected locally every few months to paralyze the muscle, reduce the discomfort, and, in some cases, improve functioning.[33,34] Dopamine-depleting agents, such as reserpine, have been used, but are now practically defunct because of their serious side effects, including orthostatic hypotension and depression.[35,36] Vitamin E has been suggested, but the currently available evidence is that it has little impact, particularly on established tardive dyskinesia.[37]

Finally, there is the option of switching to an atypical antipsychotic, such as risperidone, which has a much lower risk of tardive dyskinesia compared with the conventional agents. When treating the elderly, a population that will develop tardive dyskinesia at a rate 10-fold higher than younger patients, conventional neuroleptics should be a last resort; atypical agents are the drugs of choice for BPSD.

CONCLUSION

In conclusion, conventional neuroleptics are associated with EPS in elderly patients treated for psychiatric disorders. Atypical antipsychotics, in particular risperidone, have been demonstrated in clinical trials to have a lower potential for EPS than conventional neuroleptics. Both classes of drug, however, have some neurotoxicity, and the elderly population receiving medication for BPSD in particular should be closely monitored for the occurrence of movement disorders as side effects.

Drug names: biperiden (Akineton), clozapine (Clozaril and others), haloperidol (Haldol and others), propranolol (Inderal and others), reserpine (Serpasil and others), risperidone (Risperdal), thiothixene (Navane and others).

REFERENCES

1. Ayd FJ. A survey of drug-induced extrapyramidal reactions. JAMA 1961; 175:1054–1060
2. Wirshing WC, Cummings JL. Extrapyramidal syndromes in the elderly: diagnosis and management. Geriatrics 1989;44:47–51, 54
3. Casey DE. Neuroleptic drug-induced extrapyramidal syndromes and tardive dyskinesia. Schizophr Res 1991;4:109–120
4. Casey DE. Neuroleptic-induced acute extrapyramidal syndromes and tardive dyskinesia. Psychiatr Clin North Am 1993;16:589–610
5. Miller CH, Fleischhacker WW. Managing antipsychotic-induced acute and chronic akathisia. Drug Saf 2000;22:73–81
6. Delay J, Deniker P, Green A, et al. Le syndrome excito-moteur provoqué par les médicaments neuroleptiques. Presse Med 1957;65:1771–1774
7. Tarsy D. Neuroleptic-induced extrapyramidal reactions: classification, description and diagnosis. Clin Neuropharmacol 1983;6:9–26
8. Wirshing WC. What is schizophrenia? J Calif Alliance Mentally Ill [serial online] 2000;8:5–8. Available at: http://www.mhsource.com/hy/j83.html. Accessed October 2000
9. Zorn SH, Jones SB, Ward KM, et al. Clozapine is a potent and selective muscarinic M_4 receptor agonist. Eur J Pharmacol 1994;269:R1–R2
10. Ben-Aryeh H, Jungerman T, Szargel R, et al. Salivary flow-rate and composition in schizophrenic patients on clozapine: subjective reports and laboratory data. Biol Psychiatry 1996;39:946–949
11. Chouinard G, Annable L, Mercier P, et al. Long-term effects of L-dopa and procyclidine on neuroleptic-induced extrapyramidal and schizophrenic symptoms. Psychopharmacol Bull 1987;23:221–226
12. Friis T, Christensen TR, Gerlach J. Sodium valproate and biperiden in neuroleptic-induced akathisia, parkinsonism and hyperkinesia. Acta Psychiatr Scand 1983;67:178–187
13. Tonda ME, Guthrie SK. Treatment of acute neuroleptic-induced movement disorders. Pharmacotherapy 1984;14:543–560
14. Arana GW, Goff DC, Baldessarini RJ, et al. Efficacy of anticholinergic prophylaxis for neuroleptic-induced acute dystonia. Am J Psychiatry 1988; 145:993–996
15. World Health Organization Heads of Centres Collaborating in WHO Co-ordinated Studies on Biological Aspects of Mental Illness. Prophylactic use of anticholinergics in patients on long-term neuroleptic treatment. Br J Psychiatry 1990;156:412
16. McGrath JJ, Soares KVS. Cholinergic medication for neuroleptic-induced tardive dyskinesia (Cochrane Review). In: The Cochrane Library, vol 2. Oxford, England: Update Software; 2001
17. Feinberg M. The problems of anticholinergic adverse effects in older patients. Drugs Aging 1993;3:335–348
18. Monane M, Avorn J, Beers MH, et al. Anticholinergic drug use and bowel function in nursing home patients. Arch Intern Med 1993;153:633–638
19. König P, Chwatal K, Havelec L, et al. Amantadine versus biperiden: a double-blind study of treatment efficacy in neuroleptic extrapyramidal movement disorders. Neuropsychobiology 1996;33:80–84
20. Meszaros K, Lenzinger E, Hornik K, et al. Biperiden and haloperidol plasma levels and extrapyramidal side-effects in schizophrenic patients. Neuropsychobiology 1997;36:69–72
21. Miller CH, Fleischhacker WW. Managing antipsychotic-induced acute and chronic akathisia. Drug Saf 2000;22:73–81
22. Jeste DV. Tardive dyskinesia in older patients. J Clin Psychiatry 2000; 61(suppl 4):27–32
23. Jeste DV, Caligiuri MP, Paulsen JS, et al. Risk of tardive dyskinesia in older patients: a prospective longitudinal study of 266 outpatients. Arch Gen Psychiatry 1995;52:756–765
24. Jeste DV, Lacro JP, Palmer B, et al. Incidence of tardive dyskinesia in early stages of low-dose treatment with typical neuroleptics in older patients. Am J Psychiatry 1999;156:309–311
25. Jeste DV, Lacro JP, Bailey A, et al. Lower incidence of tardive dyskinesia with risperidone compared with haloperidol in older patients. J Am Geriatr Soc 1999;47:716–719
26. Katz IR, Jeste DV, Mintzer JE, et al, for the Risperidone Study Group. Comparison of risperidone and placebo for psychosis and behavioral disturbances associated with dementia: a randomized, double-blind trial. J Clin Psychiatry 1999;60:107–115
27. De Deyn PP, Rabheru K, Rasmussen A, et al. A randomized trial of risperidone, placebo and haloperidol for behavioral symptoms of dementia. Neurology 1999;53:946–955
28. Jeste DV, Potkin SG, Sinha S, et al. Tardive dyskinesia: reversible and persistent. Arch Gen Psychiatry 1979;36:585–590
29. Van Harten PN, Kampuis DJ, Matroos GE. Use of clozapine in tardive dystonia. Prog Neuropsychopharmacol Biol Psychiatry 1996;20:263–274
30. Karp BI, Goldstein SR, Chen R, et al. An open trial of clozapine for dystonia. Mov Disord 1999;14:652–657
31. Chouinard G, Jones B, Remington G, et al. A Canadian multicenter placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients. J Clin Psychopharmacol 1993;13:25–40
32. Wirshing DA, Marshall BD Jr, Green MF, et al. Risperidone in treatment-refractory schizophrenia. Am J Psychiatry 1999;156:1374–1379
33. Brashear A, Lew MF, Dykstra DD, et al. Safety and efficacy of NeuroBloc (botulinum toxin type B) in type A-responsive cervical dystonia. Neurology 1999;53:1439–1446
34. Brin MF, Lew MF, Adler CH, et al. Safety and efficacy of NeuroBloc (botulinum toxin type B) in type A-resistant cervical dystonia. Neurology 1999;53:1431–1438
35. Simpson GM. The treatment of tardive dyskinesia and tardive dystonia. J Clin Psychiatry 2000;61(suppl 4):39–44
36. Fahn S. Long-term treatment of tardive dyskinesia with presynaptically acting dopamine-depleting agents. Adv Neurol 1983;37:267–276
37. Soares KVS, McGrath JJ. Vitamin E for neuroleptic-induced tardive dyskinesia (Cochrane Review). In: The Cochrane Library, vol 2. Oxford, England: Update Software; 2001