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Managing Antipsychotic-Induced Parkinsonism

David C. Mamo, Robert A. Sweet and *Matcheri S. Keshavan*

Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, Philadelphia, USA

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Abstract

Notwithstanding the advent of clozapine and other 'atypical' antipsychotic agents, the conventional ('typical') antipsychotic agents remain in widespread use. Antipsychotic-induced parkinsonism is a highly prevalent adverse effect that may result in increased morbidity and noncompliance.

Bedside examination is generally sufficient for the detection of the onset of parkinsonism and should be carried out frequently in the first 3 months of treatment. In addition to decreasing patient discomfort, monitoring for antipsychotic-induced parkinsonism also serves to identify the minimally effective dosage required for the individual patient.

Several strategies are utilised in the management of antipsychotic-induced parkinsonism including dosage reduction, switching to other antipsychotic agents and the use of antiparkinsonian drugs such as anticholinergic agents and amantadine.

Anticholinergic agents remain the mainstay of the pharmacological management of antipsychotic-induced parkinsonism in younger patients. Amantadine is a better tolerated agent for elderly patients, with similar efficacy to the anticholinergic agents. The routine use of prophylactic anticholinergics is not recommended and is clearly contraindicated in the elderly. An individualised risk-benefit assessment is necessary for the younger patient in whom prophylactic use of anticholinergic drugs is considered.

Antipsychotic medications remain the mainstay of treatment for both acute and chronic psychotic disorders. During this decade we have witnessed the evolution from the concept of 'neuroleptic' drugs to 'antipsychotic' drugs. The change has been brought about by the introduction of clozapine,[1]

an 'atypical' antipsychotic agent that produces fewer extrapyramidal symptoms (EPS) across the therapeutic range.[2,3] Subsequent atypical antipsychotic agents, with the possible exception of quetiapine,[4] are not entirely free of EPS.[5] Risperidone is associated with a low incidence of parkinsonism at lower dosages, but shows dose-related parkinsonism above a dosage range of 2 to 6 mg/day.[6,7] Similarly, olanzapine shows minimal parkinsonism at dosages below 20 mg/day.[8] Nevertheless, typical antipsychotics are still in widespread use for a number of reasons including cost considerations and their established record of efficacy and safety during more than 4 decades of use.

Antipsychotic-induced parkinsonism usually develops as an acute (over a period of days) or subacute (over a period of weeks) syndrome. Additionally, in some elderly patients parkinsonism may persist after termination of antipsychotic treatment. Antipsychotic-induced parkinsonism is a troublesome adverse effect that may result in noncompliance, slowing of cognition, and disfigurement. In older patients it may result in greater dependency, gait disturbance, urinary incontinence and increased mortality.[9]

1. Epidemiology

The prevalence of antipsychotic-induced parkinsonism during treatment with typical antipsychotic medications varies between 50 to 75%, but can be higher in the elderly population.[10] Among elderly patients, those with dementia of the Alzheimer's type are at a higher risk for antipsychotic-induced parkinsonism than elderly patients with major depression with psychosis.[11] Up to the age of 80 years, women are more susceptible to antipsychotic-induced parkinsonism than men.[12] A history of antipsychotic-induced EPS is a strong predictor of having EPS with re-exposure to antipsychotics.[13] Drug-induced parkinsonism occurs more commonly with the more potent antipsychotics.[14] This effect is most likely related to the greater anticholinergic effects of lower potency antipsychotics. This is consistent with the well established but simplistic hypothesis that parkinsonism results from an imbalance between dopaminergic and acetyl-cholinergic receptor blockade in the basal ganglia.[14]

The atypical antipsychotics have become attractive largely due to decreased or absent parkinsonian adverse effects, fuelling another hypothesis namely that a high ratio of serotonin 5-HT_{2A} receptor to dopamine D_2 receptor antagonism may be protective against the development of EPS.[15]

2. Detection and Monitoring

Antipsychotic-induced parkinsonism is clinically identical to Parkinson's disease in its presentation, but some important differences arise in its management as will be described in section 3. The classical triad of the syndrome are brady- and hypokinesia, resting tremor and rigidity. Brady- and hypokinesia are characterised by a reduction in the rate and amplitude of spontaneous movements and are clinically exhibited as mask-like faces, decreased arm swing during walking, shuffling gait, softer and weaker voice, and difficulty with the initiation of movement. It is therefore important to distinguish brady- and hypokinesia from the psychomotor retardation associated with depression as well as the negative symptoms of psychosis including affective flattening and avolition/apathy. The latter may lead the physician to increase the dosage of the antipsychotic.

Generally, the presence of other signs of parkinsonism will give a clue to the true origin of these clinical observations. Rigidity refers to an increased tone of the truncal and limb muscles. Clinically this is detected as a ratchet-like restriction to passive movement, often referred to as 'cogwheel' rigidity. The classic pill-rolling tremor of parkinsonism is an uncommon manifestation of antipsychotic-induced parkinsonism, though tremor of outstretched hands is often seen. The 'rabbit syndrome' is an even less common variant of antipsychotic-induced parkinsonism presenting as a perioral lip tremor of the same frequency (3 to 6Hz) as the pill-rolling tremor of Parkinson's disease.[16] As in Parkinson's disease, tremor and rigidity are often asymmetrical.

Bedside examination for the above clinical signs are generally sufficient for the detection of the onset of parkinsonism.[17] A number of clinical research scales have been developed to systematically assess for these adverse effects. The Simpson-Angus Extrapyramidal Side Effect (SEPSE) scale is one such scale in clinical and research use.[18] The SEPSE scale is a 10-item scale assessing the 7 core symptoms of rigidity, together with gait, tremor, salivation and glabellar tap. It can be reliably used in the young and in elderly adults.[19] Another approach is the use of an instrumental device to quantify wrist rigidity, which offers increased sensitivity and greater reliability than clinical examination.[20]

Monitoring for iatrogenic parkinsonism may also serve another purpose besides avoiding clinically significant adverse effects that may cause the patient discomfort and risk noncompliance. Antipsychotic dosage and plasma concentrations have not been shown to predict clinical outcome in the treatment of psychosis.[21] However, during acute treatment, dose titration until the onset of minimal cogwheel rigidity or hypokinesia seems to be a generally successful strategy. This is referred to as the 'neuroleptic threshold', a concept first proposed by Haase in 1961.[22] In a group of patients diagnosed with schizophrenia and schizoaffective disorder, McEvoy et al.[23] showed that giving dosages of haloperidol higher than those needed to reach the neuroleptic threshold did not result in a clinically significant improvement in the patients' psychosis, but led to a significant increase in distressing EPS. In the same study, patients who did not respond to their neuroleptic threshold dosage of haloperidol at 5 weeks required additional time at the same dosage rather than an increased dosage to achieve remission. These findings are consistent with observations made by Haase[24] who noted that fine motor hypokinesia in handwriting tests was indicative of the neuroleptic threshold dosage whereas the more obvious coarse EPS were not associated with an improved therapeutic effectiveness.[24]

In order to effectively diagnose and manage antipsychotic-induced parkinsonism, the physician must be aware of when it is most likely to arise and therefore rigorously monitor for its development. A number of studies in which daily monitoring was performed after the initiation or increase in dosage of an antipsychotic in young adults with schizophrenia, have found that parkinsonism may be detected within 24 to 48 hours.[23,25] In the elderly population with dementia, the onset of wrist and elbow rigidity was detected within 96 hours of starting perphenazine treatment, and measures of parkinsonism at 2 weeks highly correlated with the degree of increase in wrist and elbow rigidity at 96 hours.[26] In younger patients, maintaining the antipsychotic dosage at the level where minimal parkinsonism was first detected reduced the ultimate severity of parkinsonian adverse effects.[27]

It therefore seems prudent to monitor for parkinsonism at least weekly immediately after starting or increasing the dosage of an antipsychotic. More frequent monitoring for early parkinsonism to optimise the later outcome seems justifiable in younger adults, though this has not been studied in the elderly population. Since most cases of antipsychotic-induced parkinsonism present within 11 weeks after initiation of antipsychotic treatment or a dosage increase,[27] the frequency of monitoring may be decreased after 3 months.[28]

The clinician should be alert to the possibility of drug-drug interactions resulting in an increase in antipsychotic drug concentrations when prescribing concurrent medications, including tricyclic antidepressants, selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitors and antiarrhythmics.[29] Even in the absence of drug interactions, it should be borne in mind that the age-related decrease in endogenous dopamine[30] may result in a steady rise in parkinsonism at a stable dosage of antipsychotic drug in the elderly population. Subsequent monitoring remains necessary, therefore, even if the patient is maintained on a stable dosage of antipsychotic medication.

3. Pharmacological Treatment

There are several strategies that can be used in the management of antipsychotic-induced parkinsonism. This includes dose reduction, switching agents or the addition of antiparkinsonian drugs. While many factors influence the choice among these options, an important distinction is whether the antipsychotic-induced parkinsonism emerges in the context of the acute treatment of psychosis or during continuation and maintenance treatment.

For the patient whose psychosis is stabilised, the simplest and probably most logical approach would be to decrease the dosage of the offending medication. Because antipsychotic medications have long half-lives, the improvement in antipsychotic-induced parkinsonism will not be immediate. Since the maintenance dosage of antipsychotic drugs can be smaller than that used in acute management[31] and tolerance to antipsychotic-induced parkinsonism occurs with prolonged therapy,[32,33] targeting the dosage which results in minimal antipsychotic-induced parkinsonism during acute treatment should result in less antipsychotic-induced parkinsonism during maintenance treatment.[34] Though a small adjustment in dosage may actually be all that is necessary, this may in some instances result in a deterioration in the patient's psychosis. At this point the physician may either switch to another class of antipsychotic medication such as a lower potency typical antipsychotic or an atypical antipsychotic, or add another medication to counteract the parkinsonian adverse effects.

While it is generally not considered good practice to treat an adverse effect with another medication, it is often considered a practical solution when other approaches fail. Antipsychotic-induced parkinsonism often occurs in the presence of acute psychotic symptoms and the physician may feel hesitant about switching medications at that time, particularly if the patient was improving. Switching medication is certainly feasible, but clinically this often results in a delayed antipsychotic response until equipotent dosages are established.

3.1 Anticholinergics

Anticholinergic medications in their oral or parenteral forms are the most common medications used to treat antipsychotic-induced parkinsonism. Though they differ in their potency and sedative effects, there is no evidence that efficacy in treating antipsychotic-induced parkinsonism differs among these agents. All cause peripheral adverse effects consisting of blurred vision, dry mouth, tachycardia, urinary retention and constipation. These adverse effects may be particularly problematic in elderly patients who may already be compromised with sensory deficits, urinary outflow obstruction, intestinal motility disturbances and cardiac arrhythmias. Central adverse effects of anticholinergic medications include disrupted short term memory and frank delirium with disorientation, hallucinations, and delusions. Once again elderly patients, particularly those with a dementing disorder, are particularly susceptible to anticholinergic central effects. Despite these concerns, Kalish et al.[35] found that in only one-third of elderly patients prescribed an anticholinergic medication had an attempt been made to control parkinsonian adverse effects by reducing the antipsychotic dosage. Similarly, in only half of those receiving dopaminergic antiparkinsonian drugs had an attempt been made to reduce the antipsychotic dosage before initiating treatment.

The presence of antipsychotic-induced parkinsonism has been shown to be a risk factor for the development for tardive dyskinesia,[36] but there is no evidence that anticholinergic treatment prevents the emergence of tardive dyskinesia (see section 3.3). Evidence for a prophylactic effect of anticholinergic drugs on tardive dyskinesia would have important clinical implications. The drugs often temporarily aggravate existing tardive dyskinesia, but this effect is reversible upon discontinuation of the anticholinergic agent.

An often neglected finding regarding the use of anticholinergic agents is that their concomitant use with antipsychotics may reduce the clinical effectiveness of the antipsychotic agent on positive symptoms of schizophrenia.[24,37,38] While the

mechanism of action is unknown, central pharmacodynamic and peripheral pharmacokinetic interactions may be involved.[24] If these observations are correct, then they would support 2 important clinical guidelines regarding the management of antipsychotic-induced parkinsonism. First, the titration of the antipsychotic to the 'neuroleptic threshold' measured clinically as described in section 2 together with the use of other medications (e.g. benzodiazepines) for the management of agitation would appear to be superior to the seemingly counterproductive strategy of using higher starting dosages of antipsychotics which often necessitates the use of anticholinergic drugs. Secondly, it can be argued that during maintenance treatment, any benefits of adding an anticholinergic agent for emergent antipsychotic-induced parkinsonism would be achieved equally well by lowering the dosage of the antipsychotic.[34]

3.2 Dopaminergics

The only useful dopaminergic agent available for the treatment of antipsychotic-induced parkinsonism is amantadine. At a dosage of 100 to 400 mg/day amantadine is a good alternative to anticholinergic agents, with a comparable effect to benzatropine (benztropine mesylate).[39] Originally introduced as an antiviral agent, amantadine is effective in both Parkinson's disease and antipsychotic-induced parkinsonism. Its mechanism of action has not been fully elucidated, but may be related to its ability to enhance dopamine release and inhibit its reuptake into the presynaptic nerve terminal.[40] It may also have a postsynaptic effect by increasing the number of postsynaptic dopamine receptors or altering their conformation.[41] Its adverse effects include dizziness, insomnia and nausea; dry mouth, blurred vision and excitement have also been reported. Psychosis is uncommon and occurs at high dosages. Since the drug is excreted primarily in the urine, lower dosages are required when the drug is used in the elderly and in patients with renal disease. With long term use, livido reticularis of the lower extremities may occur.[42] Due to its lower incidence of anticholinergic adverse effects it is a useful agent in conditions where anticholinergic medications are contraindicated.[43]

Levodopa, a dopamine precursor, and bromocriptine, a direct dopamine agonist, are not effective in treating antipsychotic-induced parkinsonism, and may exacerbate the psychotic features for which the antipsychotic has been prescribed.[44] The distinction between idiopathic Parkinson's disease and antipsychotic-induced parkinsonism should generally pose no difficulties. The differential effects of levodopa and on these 2 conditions, however, highlights the need to make this differential diagnosis. Generally, levodopa and bromocriptine should not be used for the treatment of antipsychotic-induced parkinsonism. However, some patients with antipsychotic-induced parkinsonism may have a subclinical form of parkinsonism that was uncovered by the antipsychotic.[45] Therefore, some patients with refractory 'apparent' antipsychotic-induced parkinsonism may respond to these agents.

3.3 Prophylactic Treatment

The prophylactic use of antiparkinsonian agents with the initiation of treatment with, or an increase in the dosage of, an antipsychotic, is a controversial topic.[46] For the reasons outlined in section 3.1, prophylactic anticholinergic treatment is clearly contraindicated in the elderly. In younger patients, however, it remains a common practice. Since antipsychotic-induced parkinsonism generally presents within 3 months, others have argued that patients are better off protected from these effects during this initial interval since the adverse effects may decrease compliance with the antipsychotic medication at this critical period.[47] Studies examining the necessity of the use of prophylactic antiparkinsonian medications have yielded conflicting results, with discontinuation studies reporting that between 10 to 68% of patients withdrawn from antiparkinsonian drugs after a 3-month period of prophylactic treatment developed parkinsonism.[46] Even those patients with whom a decision is made to provide prophylactic anticholiner-

gic treatment should have a trial of anticholinergic withdrawal during maintenance treatment.

In its consensus statement, the World Health Organization[48] concluded that the prophylactic use of anticholinergics in patients receiving antipsychotic medications is not recommended and should only be used when parkinsonism develops and other measures (dosage reduction and switching to another antipsychotic agent) are not effective. While this statement serves as a warning about the potentially serious hazards of routine prophylactic use of anticholinergic agents in antipsychotic-induced parkinsonism,[49] it remains for the treating physician to make an individualised risk-benefit assessment.

4. Conclusion

Antipsychotic-induced parkinsonism remains an important and highly prevalent condition even with the advent of newer, atypical antipsychotic medications. It is not only potentially disfiguring and disabling, but may cause significant morbidity in elderly patients. The use of lower dosages of antipsychotic medications with gradual titration is the most sensible strategy for the prevention of antipsychotic-induced parkinsonism.

Monitoring for the emergence of parkinsonism has the dual purpose of early identification of these adverse effects as well as identifying a minimally effective dosage with minimal antipsychotic-induced parkinsonism for the particular patient. Once clinically significant antipsychotic-induced parkinsonism appears, a reduction in dosage should be considered first. Switching to an 'atypical' antipsychotic is an alternative, though it should be remembered that even these medications, with the possible exception of clozapine and quetiapine, may cause parkinsonism at higher dosages.

When other strategies fail, anticholinergic drugs remain the mainstay of the pharmacological management of parkinsonian adverse effects of antipsychotic medications in younger patients. Their potential for worsening positive symptoms and relapse in maintenance therapy is often overlooked. Amantadine is just as effective and causes less morbidity than anticholinergic medications. The use of prophylactic antiparkinsonian drugs remains controversial, though the use of prophylactic anticholinergic drugs is clearly contraindicated in elderly patients. Prophylactic use of antiparkinsonian drugs may be useful in selected patients, but a trial off these medications is warranted after 3 months of their coadministration with the antipsychotic drug.

Thus, though antipsychotic-induced parkinsonism remains a pernicious problem in the pharmacotherapy of patients with psychotic symptoms, when recognised early it can be readily managed using the strategies outlined in this review.

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References

1. Kane J, Honigfeld G, Singer J, et al. Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. Ach Gen Psychiatry 1988; 45 789-96
2. Gerlach J. New antipsychotics: classification, efficacy and adverse effects. Schizophr Bull 1991; 17: 289-309
3. Tandon R. Neuropharmacologic basis for clozapine's unique profile [letter]. Arch Gen Psychiatry 1993; 50: 158-9
4. Small JG, Hirsch SR, Arvanitis LA, et al. Quetiapine in patients with schizophrenia. A high- and low-dose double-blind comparison with placebo. Seroquel Study Group. Arch Gen Psychiatry 1997; 54: 549-57
5. Hoffman DC, Donovan H. Catalepsy as a rodent model for detecting antipsychotic drugs with extrapyramidal side effect liability. Psychopharmacology (Berl) 1995; 120: 128-33
6. Marder SR, Meibach RC. Risperidone in the treatment of schizophrenia. Am J Psychiatry 1994; 151: 825-35
7. Peuskens J. Risperidone in the treatment of patients with chronic schizophrenia: a multinational, multi-center, double-blind, parallel-group study versus haloperidol. Risperidone Study Group. Br J Psychiatry 1995; 166: 712-26
8. Beasley CM Jr, Hamilton SH, Crawford AM, et al. Olanzapine versus haloperidol: acute phase results of the international double-blind olanzapine trial. Eur Neuropsychopharmacol 1997; 7: 125-37
9. Wilson JA, Maclennan WJ. Review: drug-induced parkinsonism in elderly patients. Age Ageing 1989; 18: 208-10
10. Casey DE. Side effect profiles of new antipsychotics. J Clin Psychiatry 1996; 57 (S11): 40-5
11. Sweet RA, Mulsant BH, Pollock BG, et al. Neuroleptic-induced parkinsonism in elderly patients diagnosed with psychotic major depression and dementia of the Alzheimer's type. Am J Geriatr Psychiatry 1996; 4: 311-9
12. Ayd FJ. A survey of drug-induced extrapyramidal reactions. JAMA 1961; 175 (12): 1054-60

13. Keepers GA, Casey DE. Use of neuroleptic-induced extrapyramidal symptoms to predict future vulnerability to side effects. Am J Psychiatry 1991; 148: 85-9
14. Snyder S, Greenberg D, Yamamura H. Antischizophrenic drugs and brain cholinergic receptors. Arch Gen Psychiatry 1974; 31: 58-61
15. Meltzer HY, Matsubara S, Lee JC. The ratios of serotonin$_2$ and dopamine$_2$ affinities differentiate atypical and typical antipsychotic drugs. Psychopharmacol Bull 1989; 25: 390-2
16. Villeneuve JL. The rabbit syndrome: a peculiar extrapyramidal reaction. Can Psychiatr Assoc J 1972; 17: 69-72
17. Sweet RA, Pollock BG, Rosen J, et al. Early detection of neuroleptic-induced parkinsonism in the elderly patients with dementia. J Geriatr Psychiatry Neurol 1994; 7: 251-4
18. Simpson GM, Angus JWS. A rating scale for extrapyramidal side effects. Acta Psychiatr Scand 1970; 21: 211-8
19. Sweet RA, DeSensi EG, Zubenko GS. Reliability and applicability of movement disorder rating scales in the elderly. J Neuropsychiatry Clin Neurosci 1993; 5: 56-60
20. Caliguri MP. Portable device for quantifying parkinsonism wrist rigidity. Mov Disord 1994; 9: 57-63
21. Shriqui CL. Neuroleptic dosing and neuroleptic plasma levels in schizophrenia: determining the optimal regimen. Can J Psychiatry 1995; 40 (2 Suppl.): 38S-48S
22. Haase HJ. Extrapyramidal modifications of fine movements: a 'conditio sine qua non' of the fundamental therapeutic action of neuroleptic drugs. In: Bordeleau JM, editor. Systeme extrapyramidal et neuroleptiques. Montreal: Editions Psychiatriques 1961: 329-53
23. McEvoy JP, Hogarty GE, Steingard S. Optimal dose of neuroleptic in acute schizophrenia. Arch Gen Psychiatry 1991; 48: 739-45
24. Haase HJ. Clinical observations on the actions of neuroleptics. In: Haase HJ, Janssen PA, editors. The actions of neuroleptic drugs: a psychiatric, neurological, and pharmacological investigation. Amsterdam: N Holland, 1965: 1-98
25. Haase HJ, Janssen PAJ, editors. The actions of neuroleptic drugs. New York: Elsevier, 1985
26. Sweet RA, Pollock BG. Neuroleptics in the elderly: guidelines for monitoring. Harvard Rev Psychiatry 1995; 2: 327-35
27. Ayd FJ. Early onset neuroleptic-induced extrapyramidal reactions: a second survey, 1961-1981. In: Coyle JT, Enna SJ, editors. Neuroleptics: neurochemical, behavioural, and clinical perspectives. New York: Raven Press, 1983: 75-92
28. Sweet RA, Pollock BG. Neuroleptics in the elderly: guidelines for monitoring. Harv Rev Psychiatry 1995; 2 (6): 327-35
29. Pollock BG. Recent developments in drug metabolism of relevance to psychiatrists. Harv Rev Psychiatry 1994; 2: 204-13
30. Palmer AM, DeKosky ST. Monamine neurons in aging and Alzheimer's disease. J Neural Trans 1993; 91: 135-59
31. Branchey MH, Branchey LB, Richardson MAR. Effects of neuroleptic adjustment on clinical condition and tardive dyskinesia in schizophrenic patients. Am J Psychiatry 1981; 138: 608-12
32. Ayd FJ. Neuroleptics and antiparkinsonian drugs. Int Drug Ther Newsl 1971; 6: 33-6
33. Shapiro AK. Psychochemotherapy. In: Grenell RO, Gabay S, editors. Biological foundations of psychiatry. New York; Raven Press, 1971: 793-840
34. Miller R. Dose-response relationships for the antipsychotic effects and parkinsonian side-effects of typical neuroleptic drugs: practical and theoretical implications. Prog Neuropsych Biol Psychiatry 1997; 21: 1059-94
35. Kalish SC, Bohn R, Mogun B, et al. Antipsychotic prescribing patterns and the treatment of extrapyramidal symptoms in older people. J Am Geriatr Soc 1995; 43 (9): 967-73
36. Kane JM, Woerner M, Borenstein M, et al. Integrating incidence and prevalence of tardive dyskinesia. Psychopharmacol Bull 1986; 22 (1): 254-9
37. Singh M. Therapeutic reversal with benztropine in schizophrenia. J Nerv Ment Dis 1975; 160: 258-66
38. Johnston EC, Crow TJ, Ferrier IN, et al. Adverse effects of anticholinergic medication on positive schizophrenic symptoms. Psychol Med 1983; 13: 513-27
39. DiMascio A, Bernardo DL, Greenblatt DJ, et al. A controlled trial of amantadine in drug-induced extrapyramidal disorders. Arch Gen Psychiatry 1976; 33: 599-60
40. Aoki F, Sitar D. Clinical pharmacokinetics of amantadine hydrochloride. Clin Pharmacokinet 1988; 14: 35-51
41. Gianutsos G, Stewart C, Dunn JP. Pharmacologic changes in dopaminergic systems induced by long-term administration of amantadine. Eur J Pharmacol 1985; 110: 357-61
42. Hamlin T. Current concepts in therapy: agents for treatment of Parkinson's disease. N Engl J Med 1975; 256: 699-701
43. Yadalam KG. Drug-inducedparkinsonism. In: Keshavan MS, Kennedy JS, editors. Drug-induced dysfunction in psychiatry. New York: Hemisphere Publishing Corporation, 1992: 119-29
44. Yaryura-Tobias JA, Wolpert A, Dana L, et al. Action of L-dopa in drug induced extrapyramidalism. Dis Nerv Syst 1970; 31: 60-3
45. Rajput A, Rozdilsky B, Hornykiewicz O, et al. Reversible drug-induced parkinsonism: clinicopathologic study of two cases. Arch Neurol 1982; 39: 644-6
46. Tonda ME, Guthrie SK. Treatment of acute neuroleptic-induced movement disorders. Pharmacotherapy 1994; 14 (5): 543-60
47. Winslow RS, Stillner V, Coons DJ, et al. Prevention of acute dystonic reactions in patients beginning high potency neuroleptics. Am J Psychiatry 1986; 143: 706-10
48. 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: a consensus statement. Br J Psychiatry 1990; 156: 412
49. Barnes TRE. Comment on WHO consensus statement. Br J Psychiatry 1990; 156: 413-4

Correspondence and reprints: Dr *David C. Mamo*, Department of Psychiatry, Western Psychiatric Institute and Clinic, 3811 O'Hara Street, Pittsburgh, PA 15213-2593, USA.
E-mail: mamodc@msx.upmc.edu