

Treatment of Acute Neuroleptic-Induced Movement Disorders

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Acute extrapyramidal syndromes (EPS), including dystonia, parkinsonism, and akathisia, are associated with the use of virtually all neuroleptic agents. They may be alleviated by reducing the neuroleptic dosage, switching to a lower-potency drug, or administering an adjunctive agent such as an anticholinergic, amantadine, benzodiazepine, or β -blocker. Akathisia may be only partly dispelled by anticholinergics; alternatives are β -blockers, benzodiazepines, and clonidine. In patients receiving long-term neuroleptic therapy, both the prophylactic use and the duration of treatment with concomitant anti-EPS drugs are controversial. Administration of prophylactic anti-EPS drugs should be based on the likelihood that the patient will develop EPS, as well as the risk of adverse reactions resulting from extended use of the agents in a specific patient. The decision to continue anti-EPS therapy should be reevaluated frequently, especially in elderly patients.

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Antipsychotic or neuroleptic agents have been used in clinical practice for the past 30 years. They revolutionized the management of psychoses, but they are associated with significant side effects. Almost immediately after their introduction, a

range of extrapyramidal syndromes (EPS) was observed. Although neuroleptics belong to several different chemical classes including phenothiazines, thioxanthenes, butyrophenones, dihydroindolones, dibenzoxazepines, and diphenylbutylpiperidones, they are all dopamine antagonists and induce EPS to various degrees.^{1,2} Other drugs that cause central dopamine receptor blockade, such as metoclopramide (an antiemetic) and amoxapine (an antidepressant), can also produce extrapyramidal movement disorders.^{3,4}

Antipsychotic-induced EPS fall into four categories: parkinsonism-like movements, acute dystonia, akathisia, and tardive dyskinesia. This article focuses only on the acute movement disorders; several excellent reviews have been written on tardive dyskinesia.^{1,5,6}

Pharmacology

The production of voluntary movement results from complex interactions among the motor cortex, basal ganglia, and spinal cord. The corticospinal, or pyramidal, tract is one of the major pathways by which electrical signals are conducted from the motor cortex to the anterior motor neurons of the spinal cord. Collateral pathways split from the corticospinal tract toward

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the basal ganglia by way of the caudate nucleus and putamen, two structures known collectively as the neostriatum. The basal ganglia are a collection of subcortical and midbrain structures made up of the globus pallidus, substantia nigra, neostriatum, and subthalamic nucleus. The collateral pathways, which travel through the basal ganglia, are considered to be separate from the pyramidal tract and are called the extrapyramidal tracts.

The extrapyramidal system modulates and modifies the motor signals sent by the corticospinal tract. Sensory and motor information travels from the cortex to the basal ganglia, where it is integrated, refined, and relayed through the thalamus back to the prefrontal cortex and, ultimately, the spinal cord (Figure 1).⁷

Dopamine is one of several neurotransmitters that act on the extrapyramidal system. At least five important dopamine pathways have been delineated in the human brain.⁸ Neuroleptics are thought to produce effects on movement primarily

through their actions on dopamine pathways in the basal ganglia, whereas dopamine cell bodies located in the substantia nigra or ventral tegmental areas that project to the limbic system and the cortex (mesolimbic and mesocortical systems) appear to affect mood and thought processes.⁵ Neuroleptic effects on movement are thought to be mediated primarily by another dopamine pathway, the nigrostriatal pathway, which consists of cell bodies in the substantia nigra that project to the neostriatum.⁹

In addition to dopamine, the glutamatergic, γ -aminobutyric acid (GABA), acetylcholine, and serotonin neurotransmitter systems affect extrapyramidal movement. Cortical afferent tracts, which are primarily glutamatergic, project into the striatum (putamen) where they terminate on GABA neurons. The GABA neurons in the putamen then project to the globus pallidus, as well as the substantia nigra. Glutamate generally acts as an excitatory neurotransmitter in the brain, and GABA

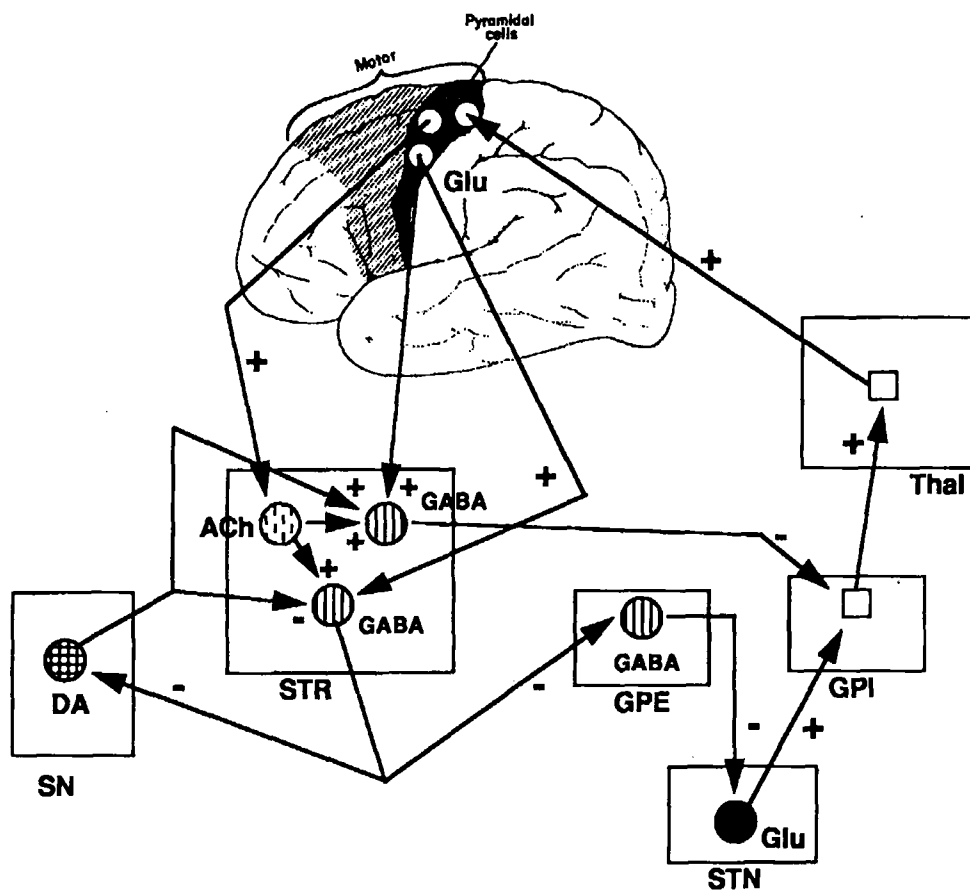


Figure 1. Summary of basal ganglia circuitry. SN = substantia nigra; STR = neostriatum; GPE = globus pallidus externa; GPI = globus pallidus interna; STN = subthalamic nucleus; Thal = thalamus; ACh = acetylcholine; DA = dopamine; GABA = γ -aminobutyric acid; Glu = glutamate; \square = unknown neurotransmitter; + = excitatory, - = inhibitory.

is usually inhibitory. The exact role of GABA is not clearly defined, but this neurotransmitter appears to maintain normal basal ganglia function through a complex system of negative feedback loops. Glutamatergic input to the striatum is modulated by dopamine neurons originating from the substantia nigra, by acetylcholine interneurons in the striatum, and by input from other GABA neurons within the striatum. Dopamine appears to have an overall inhibitory effect on the thalamic output to the prefrontal cortex that is antagonized by the acetylcholine interneurons in the striatum.⁷

Although the mechanism of action of neuroleptic agents has not been definitively identified, the antipsychotic action of the drugs is thought to result from the postsynaptic blockade of dopamine receptors in the mesocortical and mesolimbic systems.⁸ Unfortunately, most neuroleptics are relatively nonselective with regard to which dopamine pathways are affected, and dopamine receptors in the striatum are also blocked. This causes a relative deficiency of dopaminergic activity in the striatum, and a disturbance in the balance between striatal dopaminergic and cholinergic systems. Neuroleptic-induced EPS may result primarily from blockade of dopamine receptors in the striatum, but the imbalance between acetylcholine and dopamine systems in this area is also an important factor. Many treatment regimens aim to restore this balance by either reducing acetylcholine or increasing dopamine neurotransmission in the striatum. In addition to their dopamine receptor-blocking actions, neuroleptic agents may also block cholinergic receptors, α -adrenergic receptors, and histamine₁ receptors.^{10, 11}

The propensity for a neuroleptic agent to induce EPS depends not only on its dopamine receptor-blocking potency but also on its inherent anticholinergic activity. Neuroleptic agents are classified as low or high potency based on their degree of dopamine receptor blockade. The high-potency agents possess a greater affinity for the dopamine receptor and lower cholinergic (muscarinic) receptor affinity than the low-potency agents; thus they cause a greater disruption in the balance between dopamine and acetylcholine, and are more likely to result in EPS.¹⁰⁻¹²

Numerous dopamine receptor subtypes (D₁, D₂, D₃, D₄, and D₅) have been found in the central nervous system. The D₂ receptors are most strongly linked to the efficacy of neuroleptic agents,¹² and their blockade at least partially causes movement disorders. The D₁ receptors appear to modulate the intensity of movement disorders.^{8, 13} The actions of the other dopamine receptor

subtypes are not well characterized. The atypical neuroleptic agent clozapine causes almost no EPS and exhibits a relatively high affinity for D₄ receptors,¹⁴ but at this time it is not clear if the decreased frequency of EPS is related to this affinity. Clozapine also has relatively higher affinity for muscarinic receptors and has lower occupancy of D₂ receptors in the basal ganglia compared with typical antipsychotics.¹⁵⁻¹⁷

The exact sites of dopamine-serotonin interactions that are most relevant to motor control are not known, but it appears that serotonin neurons projecting from the nucleus raphe dorsalis modulate dopamine pathways in the basal ganglia.¹⁸ Ritanserin, a serotonin type 2 (5-HT₂) receptor-blocking agent, decreases EPS when given to patients receiving neuroleptics without concomitant anti-EPS agents.¹⁹ Risperidone, the newly marketed atypical neuroleptic, causes fewer EPS than the standard neuroleptics and has a high affinity for 5-HT₂ receptors.^{20, 21} Clozapine also has relatively high affinity for 5-HT₂ receptors.^{12, 15} It is hypothesized that the low frequency of EPS associated with these two drugs is due to their 5-HT₂-blocking action. This argument is particularly compelling for risperidone because the drug shows virtually no affinity for muscarinic receptors.²¹

Pathophysiology and Clinical Manifestations of Drug-Induced EPS

Table 1 lists the dopamine receptor-blocking potency and relative frequency of adverse effects of commonly used neuroleptic agents.^{10, 11} The frequency of drug-induced EPS varies from 4–50% depending on the specific drug.²²⁻²⁷ The low-potency agents are associated with a higher frequency of antiadrenergic (orthostatic hypotension) and anticholinergic (dry mouth, constipation, blurred vision) effects and a lower frequency of EPS, whereas the reverse is true for the high-potency drugs. Although higher dosages of neuroleptics are generally associated with a higher frequency of EPS, most studies describe profound individual variations in susceptibility to drug-induced EPS. Thus, drug potency is probably a better predictor of EPS potential than dosage.

Some common problems associated with the treatment of these disorders are infrequent or incomplete examinations and inadequate dosages of anti-EPS agents.²⁸ Also, the relationship between the therapeutic and adverse effects of neuroleptics is ill defined. Although some investigators suggested that the onset of neuroleptic-induced EPS may serve as a clinical

Table 1. Antipsychotic Agents

Chemical Class	Traditional Equivalence (mg)	Sedation Symptoms	Adverse Effects Extrapyramidal	Anticholinergic
Phenothiazines				
Aliphatic type				
Chlorpromazine	100	+++	++	+++
Piperidine type				
Thioridazine	100	+++	+	+++
Piperazine type				
Perphenazine	10	+	+++	++
Trifluoperazine	5	+	+++	+
Fluphenazine	2	+	+++	+
Nonphenothiazines				
Thioxanthene				
Thiothixene	4	+	+++	+
Butyrophenone				
Haloperidol	2	+	+++	+
Dibenzoxazepine				
Loxapine	10	++	++	++
Dibenzazepine				
Clozapine	50	+++	+/- (Low-frequency akathisia)	+++
Dihydroindolone				
Molindone	10	++	++	++
Diphenylbutylpiperidone				
Pimozide	1	+	+++	+
Benzisoxazole				
Risperidone	6	+/-	+/-	-

+++ = high; ++ = moderate; + = low, +/- = slight or mild.
Adapted from references 10, 20, 21, and 46.

marker for therapeutic response or adequate serum neuroleptic levels, the current consensus is that this adverse effect is not linearly correlated with therapeutic response.²⁹⁻³²

Pseudoparkinsonism

Neuroleptic agents are the major cause of drug-induced parkinsonism.⁹ The most common manifestations of this syndrome are bradykinesia, resting tremor, and akinesia. Other features are masked facies due to rigidity and akinesia of facial muscles, slow initiation of motor activity, soft and monotonous speech, flexed posture, decreased arm swing, and shuffling gait.¹ The patients usually have symmetric akinesia and rigidity, however, in the early stages, asymmetric symptoms may occur.¹ Rigidity of the extremities, neck, or trunk may appear days to weeks after the onset of bradykinesia.

Neuroleptic-induced parkinsonism occurs in approximately 20-40% of all patients treated with these drugs and is clinically indistinguishable from postencephalitic parkinsonism or idiopathic parkinsonism.^{1, 5, 33-35} The age distribution of the disorder closely parallels that of Parkinson's disease, with increased frequency after 40 years,

perhaps due to decreases in dopamine levels and nigral cell counts with advancing age.^{1, 23, 36} However, drug-induced parkinsonism is also patient specific and dose related, and young adults and children are occasionally affected.⁵ This condition occurs at various times after initiating neuroleptic therapy, but typically within 30-90 days.²³ Severe parkinsonism may also develop after the concomitant discontinuation of both antiparkinsonian and neuroleptic agents,¹ possibly because the former are more rapidly eliminated from the body. The frequency and severity of this disorder are dependent on the degree of dopamine receptor blockade induced by the neuroleptics in the nigrostriatal pathway.^{1, 2, 9} Many individuals receiving low-potency neuroleptics have a therapeutic antipsychotic response without extrapyramidal dysfunction, probably due to the significant cholinergic receptor blockade caused by these drugs.

Acute Dystonic Reactions

Acute dystonic reactions occur in 2-10% of patients treated with neuroleptic agents.^{5, 23, 37} Their frequency is highest among men under age 30

years.²³ The reactions typically occur within 24–48 hours after the first dose, but they can also occur or recur when dosages are increased.³⁷ The slow-release injectable neuroleptics, such as fluphenazine decanoate and haloperidol decanoate, usually produce reactions within 72 hours after injection.¹

These reactions are of sudden onset and typically consist of bizarre movements involving tonic contractions of skeletal muscles of the eyes, face, neck, and throat.^{1, 38} Common symptoms consist of intermittent or sustained muscular spasm manifested as torticollis, swollen tongue, trismus, and oculogyric crisis, and occasionally opisthotonus can occur.^{1, 23, 37} Torticollis is most frequent in younger people and males, and tends to decrease with increasing age.^{24, 37, 39, 40}

Dystonic reactions most commonly occur when neuroleptic-induced postsynaptic dopamine blockade is followed by a rapid fall of the neuroleptic concentration in the striatum. Based on this observation, one theory postulates that the reactions are a result of the compensatory release of dopamine that is activated when dopamine autoreceptors are blocked. Since an increased amount of dopamine is present when the neuroleptic concentration falls, a dyskinesia similar to those caused by levodopa is seen. However, studies with drugs that inhibit synthesis of, or deplete, dopamine usually find that these agents either cause or potentiate dystonic reactions, which suggests that the reactions result from a decrease rather than an increase of dopamine.⁴¹ Dopamine dysregulation may also lead to changes in the cholinergic system, resulting in increased cholinergic activity in the basal ganglia.

Akathisia

Akathisia is a common and distressing form of EPS that can occur within days to months after initiating therapy.¹ It occurs in approximately 20% of patients receiving neuroleptic drugs, and the frequency ranges from 5–50% or more in patients receiving moderate dosages of high-potency agents.^{23, 26} The frequency also increases as the dosage is escalated. Akathisia is commonly associated with noncompliance and may even lead to suicide attempts in some individuals.^{4, 42} Therefore, early recognition and treatment are of great clinical importance.

The definition of akathisia includes both subjective and objective components. The subjective component often is a feeling of inner anxiety or tension, and the objective component includes motoric restlessness, inability to remain

still, and pacing.^{1, 2, 10, 26} Since akathisia can manifest as increased anxiety, it is often difficult to distinguish it from re-emerging psychosis or anxiety due to underlying psychiatric illness.⁴ The pathophysiology of akathisia is poorly understood. When induced by neuroleptics, it may reflect postsynaptic blockade in the frontal cortex innervated by the mesocortical dopamine pathway.⁵ Alternatively, it may result from dysregulation of any of the neuromodulators of this pathway, such as norepinephrine or GABA.

Treatment

The EPS may be bothersome or unbearable, and pharmacologic treatment can improve patient compliance with neuroleptic agents.⁴² Treatment may be by any of several different modalities. In some cases, EPS may be terminated or decreased by reducing the dosage of the neuroleptic.^{27, 31, 33} Switching from a high-potency to a low-potency drug that has more anticholinergic activity may also decrease EPS.^{1, 28} If these strategies are inappropriate or ineffective, a centrally acting anticholinergic or dopaminergic agent might be tried.⁴³

Of all the extrapyramidal reactions, dystonias are the most responsive to treatment; they are easily controlled by parenteral or oral administration of anticholinergics.¹ Benzodiazepines may also be useful in the treatment of acute dystonias. Parkinsonism has been successfully treated with anticholinergic and dopaminergic drugs. Several drugs are effective in patients with akathisia, including anticholinergics, benzodiazepines, clonidine, β -adrenergic blockers, amantadine, amitriptyline, opioids, and lithium.^{44, 45}

Anticholinergic Agents

Parkinsonism

Table 2 lists the commonly used anti-EPS agents, their relative potencies, and usual dosing regimens.^{46–59} Currently available anticholinergics do not differ in efficacy, and all decrease rigidity more than tremor.^{28, 60, 61} Although they differentially bind to muscarinic receptor subtypes, this does not appear to affect their usefulness in this setting.⁶² The primary differences among them are their duration of action and extent of sedation. Benztropine is typically given 1–3 times/day, and diphenhydramine 2–4 times/day. Trihexyphenidyl has a shorter duration of effect and tends to be dosed 3–4 times/day.^{28, 63, 64} Diphenhydramine and benztropine are quite sedating, but trihexyphenidyl may be less sedating.^{28, 46}

Table 2. Common Dosages of Anti-EPS Agents

	Daily Dose (mg)	Dosing Frequency	Route	Indications
Anticholinergic				
Benztropine	1-6	q.d.-t.i.d.	p.o./i.m./i.v.	Akathisia, acute dystonic reaction, parkinsonism
Trihexyphenidyl	5-15	t.i.d.-q.i.d.	p.o.	
Diphenhydramine	50-200	b.i.d.-q.i.d.	p.o./i.m./i.v.	
Biperiden	2-16	q.d.-t.i.d.	p.o./i.m./i.v.	
Procyclidine	5-30	t.i.d.	p.o.	
Dopaminergic				
Amantadine	100-300	b.i.d.-t.i.d.	p.o.	Parkinsonism
Benzodiazepines^a				
Lorazepam	1-5	q.d.-t.i.d.?	p.o./i.m./i.v.	Akathisia, ?acute dystonic reaction
Diazepam	2-10	t.i.d.?	p.o./i.v.	
Clonazepam	0.5-1.5	q.d.-t.i.d.?	p.o.	
β-Blockers				
Propranolol	30-80	b.i.d.-t.i.d.	p.o.	Akathisia
Metoprolol	50-200	b.i.d.	p.o.	

^aDosing frequencies for benzodiazepines are based on the minimal information available. 90-95
Adapted from references 46-59.

Acute Dystonic Reactions

These are often treated with parenteral drugs, but many less severe reactions can be managed adequately with oral agents, although the onset of effect is longer than with parenteral treatment. Anticholinergics usually result in improvement within 10 minutes of parenteral administration, and peak benefits occur within 30 minutes.²³ Comparisons of intravenous and intramuscular administration among different anticholinergics in acute dystonia have not been published, but benefit reportedly occurs more slowly after benztropine than diphenhydramine.²⁷

The usual intravenous or intramuscular dose of diphenhydramine is 25-50 mg, and for benztropine 0.5-2 mg; doses may be repeated in 30 minutes.²⁷ Once the acute dystonia is controlled, anticholinergics should be continued orally for at least three to four doses,²³ and possibly as long as 7-28 days.^{39, 65} Typical therapy consists of oral benztropine 1-2 mg 1-3 times/day, or oral diphenhydramine 25-50 mg 2-4 times/day.^{10, 66} If neuroleptic therapy is discontinued, anticholinergics should be continued for at least 3 days and then tapered, because residual dopamine-blocking activity may continue.⁶⁵ The tapering schedule should be based on the dosage and duration of anticholinergic treatment. Abrupt discontinuation of anticholinergic agents in a patient who has received large daily doses for a prolonged period of time could result in a cholinergic rebound syndrome, such as that reported after abrupt withdrawal of highly anti-

cholinergic tricyclic antidepressants such as amitriptyline.⁶⁷

Akathisia

Dystonias and parkinsonism generally respond favorably to anticholinergic agents, but akathisia responds less favorably.⁴³ Treatment of akathisia was evaluated in 44 patients receiving maintenance doses of haloperidol 10 mg/day and 67 receiving thiothixene 0.44 mg/kg/day. Thirty-two patients in both groups had akathisia that was treated with either benztropine 8 mg/day or trihexyphenidyl 15 mg/day.⁶⁸ The presence and severity of akathisia were rated on a 7-point involuntary movement and extrapyramidal scale formulated by the investigators. Akathisia was suppressed in 44% of the patients receiving haloperidol and in all but three patients receiving thiothixene. The authors hypothesized that the refractory akathisia experienced by patients receiving haloperidol may have been related to unusually low anticholinergic levels, and speculated that dosages exceeding the upper limit recommended by the manufacturer might have resulted in a better response. However, they did not report how well patients tolerated the relatively large dosages of anticholinergics given in this study. Although some patients might respond to high dosages of benztropine or trihexyphenidyl, it is likely many would not be able to tolerate the associated side effects.

It was initially observed that anticholinergic agents work well in patients whose akathisia is accompanied by parkinsonism.²⁶ Two additional

studies^{69, 70} and one case report⁴⁷ confirmed this. Factors that complicate the comparison of studies evaluating anticholinergics in the treatment of akathisia include the use of different dosages, dissimilar patient populations, and the variety of rating scales for EPS. In addition, although drug concentrations may affect the therapeutic outcome, serum anticholinergic concentrations were measured only rarely.⁷¹

Summary

Although anticholinergic drugs are often beneficial in patients suffering from neuroleptic-induced EPS, their beneficial effects must be considered in balance with their bothersome peripheral side effects such as dry mouth, blurred vision, tachycardia, urinary retention, and constipation. Since anticholinergic effects are additive, combinations of psychotropic agents with anticholinergic properties may produce an anticholinergic delirium, characterized by hallucinations, delusions, and confusion.⁶¹ This adverse event, which seems particularly prominent in the elderly, may be misdiagnosed as an acute episode of psychosis. When administered in the short term, anticholinergics decrease performance on tests of memory acquisition in both schizophrenic patients and healthy controls.^{72, 73} In addition, many elderly patients with neuroleptic-induced parkinsonism may show clinical signs of dementia, and further decrements in central acetylcholine neurotransmission may cause significant impairment in cognitive function.⁹

These drugs also affect the psychotic process. They weakly antagonize the beneficial effects of neuroleptics on positive symptoms⁷⁴ and worsen positive symptoms in otherwise drug-free schizophrenic patients.^{75, 76} Conversely, they may have beneficial effects on negative schizophrenic symptoms,^{77, 78} and their withdrawal may occasionally result in worsening of the clinical state.⁷⁹ Consequently, the clinical response after adding or withdrawing an anticholinergic from the drug regimen of a schizophrenic patient must be closely monitored.

Dopaminergic Agents

Parkinsonism and Akathisia

The most direct approach to the treatment of parkinsonian symptoms is to increase striatal dopamine neurotransmission. In Parkinson's disease this is accomplished with a dopamine precursor (L-dopa), a direct dopamine agonist (bromocriptine), or an indirect agonist (amanta-

dine). The action of L-dopa in drug-induced EPS was evaluated in 20 schizophrenic patients who were receiving antiparkinson therapy for EPS.⁸⁰ Patients were tapered off their anti-EPS drug before initiating therapy with L-dopa. Sixteen patients developed severe deterioration in psychomotor symptoms on discontinuing antiparkinson therapy and never received L-dopa. The four remaining patients eventually received L-dopa 500 mg/day, with a 200-mg incremental increase every other day to a maximum range of 1.4–2.6 g/day. Unfortunately, these four patients had a deterioration in behavioral status in combination with no or minimal reduction in EPS. Overall, the authors concluded that L-dopa is not helpful in the treatment of drug-induced parkinsonism, since it exacerbates existing psychotic symptoms without relieving EPS. Because of the risk of psychosis, L-dopa and bromocriptine are not used to treat neuroleptic-induced parkinsonism.^{1, 18, 81}

The only prodopaminergic drug indicated for the treatment of neuroleptic-induced EPS is the indirect agonist amantadine. Unlike anticholinergic agents, amantadine does not adversely affect memory⁷² or produce autonomic side effects. Another advantage is its ability to lower elevated prolactin levels, a side effect of neuroleptic agents.⁸²

In a series of four case reports, amantadine was not effective in treating neuroleptic-induced akathisia because tolerance developed after 1 week of therapy.⁸³ However, most controlled trials evaluating amantadine 100–400 mg/day found it to be as effective as anticholinergic agents in controlling EPS, including parkinsonian symptoms and akathisia, with fewer anticholinergic adverse effects.^{80–89} Of importance, exacerbations of psychosis or other detrimental effects on mental status were not observed with the small dosages of amantadine. Although the frequency of side effects caused by amantadine is low, dry mouth, excitement, and blurred vision have been reported in patients taking this drug for EPS.⁸⁵

Summary

Available data indicate that amantadine has similar efficacy as benztropine for parkinsonism symptoms, but few data are available concerning its use for akathisia, and none regarding its efficacy in the treatment of acute dystonic reactions. A drawback of amantadine is higher cost compared with the more commonly used anticholinergic agents. However, because of the lower frequency of anticholinergic side effects, amantadine might be an attractive alternative in patients who poorly tolerate anticholinergics due to such disorders as

benign prostatic hyperplasia, narrow-angle glaucoma, and pre-existing dementia.

Benzodiazepines

Diazepam, lorazepam, and clonazepam have been used in the treatment of acute dystonia^{70, 90-92} and akathisia^{49, 91, 93, 94} with some success. Only a single study evaluated their efficacy in the treatment of neuroleptic-induced parkinsonism.⁹⁵

Akathisia

Akathisia may result from a hypersensitivity of the noradrenergic locomotor neurons, which could modulate dopaminergic pathways. Benzodiazepines may counterbalance increased noradrenergic activity through their interaction with inhibitory GABA neurons.⁹⁴

In an open trial, lorazepam 1.5-5 mg (mean dose 2.34 mg) was administered to 16 patients with neuroleptic-induced akathisia.⁹⁴ Patients were evaluated on days 7 and 14 of therapy using clinical observations and a rating scale formulated by the investigators.⁹⁶ Lorazepam reduced (Dunn Rankin, $p < 0.001$) akathisia scores in nine patients. Moderate improvement occurred in five patients, and no change was evident in two. Five of the patients who improved also received the anticholinergic biperiden, however, making the results difficult to interpret.

In the second open trial, oral clonazepam 0.5 mg/day was evaluated in 10 young patients (mean age 17.1 yrs) who were experiencing distressing neuroleptic-induced akathisia.⁴⁹ Nine patients also received benztropine (mean dose 2.8 mg/day, range 2-4 mg/day) during the trial. All patients were assessed using the akathisia subscale of the Chouinard EPS rating scale (severity scores on specific items in this scale may range from 0 = absent to 6 = most severe).⁹⁷ The mean score decreased from 4.1 before treatment to 1.6 after 1 week of treatment (Wilcoxon matched pairs test, $p < 0.005$). All 10 patients reported subjective improvement. The authors concluded that clonazepam, when added to routine antiparkinson therapy, effectively controls neuroleptic-induced akathisia.

Akathisia and Dystonia

Although benzodiazepines are not routinely used for dystonia, a single double-blind study yielded encouraging results. Diazepam was compared with diphenhydramine in patients requiring immediate relief from severe acute neuroleptic-induced dystonia or akathisia.⁷⁰ Forty intravenous

treatments were received by 27 patients. Subjects were rated on a 4-point scale for dystonia or akathisia (0 = no symptoms to 3 = severe symptoms) before and at 5, 15, 30, and 120 minutes after intravenous diazepam or diphenhydramine. Of the 20 patients with dystonia, 10 received diazepam 5 mg and 10 diphenhydramine 50 mg. Of the 20 with akathisia, 11 were treated with diphenhydramine and 9 with diazepam. Both drugs were equally effective in relieving dystonic reactions or akathisia symptoms, with a significant reduction (paired *t* test, $p < 0.01$) in scale scores after 5 minutes.

Akathisia and Parkinsonism

In a Japanese study 117 patients with chronic schizophrenia being treated with concomitant neuroleptic and anti-EPS agents were withdrawn from the latter for 6 weeks. During this time patients were monitored weekly for signs of either neuroleptic-induced akathisia or parkinsonism.⁹⁵ Patients were scored for akathisia using a 0 (absent) to 4 (extremely severe) rating scale for motor restlessness, internal discomfort, and unpleasant sensation. A similar scale (0-4) for parkinsonism rated rigidity, akinesia, tremor, posture, and gait. At the end of 6 weeks, patients who had developed EPS were randomized to receive either clonazepam 1.5 mg/day or a resumption of their anti-EPS drug (biperiden, trihexyphenidyl, promethazine, prophenamine, methixene, or amantadine) using a double-blind design, and followed with weekly EPS ratings for an additional 6 weeks. If EPS symptoms persisted, an additional dose of clonazepam 1.5 mg was administered daily. Twelve patients were randomized to receive clonazepam, and 10 their previous anti-EPS drug. Clonazepam was effective in seven of eight patients with akathisia, but in only one of the four with parkinsonism. The anti-EPS agent was effective for akathisia in four of six patients and for parkinsonism in four of five. Although the authors concluded that their results confirmed the efficacy of clonazepam in the treatment of akathisia, no statistical analysis was performed, and the study population was too small to support this conclusion.

Summary

Although the evidence does not convincingly support benzodiazepines as first-line agents in the treatment of akathisia or dystonia, they might be considered in patients with relative contraindications to anticholinergics, such as narrow-

angle glaucoma and prostatic hyperplasia. The aforementioned studies reported positive results with these drugs, but most samples were quite small. Also, because some trials administered benzodiazepines in conjunction with anticholinergic agents, it is unclear if benzodiazepines work alone or if they potentiate the effects of anticholinergics. Since study durations generally were short, it is unclear if tolerance develops with continued use. Therefore, no firm conclusions regarding long-term oral benzodiazepines can be drawn based on currently available data, but these drugs might be indicated when others fail to alleviate dystonia or akathisia.

β -Adrenergic Blockers in Akathisia

Currently, although some β -blockers appear to be effective in neuroleptic-induced akathisia,^{44, 45} not all studies reached that conclusion.^{98, 99} The mechanism by which the agents reduce akathisia is unclear.⁵⁰ The effects may be mediated through β_1 - or β_2 -blockade of receptors located either peripherally or centrally.⁵¹

Propranolol

Propranolol is a highly lipophilic, nonselective β_1 - and β_2 -receptor antagonist. Most studies evaluating the drug in akathisia concluded that it is efficacious (Table 3).^{48, 50, 51, 54-58, 100, 101} Clinical response typically occurs within 1 hour of the first dose, and maximum response is usually observed within 24-48 hours.^{50, 51, 55} In one direct comparison with benztropine, propranolol more effectively alleviated symptoms of akathisia.¹⁰⁰ Patients who received benztropine experienced some memory impairment, an adverse effect that also was documented by other investigators.^{71, 102-104} Propranolol effectively treats akathisia, but, unfortunately, concomitant parkinsonian symptoms remain unaffected. Many patients with neuroleptic-induced akathisia also suffer from parkinsonism, and thus require an antiparkinsonian agent in addition to propranolol.

Two studies concluded that propranolol is not efficacious in the treatment of akathisia.^{98, 99} In one of these trials, a single intravenous dose of benztropine was compared with propranolol.⁹⁹ Benztropine reduced both the subjective and objective components of akathisia, but propranolol was not effective in either of these measures. It is possible that the dose of propranolol (1 mg) was too small, or that several doses are required in the treatment of akathisia. However, since the other studies did not directly compare anticholinergic

agents with propranolol, it cannot be stated conclusively that one is superior to the other, although anticholinergics probably are effective in some proportion of patients. This complicates the evaluation of results with propranolol, because in at least two studies, patients received both anticholinergic drugs and propranolol.^{48, 54}

In individual patients it can be difficult to determine whether motoric restlessness and general agitation are due to akathisia or the underlying disease state. In one study propranolol successfully alleviated both subjective and objective ratings of akathisia but did not affect anxiety ratings.⁵⁸ This suggests that akathisia and anxiety may be dissociated, and underlying anxiety may also require treatment.

Propranolol 30-80 mg/day shows promising results in treating drug-induced akathisia. Adverse effects on blood pressure and heart rate are minimal at these dosages, but mild wheezing occasionally occurs in patients with asthma.⁵¹

Other β -Blockers

Since most studies agree that propranolol effectively treats neuroleptic-induced akathisia, investigators have questioned whether similar benefits might exist with less lipophilic or more cardioselective β -antagonists. Drugs that have been studied include betaxolol, a lipophilic β_1 -blocker; sotalol, a hydrophilic, nonselective β -blocker; nadolol, a hydrophilic, nonselective β -blocker; metoprolol, a lipophilic β_1 -blocker; and atenolol, a hydrophilic β_1 -blocker.

Metoprolol was compared with propranolol in five patients receiving neuroleptics in an open-design trial.⁵⁵ Both drugs effectively reduced akathisia but, even at high dosages, metoprolol produced less improvement. Clinically significant decreases in mean pulse (17.2 beats/min) and blood pressure (15.2 mm Hg) were also observed with metoprolol but not with propranolol. No statistical comparisons were performed, but the authors concluded that both agents were effective. However, metoprolol was effective only in controlling akathisia at noncardioselective dosages. In addition, since low dosages of propranolol alleviated akathisia, but did not produce signs of significant peripheral β_1 -blockade (e.g., reduction in pulse rate or blood pressure), it was concluded that the antiakathisia mechanism involves either central or peripheral β_2 -receptor blockade.

In contrast, another study found metoprolol efficacious in relieving akathisia at β_1 -selective dosages.¹⁰¹ Nine patients received metoprolol for

Table 3. Studies of β -Blockers in Akathisia

Drug	Daily Dose (mg)	Study Design	No.	Results	Statistics
Propranolol ⁵⁰	30	Open	12	9/12 complete remission.	None performed.
Propranolol ⁵¹	30-80	Open	14	9/14 complete remission.	None performed.
Propranolol vs benztropine ¹⁰⁰	40-80 1.5-4	Open, parallel	Pro (9) Ben (8)	50% decrease in objective and subjective ratings for Pro; no change in objective and subjective ratings for Ben	ANOVA. Pro: $p \leq 0.001$ over time in objective and subjective scales.
Propranolol vs lorazepam ⁴⁸	20-30 2	Single-blind, crossover	6	Improvement in both subjective and objective ratings for Pro; improvement in objective for Lor.	ANOVA. Pro: objective $p=0.001$, subjective $p=0.017$. Lor: objective $p=0.048$.
Propranolol vs placebo ⁵⁸	20-60	Double-blind, crossover	12	Improvement on both subjective and objective ratings in comparison with Plb.	ANOVA. Pro: $p < 0.001$ for both subjective and objective rating scales.
Propranolol vs placebo ⁵⁴	60	Double-blind	Pro (10) Plb (10)	Pro more effective than Plb on a scale measuring both subjective and objective features of akathisia.	ANOVA. $\chi^2 p < 0.001$.
Propranolol vs placebo ⁹⁸	60-80	Double-blind	Pro (6) Plb (5)	Neither group showed any improvement in akathisia.	No significant differences.
Propranolol vs benztropine vs placebo ⁹⁹	i.v. doses Pro: 1 mg Ben: 2 mg	Single-dose, double-blind, randomized	6	Global rating scale showed improvement for Ben at 15, 30, and 60 min; Pro showed no significant effects.	Ben: $p < 0.05$ global score better than Plb at 15, 30, and 60 min; subjective scale better than Plb at 60 minutes.
Propranolol vs metoprolol ⁵⁵	30-80 200-400	Open, crossover	5	Both agents were effective, but Pro was more effective.	Not performed
Propranolol vs metoprolol ¹⁰¹	40-60 50-100	Open, crossover	9	Both agents effective in subjective and objective measures.	ANOVA. Pro: $p < 0.007$. Met: $p < 0.003$.
Propranolol vs metoprolol ⁵⁶	60 75	Open, randomized, crossover	8	Both agents effective, but those receiving Pro first improved more.	ANOVA. Order by time interaction subjective ($p < 0.03$), objective ($p < 0.04$).
Propranolol vs atenolol ⁵⁷	20-60 25-100 mg	Open, crossover	7	Pro effective on both objective and subjective scales; Atn not effective.	ANOVA Pro: $p < 0.05$, improved on both scales. Atn: $p < 0.05$, worse on both scales.
Nadolol vs placebo ¹⁰⁵	40-80	Double-blind	Nad (10) Plb (10)	Nad not more effective than Plb.	<i>t</i> tests; not significant.
Propranolol then sotalol then betaxolol ¹⁰⁶	20-40 40-80 10-20	Open	16	Pro decreased akathisia in 8/16; 6 received sotalol, and akathisia did not improve in any; 4 then received betaxolol and all improved.	Not performed.

Pro = propranolol; Nad = nadolol; Met = metoprolol; Plb = placebo; Atn = atenolol; Ben = benztropine; Lor = lorazepam.

3-11 days and then were directly crossed over to propranolol for 3-19 days. Significant improvements in both subjective and objective measures of

akathisia occurred with both drugs. In a follow-up nonblinded, randomized study, eight patients received either propranolol or metoprolol for 1 day,

followed by a 1-day washout and crossover to the alternative agent for 1 day.⁵⁶ Both drugs were effective, but patients receiving propranolol first showed greater improvement.

Hydrophilic β -blockers are not as successful as lipophilic β -blockers in the treatment of akathisia. In an open study, atenolol did not control akathisia in seven patients when taken for up to 3–4 days.⁵⁷ A placebo-controlled, double-blind study of nadolol in 20 psychiatric patients with neuroleptic-induced akathisia reported no significant differences from placebo in either subjective or objective assessments, even after 15 days of treatment.¹⁰⁵ This lack of efficacy may be because hydrophilic β -blockers do not enter the central nervous system as readily as lipophilic β -blockers. This suggests that blockade of central β -receptors might be necessary to control akathisia.

The effects of propranolol, sotalol, and betaxolol were compared in an open trial in 16 patients suffering from neuroleptic-induced akathisia.¹⁰⁶ Propranolol was effective in eight patients and led to partial improvements in three. Responses occurred within 48 hours. The eight responders received propranolol for 6 months; six of them continued on to phase II, which was initiated with a 2-week washout period, followed by sotalol for 2 days. None of the six responded to sotalol, even when the dosage was increased to 80 mg/day. Four of these patients then received betaxolol after a 2-week washout period, and experienced relief of akathisia within 2 days. Since sotalol did not relieve symptoms, the authors concluded that lipophilic agents such as betaxolol and propranolol are likely to be effective through a central β_1 mechanism. Although the results obtained by most other authors^{56, 101, 107} support this conclusion, lipophilic β_1 -specific agents such as metoprolol have not always treated akathisia as effectively as propranolol.⁵⁵

Certain patients may be unable to use β -blockers due to underlying cardiovascular disease. Two case reports suggest that pindolol, which has intrinsic sympathomimetic activity at dosages of 5 mg/day, might be an attractive choice for treating neuroleptic-induced akathisia in patients with sinus bradycardia.^{108, 109}

Lipophilic β -blockers, especially propranolol, effectively ameliorate symptoms of this disorder. Based on currently available reports, propranolol 30–80 mg/day or metoprolol 50–200 mg/day would be the most effective. Unfortunately, in many studies, patients also received amantadine, anticholinergic agents, or benzodiazepines in addition to the β -blockers, drugs that may have

potentiated the effects of the β -blockers. However, these other agents are necessary because they treat neuroleptic-induced parkinsonism, whereas β -blockers do not. The addition of benzodiazepines may be beneficial in treating the inner restlessness that often accompanies akathisia but that may not respond to β -blockers alone. Although lipophilic β -blockers are most effective, further research is necessary to determine whether β_1 - or β_2 -receptor blockade, or a combination of both, is responsible for the beneficial effects.

Other Agents

Since β -blockers may work by central adrenergic blockade, other drugs with central activity have been investigated. Clonidine, an α_2 -adrenergic agonist, is believed to exert its effects by decreasing central noradrenergic neurotransmission by autoregulation. In an open, on-drug/off-drug trial, six patients with drug-induced akathisia received clonidine 0.2–0.8 mg/day.¹¹⁰ All patients improved, and four experienced complete relief. The dosage was limited in two patients by postural hypotension and sedation. Maximum benefit occurred within 24–48 hours. After the drug was discontinued, symptoms of akathisia returned to pretreatment levels within 24–48 hours. During observation for 1 month, no patients developed tolerance to clonidine. On the basis of this preliminary trial, the authors concluded that clonidine may be effective in this disorder, although side effects may limit its acceptability.

A single-blind clonidine study was conducted in six schizophrenic patients with akathisia who had a rating of at least 1 on a modified Simpson-Angus EPS scale.¹¹¹ The dosage was adjusted, based on improvement and side effects, from 0.05–0.2 mg/day over 3–15 days, to a maximum of 0.15–0.4 mg/day. All patients had improvement in objective and subjective symptoms at maximum dosages (paired Student's *t* test, $p < 0.005$ and $p < 0.008$, respectively), and four had improvement in subjective symptoms by days 2–4 of the study. The upward titration was limited in five patients by hypotension, and four patients experienced sedation. Clonidine also caused a small but significant reduction (paired Student's *t* test, $p < 0.026$) in anxiety, which the authors attributed to sedation. Further research might reveal whether transdermal administration would be effective and associated with fewer side effects.

Sodium valproate 900–2400 mg/day (mean 1700 mg/day), biperiden 6–18 mg/day (mean 12 mg/day), and placebo were evaluated in 15 patients

with neuroleptic-induced EPS.⁶⁹ All patients had objective and subjective signs of akathisia, and 11 also had neuroleptic-induced parkinsonism. All 15 received each drug for 4 weeks in randomized fashion. Overall, sodium valproate did not significantly improve akathisia, whereas biperiden reduced the symptoms (Wilcoxon's test, $p < 0.01$) in 11 patients. Observed side effects for all three agents were minimal, with no significant differences among them. However, sodium valproate induced parkinsonian symptomatology in seven patients without necessarily aggravating akathisia. This suggests that the two syndromes may depend on different mechanisms.

Case reports or open trials have been conducted with amitriptyline,¹¹² opioids,¹¹³ and lithium¹¹⁴ in the treatment of neuroleptic-induced akathisia. Although the drugs may reduce the symptoms, it is difficult to draw any conclusions from the limited published data.

Prophylaxis

Approximately 90% of acute neuroleptic-induced EPS occur within the first 2–3 months of therapy.²⁷ Because most of these reactions can be controlled quickly with anticholinergic or other anti-EPS drugs, some clinicians prefer to treat them only after they occur.^{65, 74} Others believe that the occurrence of EPS may decrease patient acceptance of neuroleptic therapy, and that anti-EPS agents should be taken prophylactically for at least the first few months of neuroleptic therapy.^{28, 39, 60}

Prophylactic antiparkinson therapy to prevent neuroleptic-induced EPS is a matter of controversy. Studies evaluating the initial prophylaxis and prevention of EPS were reviewed.¹¹⁵ At least six retrospective studies have been published.^{24, 25, 38, 60, 116, 117} Results were mixed, with three^{60, 116, 117} concluding that prophylactic anti-EPS drugs are unnecessary in the majority of patients, and three^{24, 25, 38} stating that they are effective and justified. These studies relied heavily on chart review, and their designs usually did not include controls or randomization; nor were patients assessed with clinically validated EPS scales. Consequently, conclusions should be based on the results of prospective studies.

Eight prospective studies have been published (Table 4).^{39, 74, 118–123} In the largest of these, 202 newly hospitalized schizophrenic or schizoaffective patients were monitored for the occurrence of dystonic reactions.¹¹⁹ Patients received various neuroleptic drugs, including seven high-potency and two low-potency agents. Patients were not

randomized to study groups, nor were the investigators or patients blinded to therapy. A total of 116 patients received prophylaxis, and 86 did not. The occurrence of dystonic reactions was not significantly different between the groups. Of the 95 patients who received haloperidol (high-potency), however, dystonic reactions were significantly more likely to occur in patients in the nonprophylaxis group. None of the 33 patients receiving low-potency drugs developed dystonic reactions.

Another relatively large study was conducted in 112 hospitalized patients who were referred, without regard to diagnostic category, for neuroleptic treatment due to symptoms of anxiety, agitation, restlessness, or combativeness.¹²⁰ They received at least a single tablet daily of either perphenazine 12 mg or perphenazine 12 mg plus benztropine 0.75 mg. Only 6 (10%) of 60 patients receiving prophylaxis experienced EPS, compared with 17 (27%) of 62 receiving perphenazine alone. The investigators did not include a statistical analysis, but a later statistical evaluation reported a significant difference ($p < 0.01$) in the frequency of EPS between the two groups.¹¹⁵ However, these results are confounded by the fact that patients receiving perphenazine alone were treated with higher dosages (39.5 mg/day) than those who received perphenazine plus benztropine (28.7 mg/day).

One of the earliest studies evaluated 83 inpatients (diagnosis not specified) who were given either placebo or benztropine while taking one of four neuroleptics.¹²¹ The study lasted 31 days, during which significantly fewer patients who received benztropine experienced EPS. Patients received low- (chlorpromazine, thioridazine) or medium- to high-potency (perphenazine, trifluoperazine) phenothiazines, but there was no comparison of drug potency or dosage between the placebo and benztropine groups. Also, it was not stated if patients were neuroleptic free on entering the study.

In one of two studies published in 1986, 39 newly hospitalized, psychotic patients who were receiving high-potency neuroleptics (trifluoperazine, thiothixene, haloperidol, or fluphenazine) were given a 7-day course of placebo or benztropine.³⁹ Based on medical charts and nursing reports, significantly more patients receiving placebo developed acute dystonic reactions. The authors concluded that 7 days of benztropine prophylaxis was associated with a decreased frequency of acute dystonic reactions without a significant increase in anticholinergic side effects, but the daily dose of

Table 4. Prospective Studies of the Prophylaxis of EPS

Drugs	Daily Dose (mg)	Design	Results	Statistics
Various neuroleptics + benzotropine (n=109) trihexyphenidyl (n=3) diphenhydramine (n=4) no prophylaxis (n=86) ¹¹⁹	2-4 6-15 75-150	Open	Overall, patients in the prophylaxis group had similar number of dystonic reactions as the no-prophylaxis group; but in the group that received haloperidol, fewer dystonic reactions with prophylaxis.	All patients: $\chi^2 = 1.76, p > 0.1$. Haloperidol (only): $\chi^2 = 7.86, p < 0.005$.
Perphenazine alone (n=62) Perphenazine + benzotropine (n=60) ¹²⁰	1.79	Double-blind, randomized	After 6 wks, patients receiving prophylaxis experienced less EPS.	Not performed.
Various neuroleptics + benzotropine (n=42) placebo (n=41) ¹²¹	?	Double-blind, randomized	1/42 patients receiving prophylaxis suffered EPS, but 13/41 receiving placebo suffered EPS.	Significant difference $p < 0.01$, patients receiving benzotropine suffering less EPS.
High-potency neuroleptics + benzotropine (n=22) placebo (n=17) ³⁹	4	Double-blind, randomized	0/22 patients receiving benzotropine developed dystonic reactions, but 8/17 receiving placebo had dystonic reactions within 48 hours of first neuroleptic dose.	$\chi^2 = p < 0.002$ in favor of benzotropine.
Various neuroleptics + trihexyphenidyl (n=15) placebo (n=27) ¹²²	7.5-15	Double-blind, randomized	More patients dropped out in the placebo group; the prophylaxis group exhibited less akinesia and sialorrhea.	$p < 0.001$, significant difference in early termination; akinesia, $p < 0.05$; sialorrhea, $p < 0.01$.
Haloperidol + benzotropine (n=14) placebo (n=15) ¹²³	4	Double-blind, randomized	2/14 patients taking benzotropine and 5/15 patients taking placebo suffered dystonic reactions within 7 days; 3 additional patients had dystonic reactions when benzotropine was discontinued.	Difference in dystonic reactions in first 7 days, NS.
Flupenthixol + procyclidine (n=18) placebo (n=18) ⁷⁴	15	Double-blind, randomized	One patient receiving procyclidine and 6 patients in the placebo group required supplementary procyclidine; overall, placebo group exhibited more EPS.	Kruskal-Wallis $p < 0.02$ overall; total of separately scored EPS items.
Haloperidol alone (n=10) Haloperidol + procyclidine (n=10) Haloperidol + promethazine (n=13) ¹¹⁸	15 mg 75 mg	?Single-blind, randomized	7/10 patients dropped out of the haloperidol (alone) group; 3/13 dropped out of the haloperidol + promethazine group, and none dropped from the haloperidol + procyclidine group.	No significant differences were found between the haloperidol + promethazine and the haloperidol + procyclidine groups; haloperidol alone was not included in analysis.

benztropine (4 mg) was relatively low.

Also in 1986, 42 psychotic outpatients received either placebo or trihexyphenidyl in combination with their neuroleptic agents.¹²² For comparison, patients were evaluated weekly using the 10-item Simpson-Angus scale that rates the severity of primarily parkinsonian symptoms from 0 to 4.¹²⁴ Patients receiving trihexyphenidyl had significantly less akinesia and sialorrhea than those receiving no prophylaxis. Unfortunately, the dosages of neuroleptics were not compared.

Prophylaxis with benzotropine was evaluated in 29 patients with schizophrenia, bipolar disease (manic), atypical psychosis, or schizoaffective

disorder.¹²³ Patients were treated with haloperidol (mean dose \pm SD 14.1 \pm 3.3 mg) and also received lorazepam to control anxiety. They then received benzotropine or matching placebo for the first 7 days of the study, followed by open-label dosing of benzotropine on an as-needed basis to control dystonia on days 8-14. A single evaluator assessed patients twice a day for EPS using the Simpson-Angus EPS scale.¹²⁴ Overall, fewer patients in the benzotropine group experienced dystonic reactions, but the difference was not statistically significant. The sample was very small, and the concurrent administration of lorazepam may have influenced the overall frequency of dystonic reactions.

In the only prospective study that did not conclude that prophylactic anti-EPS treatment is warranted, 36 schizophrenic inpatients were given an oral neuroleptic, flupenthixol, for 10 days before the addition of placebo or procyclidine for an additional 18 days.⁷⁴ The EPS were rated before any drug, and then twice a week for the duration (18 days) using a seven-item scale developed by the investigators that scored restlessness, choreiform dyskinesia, rigidity in both face and upper body, tremor, and gait disturbance using values from 1–4 (absent–severe). Although the overall total of the separately scored EPS items was significantly lower in the procyclidine group, the investigators discouraged routine EPS prophylaxis with anticholinergic agents because they also found that psychotic symptoms did not respond as well when patients received procyclidine.

The consequences of withdrawal of prophylactic anti-EPS drugs during long-term neuroleptic treatment is an equally controversial topic.¹²⁵ Although the results of double-blind, placebo-controlled studies generally indicated that some proportion of patients receiving neuroleptics suffer from a recrudescence of EPS on discontinuing anti-EPS agents, considerable disagreement exists regarding the actual proportion of patients who require continuous anti-EPS therapy and how long the drugs should be given before a trial discontinuation is attempted.

Only four studies that addressed discontinuing anti-EPS therapy specified the duration of concomitant neuroleptic treatment before discontinuation.^{65, 126–128} In all four the duration of combined therapy was at least 3 months. Three of the studies discouraged long-term anti-EPS therapy. One reported that only 18% of patients switched from anti-EPS agents to placebo required resumption of anti-EPS treatment.⁶⁵ In another study 50% of patients switched from an anti-EPS drug to placebo required a return to active treatment, but the authors still concluded that long-term therapy was warranted only if EPS actually occurred, and that patients should be assessed frequently for the necessity of continued therapy.¹²⁶ In 42 patients with chronic schizophrenia who had been treated with combined neuroleptics and anti-EPS agents for at least 3 months, the change in severity of EPS did not differ significantly whether they were switched to placebo or continued their previous anti-EPS drug.¹²⁷

In the one study in which continued combined use of neuroleptics and anti-EPS agents was deemed necessary, 98 patients with chronic schizophrenia were randomized to receive placebo

(75%) or trihexyphenidyl 7.5–20 mg/day (25%).¹²⁸ Patients were monitored weekly for 6 weeks. In the placebo group, 51 of 75 patients required early termination, and another 21 had some less severe worsening of EPS. In contrast, 20 of 23 patients in the trihexyphenidyl group had no worsening of EPS. The difference was statistically significant ($p < 0.001$).

Overall, these studies reported that anywhere from 10–68% of patients may require resumption of anti-EPS agents after withdrawal when they have received concomitant drugs for at least 3 months. However, it was unclear in most of them whether patients were given the drugs prophylactically or because they had exhibited EPS. The results seem to suggest that a trial without treatment is probably warranted after 3 months, especially if it is unclear why therapy was initiated.

In most studies anti-EPS agents were withdrawn abruptly, and it is possible that some symptoms that could be attributed to anticholinergic withdrawal might have contributed to the need to resume them. To evaluate this possibility, anticholinergic agents were tapered during two of the withdrawal studies.^{129, 130} In neither case did this appear to affect the proportion of patients requiring resumption of treatment.

Patients often receive anti-EPS drugs for the duration of treatment with an antipsychotic, even though evidence suggests that, in a large percentage of such patients, this is unnecessary.⁶⁵ A trial period off anti-EPS therapy after about 3 months appears to be indicated in the majority of cases. If EPS should recur, they can be controlled quickly by reinitiating the agent.^{27, 60, 65} The available data suggest that the best approach to anti-EPS prophylaxis is to individualize therapy. If clinicians are concerned that the development of an acute dystonic reaction might alarm the patient, leading to future compliance problems, prophylaxis might be beneficial.⁶⁰ Patients with a history of EPS, especially dystonic reactions, are most likely to benefit.¹³¹

Conclusion

Acute EPS are common during treatment with drugs that block dopamine receptors. Although these syndromes are to some degree dose dependent, they are also quite patient specific. Direct approaches to treatment include decreasing the dosage of the responsible agent and switching to a neuroleptic agent with greater anticholinergic effects. When a particular neuroleptic has resulted in a good therapeutic response, the clinician may not be able to decrease the dosage and may not

wish to switch to a different drug. In such cases a more appropriate alternative is to administer an agent to alleviate the EPS.

Anticholinergic agents are most commonly used, and they all appear to have equivalent efficacy. Both parkinsonism and acute dystonic reactions respond well, and akathisia is alleviated in a reasonable proportion of patients. These factors, and the relatively low acquisition cost of anticholinergics, make them the first line of treatment for all types of EPS. However, it should be remembered that they may potentiate anticholinergic adverse effects when given in combination with neuroleptic agents. Dosages in the lower part of the recommended ranges should be chosen in the elderly or other patients who are likely to show high sensitivity to anticholinergic effects.

Amantadine is less commonly administered and more costly than the anticholinergic agents. It effectively treats parkinsonism and should be considered as second-line therapy, particularly in patients who cannot tolerate anticholinergic effects. Benzodiazepines appear to attenuate both acute dystonia and akathisia. Information is not available on their long-term efficacy in treating these syndromes, and long-term use is accompanied by the risk of physical dependence. Since no evidence exists that benzodiazepines effectively treat parkinsonism, they should be reserved for patients in whom akathisia is resistant to anticholinergic drugs. It is unlikely that benzodiazepines will ever be widely used in the treatment of acute dystonic reactions because the anticholinergics appear to be universally effective in this disorder.

The β -blockers, specifically propranolol, may effectively treat akathisia, but they are not effective for either acute dystonic reactions or parkinsonism. They should be considered as the second choice for akathisia in patients who do not respond to, or are intolerant of, anticholinergic agents. They should be avoided in patients with a history of asthma, and regular monitoring of blood pressure is highly recommended.

No consensus exists concerning the most appropriate prophylaxis or duration of therapy with the anti-EPS drugs. Perhaps the best strategy would be prophylactic administration in patients who previously suffered acute EPS, and as necessary in other patients. Available data also support a trial discontinuation of anti-EPS therapy after 3 months, reinitiating it if necessary.

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