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# Antipsychotic-Induced Movement Disorders: Evaluation and Treatment

## INTRODUCTION

Antipsychotic drugs are the mainstay of treatment of schizophrenia and other psychotic disorders. The therapeutic efficacy of these drugs is well established. However, these drugs are associated with a wide range of side effects, including a variety of movement disorders. The newer antipsychotics have a lower propensity to cause acute extrapyramidal side effects and tardive dyskinesia.[1]

The movement disorders associated with antipsychotics are disabling and distressing and result in behavioral disturbances (violence and aggression), nonadherence, and exacerbation of psychosis. Some of the motor signs may be misinterpreted as psychotic symptoms. The bradykinesia, limb stiffness, and mask-like facies seen in Parkinsonism are a social and functional handicap. The restlessness and agitation associated with akathisia have similar effects. Patients with tardive dyskinesia may not be distressed

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by their symptoms, but family and relatives may find them distressing. These movements are very obvious to the observer and add to the stigma of psychiatric illness. It is hence very important that a careful evaluation of these symptoms be made in all patients treated with antipsychotics, so that the balance between potential risks and benefits may be optimized. Rating scales may be used to achieve this purpose. This review focuses on the evaluation of the commonly seen movement disorders and available strategies for their management.

The commonly seen extrapyramidal side effects causing movement disorders are summarized in Table 1. For ease of classification, they have been divided into acute and delayed onset movement disorders.

## AKATHISIA

Akathisia consists of motor restlessness accompanied by subjective feelings of inner tension and discomfort, mainly in the limbs. It may coexist with Parkinsonian symptoms, but may be more common, and symptoms can be distressing and cause poor adherence to treatment. It usually appears within the first few days of treatment.[2] Sometimes it may develop only as higher doses are achieved. It may also appear as early as 12 hours after the initiation of therapy.[3] There are other data suggesting that rapidly increasing doses of high potency antipsychotic medication markedly increases the development of akathisia.[4] There have been early studies in young adult mentally ill patients and the elderly that suggest that their occurrence can be associated with a significantly increased risk of tardive dyskinesia.[5]

Symptoms commonly seen are lower-limb movements, rocking from foot to foot, shuffling of legs, or swinging one leg over the other while sitting. In severe akathisia, patients may pace up and down or they may be unable to feel comfortable in any position, such as sitting, lying, or standing, for more than a few minutes. Trunk rolling and fidgeting movements of the upper limbs may also be seen.

**Chronic akathisia.** Akathisia may also be seen in those receiving maintenance antipsychotic treatment. The accompanying subjective sense of restlessness may be less intense in chronic akathisia. In a relatively small number of people, repetitive restless movements characteristic of akathisia may not be accompanied by any sense of inner restlessness or compulsion to move. This is called pseudoakathisia and is more common in male and older patients, and may coexist with negative symptoms and tardive dyskinesia.[6]

**Mechanism of development of akathisia.** The mechanism of development of akathisia is not well understood. It is postulated that it is due to dopamine receptor blockade in brain areas other than the striatum. When akathisia occurs alone in the absence of Parkinsonian symptoms, it may be due to dopaminergic blockade in the mesocortical tract rather than in the nigrostriatal pathway. Other neurotransmitters, including central adrenergic systems, may also be involved.[7]

**Rating scales to measure akathisia.** The most widely used scale for akathisia is the Barnes rating scale for drug induced akathisia.[8] It differentiates between restlessness and any associated distress. The other scales used are the Hillside akathisia rating scale[9] and the Prince Henry Hospital akathisia scale.[10]

**Treatment of akathisia.** The treatment of choice for this poorly understood phenomenon is to lower the dosage of the antipsychotic. This strategy, however, is clinically unrealistic in many acutely ill psychiatric patients. This is a side effect that is not typically responsive to the addition of anticholinergic agents. Various authors of treatment studies looking at traditional antipsychotics have reported inconsistent findings with these agents.[11,12] The therapeutic potential of benzodiazepines may relate to their inherent anxiolytic and muscle relaxant properties.[13,14] The alpha-2 agonist clonidine has been consistently associated with efficacy;[15,16] some clinicians, however, have found it difficult to differentiate between a specific therapeutic effect and sedation. Another effective clinical

**TABLE 1. Extrapyramidal side effects**

| |
|---|
| **Acute** |
| **Parkinsonism** |
| **Acute akathisia** |
| **Acute dystonia** |
| **Chronic** |
| **Tardive dystonia** |
| **Chronic akathisia** |
| **Tardive dyskinesia** |

**TABLE 2. Motor presentations of dystonia**

| |
|---|
| **Torticollis/ Retrocollis** |
| **Trismus** |
| **Dystonia of the trunk and limbs** |
| **Blepharospasm** |
| **Oculogyric crisis** |
| **Glossopharyngeal spasms** |
| **Respiratory stridor/cyanosis** |

**TABLE 3. Symptoms of drug-induced Parkinsonism**

| |
|---|
| **Muscle rigidity** |
| **Tremor** |
| **Bradykinesia** |
| **Postural abnormalities** |
| **Salivation** |

strategy is the addition of beta-adrenergic blockers. A modest dose of propanolol (30–80mg a day) can be effective most often over the first few hours of initiating treatment.[17] Both clonidine and beta blockers have the advantage of not being typically abused, but a disadvantage is hypotension and the potential for rebound hypotension with abrupt discontinuation. Catecholaminergic agents, such as amantadine, have been associated with tolerance within a week, and the exacerbation of psychosis with their administration limits its usefulness.[18] Clozapine can be considered in refractory akathisia. Intravenous diazepam[19] and biperiden[20] have been shown to be effective treatments for severe akathisia.

The traditional high potency antipsychotics have been associated with a greater preponderance of acute dystonias in young male patients.[21] Our clinical experience also suggests that younger male patients are more predisposed to this side effect with use of the newer atypical antipsychotics, such as risperidone and ziprasidone.

**Mechanism of development of acute dystonia.** Acute dystonic reactions peak at 24 to 48 hours from the initiation of therapy.[22] This may be due to interference with presynaptic dopamine receptors, or there may be a mismatch between excess release of dopamine and coincident hypersensitivity of dopamine receptors. Antipsychotics mainly occupy D2 receptors, and the increased turnover may be expressed through overactivation of the unblocked D1 receptors.[23]

**Rating scales for acute dystonia.** No rating scales have been developed specifically for acute dystonia as they are transitory with a rapid onset and respond well to treatment.

**Treatment of dystonia.** Acute dystonias respond remarkably well to anti-Parkinsonian agents. Intramuscular benztropine or diphenhydramine will generally produce complete resolution in 20 to 30 minutes. The dose can be repeated after 30 minutes if complete recovery does not occur. Oral anticholinergics may be used in milder cases.

## TARDIVE DYSTONIA

Tardive dystonia is a more severely disabling condition, and symptoms are more sustained compared to the acute form. It has a reported prevalence of about 1.5 to 4 percent. The motor presentations are similar to those seen in acute dystonia and are distinguishable from them only by their duration. The condition is apparently identical to idiopathic torsion dystonia associated with Huntington's disease and Wilson's disease, and there is some overlap with the features of TD, with which it may coexist.[24]

**Treatment of tardive dystonia.** There are no controlled studies regarding treatment for this condition. Some patients have responded to high doses of trihexyphenydyl 60 to 80mg/day. Dopamine depleting agents, such as tetrabenazine or reserpine, have been used. Large doses of clonazepam, baclofen, or benzodiazepines have given mixed results. Tardive dystonia responds to deep brain stimulation. This is particularly useful for patients with focal dystonia. The globus pallidus internus has emerged as the most promising target for dystonia.[25]

It is very important that a careful evaluation of movement disorder symptoms be made in all patients treated with antipsychotics, so that the **balance between potential risks and benefits** may be optimized.

## ACUTE DYSTONIA

Dystonias are involuntary movements characterized by intermittent or sustained muscle action (Table 2). Movements vary from fleeting disturbance to maintained abnormal postures. It may occur in 25 to 40 percent of patients receiving conventional antipsychotics, with younger adults and children more commonly affected. The muscle stiffness and postural distortion are both painful and uncomfortable and can make patients agitated and frightened.

The muscles of the head and neck are most commonly affected. Involvement of the laryngeal and pharyngeal muscles may lead to respiratory distress, asphyxia, and choking.

## PARKINSONISM

Parkinsonian symptoms develop insidiously within days of starting antipsychotic treatment. The development of symptoms is dose dependent and emerges in about 20 to 40 percent of patients. With continuation of

medication, the Parkinsonian symptoms may gradually subside and tolerance may develop. The main features of drug-induced Parkinsonism are summarized in Table 3.

Rigidity of the limbs resistant to passive movement is the most obvious feature of drug-induced Parkinsonism. It may take on two forms: lead-pipe rigidity with sustained resistance or cog-wheel rigidity with a succession of resistance rapidly overcome by passive movement. Milder forms of rigidity are best detected on activation. The rigidity is more obvious when the subject is engaged in moving the opposite limb. Tremor and bradykinesia are seen as well. However, there are other symptoms less commonly observed, such as festinant gait, 3 to 5Hz resting tremor, or a reduction in the size of handwriting.

**Mechanism of development of Parkinsonism.** Drug-induced Parkinsonism is closely analogous chemically to idiopathic Parkinson's disease or its postencephalopathic variety. The blockade of dopamine receptors within the striatum amounts to chemical denervation resulting in relative dopamine deficiency.

**Rating scales of Parkinsonism.** There are a number of rating scales including Chouinard's extrapyramidal rating scale, the targeting abnormal kinetic effects (TAKE),[26] the extrapyramidal symptoms (EPS) scale, and the neurological rating scale for extrapyramidal side effects (Simpson-Angus scale).

The Simpson-Angus scale was the first to be developed and remains the most widely used.[27] This scale provides standardized ratings for rigidity, tremor, and salivation. The scale is entirely sign led and overemphasizes rigidity. It has only one item for tremor, and bradykinesia is measured only indirectly through the item on gait. The TAKE scale rates many manifestations of bradykinesia, but few of rigidity.

**Treatment of Parkinsonism.** Parkinsonian symptoms frequently can be eliminated with a reduction in dose or change to a lower potency antipsychotic. If it does not help, an anticholinergic drug may be added. Maximum therapeutic response occurs in 3 to 10 days. More severe symptoms may take a longer time to respond.[28] More recently quetiapine has been useful for this population.[29,30]

If symptoms remain uncontrolled, amantadine may be either added to the regimen or substituted as a single agent.[31] In severe EPS, the antipsychotic should be stopped temporarily as it may be a risk factor for neuroleptic malignant syndrome (NMS).[32] For patients with severe, refractory EPS, clozapine may be used specifically to treat the EPS, if they are judged to be severe enough to be disabling or potentially life threatening.[33] Rabbit syndrome (perioral tremor) is a form of Parkinsonism, which was initially thought to be a form of TD. This form of Parkinsonism responds well to anticholinergic agents.

## TARDIVE DYSKINESIA

Tardive dyskinesia (TD) is the main late onset condition among the EPSEs. These are involuntary movements, mainly of the tongue and mouth with twisting of the tongue, chewing, and grimacing movements of the face. It develops after chronic exposure to antipsychotics for about six months. The other features of TD are given in Table 4.

Age is the most consistent risk factor for TD. It is also more common in female patients. Other risk factors include affective disorder, poor treatment response, previous brain injury, greater total drug exposure, pre-existing Parkinsonism, and alcoholism.[34] It may be seen in up to 30 percent of patients receiving long-term conventional antipsychotics.[35,36]

**TABLE 4. Features of tardive dyskinesia**

| |
|---|
| ***OROFACIAL DYSKINESIA*** |
| **Protrusion or twisting of the tongue** |
| **Smacking and pursing of lips** |
| **Puffing of cheeks** |
| **Chewing movements of the jaw** |
| **Grimacing movements of the face** |
| ***LIMB AND TRUNK MOVEMENTS*** |
| **Purposeless, jerky, choreiform movements** |
| **Athetosis of the extremities** |
| **Limb and axial dystonias** |
| **Gait abnormalities** |
| **Lordosis** |
| **Shoulder shrugging** |
| **Rotatory movements of the pelvis** |

Movements indistinguishable from TD, especially orofacial ones, are seen in 5 to 15 percent of elderly individuals who have never been on antipsychotics.[37] These spontaneous movements are also seen in about seven percent of antipsychotic naïve schizophrenic patients at the onset of their illness.[38]

TD is a diagnosis of exclusion, so before making this diagnosis, other causes of abnormal movements should be excluded.

**Mechanism of development of TD.** The exact mechanism of TD is not known. The prolonged blockade of dopamine receptors may lead to TD by virtue of increased dopamine turnover, coupled with upregulation of receptor numbers, resulting in an imbalance between D1 and

D2 receptors. The hypersensitivity of D2 receptors may cause them to respond abnormally to the dopamine reaching them. Hypersensitivity of this nature may account for the worsening of the condition on withdrawal of antipsychotics and amelioration on their reintroduction.

Animal studies have shown that with prolonged administration, dopamine receptor blockade may actually slowly disappear, giving way to supersensitivity.[39] It is likely that complex interactions with other neurotransmitters like GABA may in part be responsible.

**Rating scales of TD.** The 12-item abnormal involuntary movement scale(AIMS) is the most popular instrument used to assess TD.[39] Other scales like tardive dyskinesia rating scale (TDRS) and extrapyramidal rating scale are also commonly used. AIMS assesses abnormal involuntary movements, including orofacial movement, extremity, trunk, and other body regions.

**Treatment of TD.** Several drugs have been suggested to have benefits in the treatment of TD, but the benefits appear to be limited.[40] Vitamin E has been proposed as a treatment to prevent or decrease the severity of TD; however, a Cochrane review concluded that vitamin E protects against deterioration of TD, but there is no evidence to suggest that it prevents it from developing.[41]

A double-blind, placebo-controlled, crossover study suggests that melatonin may be effective in the treatment of TD.[42] An open-label trial has found donepezil to be useful in suppressing TD.[43] The use of botulinum toxin in TD showed that grimacing, dysarthritic speech and involuntary movements of the tongue responded well, but that tongue protrusion dyskinesia was not affected.[44] Atypical antipsychotics have a reduced propensity to cause TD. Clozapine has a lower risk of causing TD. It also has therapeutic potential to treat TD that already exists.[45,46] Tetrabenazine and reserpine, which are both dopamine depletors, have been shown to be the most effective medications for TD and tardive dystonia.[47] Up to 87 percent of patients on reserpine and 58 percent of patients on tetrabenazine have shown abatement in symptoms of TD.[48] Branched chain amino acids given three times a day, seven days a week have recently been shown to reduce TD symptoms. It has been suggested that this may be due to decreased amine neurotransmitter synthesis.[49]

Among the atypicals, there are case reports of quetiapine[50] and risperidone[51] resulting in remission of symptoms. Naltrexone in combination with clonazepam has been shown to be effective in improving TD, possibly as a result of interaction on brain GABA and encephalinergic neurons in basal ganglia.

**Prevention of TD.** Early occurring extrapyramidal side effects are a risk factor for TD in patients taking conventional antipsychotics. A consensus recommendation suggested that all patients be examined for movement disorders before the initiation of antipsychotic drug treatment. Patients should also be monitored for EPSE at weekly intervals during acute treatment and until their medication dose has been stabilized for at least two weeks. Patients taking conventional antipsychotics should be examined for TD at least every six months, and those taking newer antipsychotics should be examined at least every year. Patients at high risk of EPSE taking first generation antipsychotics should be examined every three months, and those taking second generation antipsychotics every six months.[53]

## CONCLUSION

Conventional antipsychotic drugs continue to be used in a substantial number of patients for a variety of reasons. These are associated with a number of movement disorders, some of which can be distressing and irreversible. It is hence essential that clinicians regularly evaluate patients for these conditions to prevent their emergence and progression.

Clinicians should **regularly evaluate** patients for movement disorders to prevent their emergence and progression.

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