Drug-Induced Movement Disorders

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Significant proportion of drug-induced movement disorders is related to antipsychotic medications and neuroleptics are the commonest. Movement disorders induced by neuroleptics are divided into three time periods.[1] Early-onset type (within seven days of treatment) is known as neuroleptic-induced acute dystonia. Incidence is about 15-20% for typical neuroleptics and less than 5% for atypical medications. It is treated and can be prevented by benztropine, trihexyphenidyl or diphenhydramine. Neuroleptic-induced parkinsonism and akathisia are of intermediate-onset (within first three months), with incidence of 30% and 20% respectively. Akathisia is a combination of sensation of inner restlessness and objective motor movements to satisfy the urge to move. Amantadine is approved to treat parkinsonian symptoms. Propranolol at a daily dose of 20mg to 100mg is effective in akathisia. Switching to atypical antipsychotics also helps. Neuroleptic-induced tardive dyskinesia (TD) is the chronic form and is related to total lifetime of treatment, with cumulative incidence of 5% per year. Locally, published data on prevalence of tardive syndromes would be dated back to 1992.[2] At that time, one study in a single mental hospital demonstrated that the prevalence rates were 9.3% for tardive dyskinesia, 0.4% for tardive dystonia, and 1.2% for respiratory dyskinesia. In 2003, the point prevalence of tardive dyskinesia in the same hospital was 6.7% and the main association factor was old age.[3] The rates were much lower than Western studies but whether there is any genuine ethnic difference is unknown. The phenomenology of movement disorders associated with different medications is listed in Table 1.

In the past, tardive dyskinesia was used to describe the classical rhythmic oral-facial movements but is now renamed as tardive stereotypies. Tardive dyskinesia also includes tardive chorea, tardive dystonia, tardive akathisia, tardive tics, tardive myoclonus and tardive tremor. It is important to realise that up to 14% of non-medicated schizophrenia patients have involuntary movements. 1-8% of the elderly develop spontaneous oral facial dyskinesias, especially in the edentulous population.[1,4] Thus psychiatric disease and age themselves are probably precipitating factors. The exact pathophysiology is unknown but striatal Dopamine (D2) receptor super-sensitivity has been the traditional explanation. Other mechanisms include destruction of GABA neurons in the striatum, production of excessive free radicals and oxidative stress. Some patients might be genetically more prone to develop TD, related to the D2 dopamine receptor gene (DRD2) allele and dopamine transporter gene (DAT1) polymorphism.

Table 1: Selected Agents Associated with Drug-induced Movement Disorders

Acute and Tardive Akathisia
Antiemetics
Droperidol
Metoclopramide
Prochlorperazine
Promethazine
Antiepileptics
Carbamazepine
Psychotropics
Lithium
Haloperidol
Molindone
Phenothiazines (e.g. chlorpromazine, fluphenazine, mesoridazine, perphenazine, thioridazine, trifluoperazine)
Olanzapine (high dose)
Pimozide
Risperidone (high dose)
Thioxanthenes (e.g. thiothexene)

Active and Tardive Stereotypies
Antiemetics
Metoclopramide
Prochlorperazine
Antiepileptics
Phenytoin
Psychotropics
Amoxapine
Haloperidol
Molindone
Phenothiazines
Olanzapine (high dose)
Pimozide
Risperidone (high dose)
Thioxanthenes

Acute and Tardive Dystonia
Antiemetics
Droperidol
Metoclopramide
Prochlorperazine
Promethazine
Psychotropics
Amoxapine
Haloperidol
Molindone
Phenothiazines
Olanzapine (high dose)
Risperidone (high dose)
Thioxanthenes

Parkinsonism
Antiemetics
Droperidol
Metoclopramide
Prochlorperazine
Promethazine
Antiepileptics
Valproate
Cardiovascular Agents
Alpha-methyldopa
Reserpine
Psychotropics
Amoxapine
Haloperidol
Molindone
Phenothiazines
Olanzapine (high dose)
Risperidone (high dose)
Thioxanthenes
Vestibular Sedatives
Cinnarizine
Flunarizine
Miscellaneous
Pimozole
Tetrabenazine

The oral-facial movements of tardive stereotypies are choreic in nature, in the form of lip-smacking and lip-pursing, tongue protrusion, and licking and chewing movements. Muscles of the upper face are much less commonly involved. The truncal and limb muscles may be affected, giving rise to respiratory dyskinesias, pelvic thrusting and chorea in the extremities. The movements tend to be repetitive in appearance and distribution, rather than random as in true chorea. They may not distress the patient, particularly if limited to the lingual and buccal muscles.

Conventionally there was no effective treatment and the most important aim was prevention. Prognosis was frequently poor as patients usually needed the offending agent to manage their underlying psychiatric or medical problem. Ceasing the neuroleptics at the early stage of tardive dyskinesia might help and newer antipsychotics are safer in this respect. Whereas the vast majority of other drug-induced movement disorders resolve rapidly after discontinuation of the medication, TD may take months to years to remit. Women may have a higher rate of more severe and persistent TD.

Some cases may appear to be permanent. Although the manifestations may emerge or worsen shortly after cessation of the drug (withdrawal dyskinesias), this effect is transient and there is no evidence that TD will progress without continued provocation.

If the patient is not disturbed by the dyskinesia, it is best not to treat but observe and hope for a spontaneous recovery. In those with pronounced disability, treatment is difficult.[5] A minor tranquiliser such as the benzodiazepine clonazepam may provide mild symptomatic relief. In more severe or disabling cases, presynaptic dopamine blockade by reserpine or tetrabenazine may be used to control the dyskinesias after neuroleptic withdrawal. In recent small scale studies, piracetam and adenosine reuptake/transport inhibitors dipyridamole and nimodipine were shown to reduce the symptoms of tardive dyskinesia. Botulinum toxin injection is very effective for certain forms of focal movements. Bilateral deep brain stimulation of the internal part of globus pallidus could also reduce extrapyramidal symptoms by 50%.[6]

Drug-induced parkinsonism is most commonly caused by anti-dopaminergic agents, though some calcium antagonists can be the cause.[7] As mentioned earlier, parkinsonism develops usually 2-10 weeks after initiation of treatment. Older patients tend to be more susceptible to this complication. Akinesia is the most common presenting symptom. Resting tremor, though usually less prominent, can be as vigorous as in Parkinson's disease. Drug-induced parkinsonism tends to dissipate gradually and spontaneously after several months despite continued neuroleptic treatment. If symptoms are disabling, consideration should first be given to substituting atypical antipsychotics. If antiparkinsonian medications are needed, the first choices are anticholinergics and amantadine. These drugs may be withdrawn regularly to reassess the need of continued therapy. If parkinsonism persists, concomitant Parkinson's disease should be kept in mind as it is a common condition after all.

Neuroleptic-induced akathisia can present as fidgety movements while seated, rocking in place while standing, pacing, or the inability to sit or stand still for an extended period of time as well as the overwhelming urge to move, which can cause severe distress and an increased risk of suicide for affected patients.[8] First-line treatment of akathisia includes benzodiazepines or beta-blockers for patients who do not have symptoms of Parkinson's disease and anticholinergics for patients with Parkinson's symptoms. Despite a lowered incidence profile with newer anti-psychotics, akathisia and similar conditions continue to affect patients. Clinicians should ensure that an accurate diagnosis of akathisia is made and target symptoms are decreasing due to treatment, which does not negatively affect the mental health of the patient.

Movement disorders are also associated with other medications, such as antiemetics that block central dopamine receptors (i.e., droperidol, metoclopramide, and prochlorperazine), lithium, selective serotonin reuptake inhibitors (SSRIs), stimulants, and tricyclic antidepressants (TCAs). Tremor commonly occurs with lithium treatment and occasionally chorea. SSRIs can commonly cause tremor and, less commonly, dyskinesia, dystonia, or parkinsonism. Stimulant drugs (e.g., amphetamine, and methylphenidate) have been known to produce a variety of movement disorders such as dyskinesias, dystonia, stereotypic behaviour, and tics. The most common movement disorders associated with TCAs are myoclonus and tremor. The antiepileptic drug valproate is commonly associated with tremor. For many years, chorea has been recognised as a complication of oestrogen- and progesterone-containing products. Psychotherapeutic combination products containing a neuroleptic, such as perphenazine/amitriptyline, should not be overlooked as causative agents.

The newer atypical antipsychotics are more commonly prescribed nowadays, for their better side effect profile.[9] Risperidone is a serotonin-dopamine antagonist. It has affinity for D2 and 5-HT2 receptor, with poor affinity for D1 receptor; and it also binds to adrenergic a1 and histamine H1 receptor. Its anti-serotonergic effect decreases the risk of extra-pyramidal side effects. The incidence of new-onset tardive dyskinesia was reported to be less than 1%. Cases of tardive dystonia, especially involving the neck region, have been reported. Clozapine has a higher affinity for D1 than D2 receptors, and it blocks D4, D3, serotonin, a2 receptors. It requires frequent monitoring of blood counts due to the risk of agranulocytosis. There was evidence that clozapine improved tardive dystonia in several case reports and small series, but there were no double-blind controlled trials. Nonetheless, reduced extrapyramidal side effects (EPS) are not the same as no EPS, and most of the newer antipsychotics can still cause EPS in some patients. In general, the risk of causing EPS in increasing order is: clozapine, quetiapine, olanzapine and risperidone. The likelihood of developing EPS with a first-line second-generation anti-psychotics (or atypical anti-psychotics) depends not only on the specific agent, but also on the rapidity of dose escalation, the target dose, and the patient's intrinsic vulnerability to EPS. Even with the newer anti-psychotics, clinicians should not be lulled into believing EPS cannot happen, but need to be able to recognise and manage both overt and subtle manifestations of EPS.

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