Drug-induced movement disorders in the elderly

Drug-induced movement disorders are common in the elderly and responsible for significant morbidity and reduction in quality of life. It is important that they are recognised early to enable prompt initiation of treatment. Unfortunately some drug-induced movement disorders are difficult to treat, so prevention is important. This article reviews the most important drug-induced movement disorders seen in the elderly population including dystonia (acute and tardive), akathisia (acute and tardive), neuroleptic malignant syndrome, parkinsonism and tardive dyskinesias. It explores their clinical presentation, the most commonly implicated medications, risk factors and treatment options.

Dr Nicola Mason* Specialist Registrar in Care of the Elderly, Gloucestershire Royal Hospital GL1 3NN
Dr Pippa Medcalf Consultant in Care of the Elderly, Gloucestershire Royal Hospital GL1 3NN
*email Nicky.Mason@glos.nhs.uk

Drug-induced movement disorders (DIMDs) in the elderly are responsible for significant morbidity and reduction in quality of life for patients. They can result in poor motor functioning, including difficulties performing activities of daily living resulting in increased care needs. The symptoms can be distressing for both patients and carers, resulting in psychological problems, loss of social functioning and self esteem. These in turn can lead to poor compliance with medications, breakdown in the doctor-patient relationship, relapses of medical conditions and increased hospital admissions. In rare cases they can be life threatening, for example, neuroleptic malignant syndrome and laryngeal spasm occurring with severe dystonias. Some DIMDs are potentially treatable and early recognition is vital to reduce morbidity and, in rare cases, mortality.

Diagnosis can be difficult as DIMDs can closely resemble common medical conditions and can be indistinguishable from the idiopathic form of the condition. A detailed clinical history, including a detailed drug history is important, noting new and recently stopped medications as well as dosage changes.

DIMDs result from disruption to the dopaminergic, serotonergic and catecholaminergic receptor systems, which in turn influence extrapyramidal system function. The most common classes of drugs implicated in DIMDs are antipsychotics (eg. haloperidol) and antiemetics (eg. metoclopramide). (See Table 1 for a complete list.)

Movement disorders can be acute (onset within hours to days of exposure), subacute (within several weeks), or tardive (within several months). They fall broadly into two categories. Those causing paucity of movement, such as parkinsonism, and those resulting in excess movements, such as tremor or dyskinesias. This review article gives a broad overview of the most important DIMDs.

Dystonias

Acute dystonia

The reported prevalence of drug-induced acute dystonias (DIADs) in patients taking antipsychotics has varied widely from 2 to 94%. Ballerini et al report an incidence of 15-7% amongst drug-naïve/drug-free psychiatric inpatients prescribed antipsychotics, without anticholinergic prophylaxis.

Acute dystonia (AD) results from sustained muscle hyperactivity, resulting in abnormal posturing and pain. The pain caused can lead to difficulties with simple tasks such as mobility, breathing, speaking and vision. AD can affect any muscle group; however, the most common presentations are with torticollis, trismus and oculogyric crisis. The onset of symptoms is sudden and often within a few hours or days of...
starting, or increasing the dose of, the responsible medication. In 90% of cases of AD, the symptoms appear within five days.\(^3\)

The pathogenesis for DIADs remains unclear. It has been proposed that dopamine receptor blockade causes an imbalance between dopamine and acetylcholine, which affects the normal functioning of the basal ganglia.\(^4^,^2\) Risk factors for DIAD include young age (<30), male gender, history of dystonia, and cocaine use.\(^5^,^3\)

Anticholinergic drugs may be used to control the symptoms of AD, for example procyclidine 5 mg intramuscularly (repeated after 30 minutes if necessary). Oral treatment with anticholinergics should then continue for a week to prevent recurrence. If stridor occurs, intravenous anticholinergics and urgent admission to an acute hospital setting may be required as laryngeal spasm secondary to AD can be life threatening. The offending medication should be stopped, dose reduced or the medication substituted with an alternative non-DIMD provoking medication. For more localised dystonias, injection of botulinum toxin may be considered.\(^6\) The use of anticholinergics in the prevention of

Table 1: Drugs associated with drug-induced movement disorders

<table>
<thead>
<tr>
<th></th>
<th>Dystonia</th>
<th>Akathisia</th>
<th>NMS</th>
<th>Parkinsonism</th>
<th>Tardive dyskinesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical antipsychotics:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Butyrophenones (eg.</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>haloperidol); phenothiazines (eg. chlorpromazine); thioxanthenes (eg. flupentixol)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atypical antipsychotics:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>risperidone, sulpiride</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Antiemetics: metoclopramide; prochlorperazine</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Antiepileptics: Sodium valproate</td>
<td>Yes (rare)</td>
<td>Yes (rare)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Yes</td>
<td>Yes (rare)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Yes</td>
<td>Yes (rare)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Lithium</td>
<td>Yes(^4)</td>
<td>Yes(^2)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>SSRIs (eg. fluoxetine)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td>Yes</td>
<td>Yes(^2)</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>(eg. amitriptyline)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vestibular sedatives (eg.</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>cinnarizine)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiparkinsonians</td>
<td>Yes</td>
<td>Yes</td>
<td>On</td>
<td>On withdrawal</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>withdrawal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sedatives (eg. butyrophenone)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Yes</td>
<td></td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bromocriptine</td>
<td></td>
<td></td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticholinergics (eg.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hyoscine butylbromide)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular agents:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amiodarone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methylidopa</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium channel blocker:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>diltiazem</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^3\)www.gerimed.co.uk

GM | Midlife and Beyond | November 2010

% GM | Midlife and Beyond | November 2010

% www.gerimed.co.uk
DIAD may be appropriate for some patients at high risk of developing dystonias, but in general is not recommended for elderly patients as they are at increased risk of adverse reactions to the anticholinergics themselves.

**Tardive dystonia**

Tardive dystonias occur in approximately 2–4% of patients exposed to typical antipsychotics. They occur after months to years of treatment with dopamine receptor blockers or within three months of treatment discontinuation. The onset of symptoms is more insidious and severity can vary. In contrast to tardive dyskinesia, tardive dystonias are less common in elderly patients; the highest risk patients being young males on high potency neuroleptics. In the event of a patient developing tardive dystonia, the drug should be stopped, dose reduced or typical antipsychotic switched to atypical where possible. Anticholinergics may help symptomatically. Other strategies include botulinum toxin injection, dopamine-depleting agents (such as reserpine) and rarely, deep brain stimulation or pallidotomy (surgical ablation of the globus pallidus) may be considered. Unfortunately despite these measures, symptoms often persist.

**Akathisia**

**Acute akathisia**

Akathisia occurs in at least 20–30% of patients taking dopamine receptor blocking agents, such as antipsychotics. It is a subjective feeling of restlessness and compulsion to keep moving. These feelings result in voluntary complex semi-purposeful stereotypic and repetitive movements, such as rocking from one foot to another or crossing and uncrossing legs while sitting. Patients experience increased distress if they are asked to restrain from moving. Akathisia may be difficult to distinguish clinically from medical conditions such as restless legs syndrome and agitation seen with drug withdrawal or psychiatric conditions. It is particularly important to diagnose correctly as the distress caused by akathisia can result in aggression and suicidal behaviour. Diagnosis should be aided by the temporal relationship to medications. Also, in contrast to restless legs syndrome, akathisia should improve when the patient is asleep.

Drugs that have been reported to cause akathisia include antipsychotics, selective serotonin-reuptake inhibitors and cocaine. Pathophysiology is unclear, but may be due to an imbalance of dopamine and serotonin within cortical and subcortical structures. Onset of symptoms is usually within three days of starting the culprit medication. Risk factors include increasing dose of medication, female gender, development of parkinsonism and iron deficient anaemia.

Management involves withdrawing or reducing the dose of the responsible medication when possible. Anticholinergics may be used to reduce symptoms. Propranolol, benzodiazepines and iron (if deficient) may also have some therapeutic benefit.

**Tardive akathisia**

Akathisias that onset after three months on an established drug regimen are regarded as tardive. Prevalence of neuroleptic induced tardive akathisia has been reported at approximately 30%. Like acute akathisia, it is most commonly caused by typical antipsychotics. The symptoms are similar to those of acute akathisia; however, patients tend to report less distressing subjective symptoms and are able to suppress movements or remain still for longer periods of time. Patients may present with concurrent symptoms of dystonia, parkinsonism, tardive dyskinesias or tremor. In this situation, it may be difficult to separate out the individual movement disorders. Akathisias can also onset within a few weeks of discontinuation or dose reduction of neuroleptic medication, referred to as "withdrawal akathisia".

Management of tardive akathisias can be difficult and, particularly in the elderly, akathisia may persist for years despite discontinuation of the responsible medication. Unfortunately symptoms can worsen following cessation of the offending medication (to date, the reason for this remains unclear).

**NMS**

Neuroleptic Malignant Syndrome (NMS) is rare with a frequency of 0.07–2.2% amongst patients using neuroleptics. More than 200 cases reported in the elderly population, but this probably under represents the true incidence.

It is a potentially life threatening idiosyncratic reaction caused by drugs commonly used in elderly patients. Elderly patients are particularly susceptible due to increased risk of dehydration, cognitive changes affecting compliance and decreased
dopamine activity that occurs naturally with ageing.\textsuperscript{17} The condition occurs most commonly with high potency neuroleptic dopamine receptor antagonists.\textsuperscript{17} Other medications that may cause NMS include antiemetics, such as the phenothiazines and metoclopramide, and even less commonly lithium and cocaine.\textsuperscript{4} NMS can occur at any time during treatment but most commonly at the time of starting or increasing the dose of a dopamine antagonist. It may also occur if a dopaminergic drug, for example levodopa, is withdrawn or reduced rapidly.

NMS most commonly presents with muscle rigidity, hyperthermia, altered consciousness and autonomic disturbance. It should be considered as part of a differential diagnosis as it can mimic other common conditions encountered in the elderly population.

Investigations supporting the diagnosis included a raised creatinine phosphokinase, creatinine, urea and white cells. Urine testing is positive for protein and myoglobin.

If NMS is suspected, the patient should be managed promptly by withdrawal of the responsible medication and admission to an acute hospital setting. Metabolic disturbances should be corrected with intravenous fluids and renal function monitored closely. Cooling measures, including administration of antipyretics, should be initiated. In severe cases treatments, such as dantrolene, bromocriptine, amantadine, sodium nitroprusside, benzodiazepines and electroconvulsive therapy may be considered; however, their role is uncertain.\textsuperscript{17,4} In most cases, the symptoms resolve within two weeks. But in the case of long acting depot injections, it may take up to a month.

**Parkinsonism**

Drug-induced parkinsonism (DIP) is the second commonest cause of parkinsonism after idiopathic Parkinson’s disease (IPD)\textsuperscript{18} yet the condition is often under recognised.\textsuperscript{19} Elderly patients are particularly at risk for a number of factors, including a probable subclinical depletion in dopaminergic neurons as a consequence of ageing.\textsuperscript{4} Other risk factors include dose and rate of dose escalation, and pre-existing extrapyramidal disorder. Several drugs may cause DIP through blockage of the striatal dopaminergic receptors (see Table 1). Most commonly the antipsychotics (typical and atypical) and antiemetics (metoclopramide and prochlorperazine) are responsible.\textsuperscript{20}

The symptoms may not occur for several months after initiation of the responsible drug. Patients present with tremor, rigidity and bradykinesia. Features that may indicate DIP over IPD include symmetry of tremor, exposure to medications, and lack of pill rolling tremor. Symptoms may be difficult to detect as they can mimic the negative symptoms of schizophrenia and the psychomotor retardation of depression.

Where possible, the offending medication should be stopped and usually the symptoms then resolve. Unfortunately they may return after initial resolution or persist. In this case, it should be considered whether subclinical PD has been unmasked or whether the drug effect is irreversible. If it is not possible to stop the responsible drug, then dose reduction or changing a typical to an atypical antipsychotic should be considered. Anticholinergics can be used for symptom relief, but they may cause hallucinations and reduce efficacy of neuroleptics. Amantadine has also been used and seems better tolerated in the elderly; however, it may still cause cognitive decline, hallucinations and delirium.\textsuperscript{7}

**Tardive dyskinesias**

Tardive dyskinesias (TDs) are involuntary movements that may affect the mouth, tongue, face, limb and trunk. Older patients have five times the risk of developing TDs compared with the younger population.\textsuperscript{21} Other risk factors for TDs include higher doses, length of treatment, diabetes mellitus, affective disorder, alcoholism and female gender.\textsuperscript{2} The underlying pathogenesis for TDs are thought to be dopamine receptor hypersensitivity, GABA insufficiency and or structural abnormalities.\textsuperscript{4} Typical antipsychotics are the drug class most commonly responsible for causing TDs. Atypical antipsychotics, tricyclic antidepressants, metoclopramide and selective serotonin re-uptake inhibitors can also cause TDs.

The involuntary movements of TDs can have different characteristics including choreiform (rapid, jerky and non-repetitive), athetoid (slow continuous movements) or stereotypic (rhythmic). The mouth and face are the most common, and often first, part of the body to be affected with symptoms such as lipsmacking and jaw clenching.\textsuperscript{7} The onset of symptoms is insidious and may go unnoticed by patients initially. TDs occur at least one month after
starting the offending medication. It is important to note that TDs can also be precipitated by reducing the dose or stopping antipsychotic medication. This is thought to be as a result of rebound receptor supersensations.

No effective treatment for TDs has been identified and complete, persistent recovery is rare; therefore, prevention is the best approach. Doses should be kept to a minimum and atypical antipsychotics should be used in preference to typical antipsychotics. Vigilance for symptoms when reviewing patients enables early recognition and management, which is important as remission rates are inversely correlated with duration and severity of TDs. This is particularly important in the elderly as age is also inversely correlated to remission. If symptoms occur the culprit medication should be stopped gradually rather than stopped abruptly, particularly in the case of dopamine receptor blocking agents. Concurrent use of anticholinergics should be stopped. Several interventions have been trialed yet no definitive information on how best to treat TD has been established. Examples of medications that may be helpful include benzodiazepines, β-blockers, clonidine and dopamine-depleting drugs such as reserpine. For severe and refractory TD, neurosurgical treatments may be effective.

**Conclusion**

DIMDs are under recognised by medical professionals yet left untreated can cause significant morbidity amongst the elderly population. Many DIMDs are potentially reversible if managed promptly and appropriately. A thorough drug history should be an essential part of any medical assessment and may be a crucial factor in determining the cause of movement disorders presenting in general practice. Prevention with judicious use of medications that can cause drug-induced movement disorders is recommended. When prescribing drugs that commonly cause DIMD, such as the typical antipsychotics, one should consider if there is a reasonable alternative. If not, aim to use the lowest possible dose.

**Conflict of interest:** none declared

**References**