The articles in this series are independently researched and compiled by PSA commissioned authors and peer reviewed.

Complications of long-term neuroleptics

By Peter Tenni

The patient is a 73-year-old female nursing home resident who weighs 57 kg. She has significant dementia and her general condition has been gradually deteriorating over the six years that she has been a resident. The lady has a long history of aberrant, aggressive and resistive behaviours which have resulted in her being prescribed haloperidol at various doses since her admission. An accredited pharmacist reviewed her medication regime 12 months ago at which time she was receiving haloperidol 1 mg three times daily, and frusemide 20 mg daily for mild leg oedema. Her behavior was stable and the pharmacist suggested that the haloperidol dose could be reduced. In addition, as she had had a transient ischaemic attack three years after admission to the nursing home, an antiplatelet agent was recommended.

A second medication review was recently conducted. The medications consisted of:

- Haloperidol 1 mg three times daily
- Frusemide 20 mg daily
- Aspirin 100 mg daily.

On speaking to the nursing staff and reviewing the notes available at the facility, you find that several attempts to reduce the dose of haloperidol had resulted in increasing skeletal muscle rigidity. These increases in rigidity each improved with an increase in the dose of haloperidol, resulting in her being on the same dose as she was on a year ago. In addition, the nursing staff also point out that she has long-standing 'chewing' issues, where she is constantly moving her jaw. On multiple occasions she has 'clenched' her jaw, interfering with medication administration. The only laboratory tests available at the time of this second review are from soon after admission to the home (~5 years old) and are as follows:

Sodium	135	134–146 mmol/L
Potassium	4.9	3.4–5.3 mmol/L
Creatinine	100	45–90 micromol/L
Haemoglobin	108	115–155 g/L
Mean Cellular Volume	98	80–100 fL.

Clinical assessment

The use of anti-dopaminergic antipsychotic agents is known to be associated with a range of extrapyramidal movement disorders. There are major differences between the range of movement disorders. Some of these differences are outlined in Table 1.

In addition to differences in the nature of the movement disorders, there are differences in response to treatment.

The lady has a long history of aberrant, aggressive and resistive behaviours which have resulted in her being prescribed haloperidol at various doses since her admission.

With the exception of tardive dyskinesia, extrapyramidal disorders tend to improve with reduction of the dose or cessation of the offending agent. In addition to dose reduction and/or cessation, anticholinergic agents are useful in the management of acute dystonia, akathesia and drug-induced Parkinsonism. It is unusual that, at least in the short term, dose reduction can lead to a temporary exacerbation in symptoms, while increasing the dose is often associated with a temporary remission.

Although tardive dyskinesia is a well-known adverse effect of conventional and atypical antipsychotic agents, the biological mechanism of tardive dyskinesia is still relatively poorly understood. It is thought that long-term blockade of the dopamine receptors may lead to a change in neuronal systems related to dopaminergic neurons. One of the main theories proposed to explain tardive dyskinesia has been an imbalance in the activity of cells receptive to dopamine or acetylcholine.

This theory implies that there is an over activity of dopaminergic transmission in relation to cholinergic transmission in the striatum. Despite this theory, anticholinegics are not usually successful in the management of tardive dyskinesia, indeed cholinergic agents have been

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tried (see Table 2). Advancing age is a risk factor for both its prevalence and severity, with those who are <60 years of age being three times more likely to spontaneously remit.[5] Each year 4-5% of those who use antipsychotic drugs continuously begin to show signs of tardive dyskinesia.[5]

A range of psychoactive and other agents have been trialled in the management of tardive dyskinesia, each with limited success. These agents are summarised in a series of Cochrane reviews and Table 2 outlines some of the key points.

Although the physical features in this case are not strictly in keeping with those listed in Table 1, tardive dyskinesia may result in a range of unusual movement disorders. The duration of treatment and the worsening of the symptoms in association with dose reduction are two features that raise the possibility of tardive dyskinesia.

One aspect of treatment of tardive dyskinesia that has not been well researched is the use of atypical compared to typical antipsychotic agents. A recent 'practical tip for psychiatrists' identified switching from typical to atypical antipsychotics as the most efficacious treatment for tardive dyskinesia, with the authors reminding the reader that the best treatment remains prevention by using atypical agents first with the smallest possible doses and duration.[9]

Actions and recommendations

Contact the prescriber regarding a possible gradual change to an atypical antipsychotic agent such as risperidone or olanzapine. This would involve using both haloperidol and the atypical antipsychotic for a period of time, with a gradual reduction of the haloperidol dose. This may alleviate some of the symptoms, although the likelihood of success is minimal.

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Table 1: Features of extrapyramidal movement disorders associated with antipsychotic agents[1]

Disorder	Typical onset	Features
Acute Dystonia	First few doses	*Dystonic reactions (painful spasm of a muscle or muscle group)* • Oculogyric crisis – fixed upward stare • Torticollis – neck twisting • Trismus – clenched jaw • Opsithotonus – arching of the back • Laryngospasm – difficulty breathing, speaking or swallowing.
Akathesia	Within first few weeks of treatment	*Subjective feeling of inner restlessness, anxiety and motor restlessness* • Inability to sit still, constant pacing • Continuous agitation and restless movements • Rocking and shifting of weight while standing • Shifting of legs, tapping of feet while sitting.
Parkinsonism	Within first few months of treatment	*Rigidity and immobility* • Stiffness and slowness of voluntary movement • Mask-like facial expression • Drooling • Stooped posture • Shuffling, festinating gait • Slow, monotone speech. *Tremor* • Regular rhythmic oscillations of the extremities, especially the hands and feet • Pill-rolling movement of the fingers.
Tardive Dyskinesia	After at least six months of treatment	*Mouth* • Rhythmical involuntary movements of the tongue, lips, jaw • Protrusion of the tongue, puckering of the mouth, chewing movements. *Choreiform* • Involuntary irregular purposeless quick movements of arms/legs • Jerky, flailing movements. *Athetoid* • Continuous wormlike slow movements of arms. *Axial hyperkinesis* • To and fro clonic movements of the spine.

Table 2: Treatment class and examples of agents trialled in the management of tardive dyskinesia

Treatment class and examples (reference)	Authors' conclusions, additional comments
Cholinergic agents[2] deanol, lecithin and meclofenoxate	The clinical effects of older cholinergic drugs are unclear, as many questions remain unanswered by the too few, too small studies. Cholinergic drugs should remain of interest to researchers but currently have little place in routine clinical work
Benzodiazepines[3]	One small study found preliminary evidence that benzodiazepines may have an effect in neuroleptic induced tardive dyskinesia, although other studies have found inconclusive results, meaning routine clinical use is not currently indicated and these treatments remain experimental.
Calcium-channel blockers[4]	The effects of calcium-channel blockers for antipsychotic induced tardive dyskinesia are unknown. Their use is experimental and should only be given in the context of well designed randomised studies.
Catecholamines[5] *Noradrenergic drugs* Celiprolol, clonidine, disulfiram, fusaric acid, methyldopa, pindolol, propanolol, oxprenolol and yohimbine. *Dopaminergic drugs* Dopamine agonists: apomorphine, bromocriptine, dopamine, hydergine and lisuride. Dopamine antagonists: oxiperomide, metoclopramide, papaverine and tiapride Dopamine depleters: oxypertine, reserpine and tetrabenazine. Dopamine increasers: amantadine, amphetamine and levodopa	Although there has been a large amount of research in this area, most studies were excluded from the review due to inherent problems in the nature of their crossover designs. Usually data are not reported before the crossover and the nature of TD and its likely response to treatments makes it imprudent to use this data. The review provides little usable information for service users or providers and more well designed and reported studies are indicated
GABA ergic agents[6] Baclofen, progabide and sodium valproate.	Evidence of the effects of baclofen, progabide or sodium valproate for people with antipsychotic-induced TD is inconclusive and unconvincing. Any possible benefits are likely to be outweighed by the adverse effects associated with their use
Miscellaneous[7] Ceruletide, gamma-linolenic acid, oestrogen, lithium, phenylalanine and insulin.	There is no strong evidence to support the everyday use of any of the agents included in this review. All results must be considered inconclusive and these compounds probably should only be used within the context of a well-designed evaluative study.
Dose reduction or cessation of neuroleptics or specific neuroleptics[8]	Limited data from small studies using neuroleptic reduction or specific neuroleptic drugs as treatments for TD did not provide any convincing evidence of the value of these approaches. There is a need for larger trials of longer duration in order to fully investigate this area.