Graylands Hospital Drug Bulletin

Extrapyramidal Side Effects (EPSE) – *forgotten but not gone*

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Introduction

Are movement disorders (commonly known as extrapyramidal side effects, EPSE) 'yesterday's' side effect? One would think so looking at the plethora of medical literature that appears to focus almost exclusively on the metabolic adverse consequences of antipsychotic treatment. Certainly, given the ubiquitous use of atypical antipsychotic drugs, clinicians are less likely to observe EPSE in clinical practice.[1]

However, EPSE are not restricted solely to the typical antipsychotic agents, they are also an unwelcome adverse effect of certain atypicals,[1] especially when used at high doses and in combination. Given that EPSE cause considerable subjective distress, may lead to physical disability and poor compliance with medication,[1] EPSE should remain at the forefront of side-effect monitoring.

This Bulletin provides an overview of the current knowledge of antipsychotic induced EPSE, with an emphasis upon clinical features, prevalence, pathophysiology, treatment and monitoring. Hopefully, this information will serve to remind health professionals not to forget the importance of monitoring the occurrence of these highly distressing and often preventable adverse effects.

Definitions

EPSE is an umbrella term used to describe a wide variety of movement disorders. They can be divided into acute syndromes (those that develop generally within hours or days of treatment) and chronic or tardive syndromes (those that develop after a sustained period of exposure).[1] Acute EPSE include acute dystonia, akathisia and parkinsonism, whereas tardive dyskinesia is perhaps the most common late occurring movement disorder.[1]

Anticholinergic drugs and EPSE

Anticholinergic drugs, such as benztropine, benzhexol, biperiden and orphenadrine, are often prescribed to counteract EPSE caused by antipsychotic drugs.[1] Although there is little difference between them, benztropine is used most commonly in clinical practice. Anticholinergics are generally effective, but not all EPSE are equally responsive to these drugs.[1] For example, they have limited efficacy in the treatment of akathisia and are not at all effective in alleviating TD.[2] In fact anticholinergics can sometimes worsen the movements of TD, and when discontinued a modest improvement may be seen.[2] Other hazards associated with these drugs include: anticholinergic adverse effects (dry mouth, blurred vision, constipation, tachycardia and urinary retention), risk of abuse (they can cause euphoria), toxic confusional states and cholinergic rebound on withdrawal.[2]

Box 1: Extrapyramidal side-effects[2]

- **Acute dystonia:** involuntary muscular contraction which results in abnormal posture or movement. Typically involve muscles of the head and neck. Occurs more commonly in young adults and may appear after only a few doses. These are acute and painful and need immediate treatment sometimes with Intramuscular anticholinergics.

- **Parkinsonism:** tremor, rigidity, bradykinesia. Symptoms generally emerge within a few days of starting the offending drug but may emerge slowly over several weeks. Anticholinergic drugs are usually effective.

- **Akathisia:** sensation of inner restlessness, a compulsion to keep moving. Patients may be observed repeating purposeless movements. Acute akathisia is often associated with irritability, agitation and violent outbursts. Responds to treatment with propranolol.

- **Tardive dyskinesia:** rhythmic involuntary movements of tongue face and jaw. Develops following long-term use of antipsychotics. May be irreversible. Clozapine has been shown to be an effective treatment.

Acute dystonia

Acute dystonia (AD) is a sustained or repeated involuntary muscular contraction which results in abnormal posture or movement.[3] AD is often frightening, painful, debilitating and may negatively impact the therapeutic relationship between the doctor and patient.[3]

Clinical features

Symptoms may begin immediately, or can be delayed by hours or days, after starting treatment or increasing the dose of an antipsychotic.[2] Symptoms typically involve muscles of the head and neck. Involvement of the laryngeal and pharyngeal muscles may lead to serious problems, such as respiratory distress, asphyxia, dysphagia and choking.[3] A tense tongue or throat may indicate a moderate form of AD. Sometimes only the hands or just a few fingers may be affected. Frequently, however, AD worsens when one or more muscle groups are activated, such as while walking.[3]

Table 1: Acute dystonia – symptoms[4]

Blepharospasm	Sustained eye closure
Oculogyric spasm	Eye rotation
Grimacing	
Trismus	Jaw muscle contraction
Dysarthria	Speaking difficulties
Dysphagia	Swallowing difficulties
Torticollis	Neck distortion
Opisthotonos	Neck, head & trunk distortion
Abnormal gait	e.g. Pisa syndrome

Prevalence

AD is seen in up to 10% of those receiving conventional antipsychotics.[2] It is most common with high-potency conventional antipsychotics (e.g. haloperidol) and less common with low-potency conventional drugs (e.g. chlorpromazine) and is particularly prevalent in younger patients.[3] Other risk factors include male gender and a prior dystonic reaction. Clozapine is the only antipsychotic not to induce AD; [2] other atypicals all have the potential to induce AD at certain specific doses.[3] Dystonia may also occur as a persistent, or tardive, disorder in patients receiving long-term antipsychotic treatment, with a prevalence of around 1.5-4%.[3] The motor presentations are similar to those seen in AD, and are distinguishable from them only by their duration.[3]

Pathophysiology

Since all antipsychotics bind to D_2 receptors, it has been suggested that blockage of these receptors in the caudate, putamen and globus pallidus is partly responsible for causing AD.[3] This would also explain the diminished propensity of these drugs to cause AD in elderly patients, since D_2 activity decreases with age.[3]

Treatment

AD usually presents suddenly and requires urgent treatment, especially where spasm of laryngeal muscles induces stridor. Intramuscular administration of anticholinergic drugs (e.g. 1-2 mg of benztropine) is usually effective within 20 minutes. Occasionally, repeated injections are necessary; they should be administered at half hour intervals. Intravenous administration of an anticholinergic is only necessary in cases of highly dangerous forms of AD such as stridor.[3]

Akathisia

Akathisia is a word of Greek origin meaning 'not to sit'. It usually begins to appear within days of beginning an antipsychotic or increasing its dose.[5] The condition frequently becomes chronic if untreated and may worsen and persist on drug withdrawal.[5]Akathisia may then exist in acute, chronic and tardive forms. The prevalence of tardive akathisia is not known but is an extremely unpleasant and difficult to treat condition when it occurs.

Clinical features

The symptoms of akathisia are divided into subjective and objective. Subjective symptoms include a sensation of inner restlessness, a compulsion to keep moving, unease, anxiety, discomfort, dysphoria, nervousness and apprehension. Patients with akathisia are usually physically unable to maintain a fixed posture when seated or standing but may be able to lie still and sleep.[5]

Box 2: Brief clinical assessment for akathisia[6]

Ask about:
- Feeling of inner restlessness
- Desire to walk or pace
- Difficulty sitting or standing still
- Related distress

Observe for restless movements, such as:
- Fidgety movements
- Leg swinging while sitting
- Rocking from foot to foot
- pacing

Objective symptoms usually involve the lower limbs and feet. Patients may be observed repeating purposeless movements, such as rocking from foot to foot, pacing, crossing legs, toe-tapping and face-rubbing. A coarse tremor and myoclonic jerks may also be observed.[5] Akathisia caused by high-potency conventional antipsychotics such as haloperidol, have been shown to provoke suicidal, homicidal and violent behaviour.[4] More recently, suicidality has been linked to the subjective aspect of akathisia.[7]

Prevalence

The prevalence of akathisia varies according to definitions used and, perhaps more markedly, with antipsychotics prescribed. Generally, akathisia is

much less commonly seen with newer atypical antipsychotics than with conventional drugs, and is rare indeed with clozapine and quetiapine in particular.[2] Studies with conventional drugs reported prevalence rates as high as 68%, whereas studies undertaken on patients receiving atypicals reveal prevalence rates of between 11-15%.[5]
In the Clinical Antipsychotic Trial of Intervention Effectiveness (CATIE) study, it was estimated that 26-35% of people taking an atypical antipsychotic experienced akathisia each year, compared with 35% taking the typical antipsychotic perphenazine.[8]

Pathophysiology

The pathological basis for drug-induced akathisia has never been precisely defined but the condition seems inexorably to be associated with central, postsynaptic dopamine D_2 antagonism.[5]

Treatment

Akathisia may resolve following dose reduction, or by switching to an alternative antipsychotic.[2] If this is not possible or desirable then the mainstay of treatment is propranolol, which has been shown to be effective in reducing both subjective and objective features of akathisia.[2] Doses range from 30 to 80 mg/day and response seems to occur in the first few days of treatment. Other beta-blockers are not effective, either because they do not enter the brain in sufficient concentration or because they lack propranolol's unique action on serotonin systems.[2] Other potential treatments include anticholinergic drugs (which seem to be effective where akathisia occurs alongside parkinsonism) & benzodiazepines such as lorazepam and clonazepam.[2]

Newer treatment options

The high rate of non-response to conventional anti-akathisic agents led clinicians to search in new directions. It was suggested that 5-HT_2 receptor antagonism, by counteracting dopamine D_2 blockade may prevent the severity of akathisia. As such, there is now evidence to support the use of a variety of $5HT_2$ antagonists in akathisia: mianserin, ritanserin, cyproheptadine and trazadone.[8]

Parkinsonism

Antipsychotic-induced parkinsonism resembles idiopathic Parkinson's disease in many respects. Symptoms of drug-induced parkinsonism usually emerge within a few days of starting the offending drug but may emerge slowly over several weeks.[9]

Clinical features

The core features of drug-induced parkinsonism include bradykinesia, rigidity and tremor with a gradual onset over days or, more usually weeks.[9]

Table 2: Parkinsonism - symptoms[4]

Bradykinesia	Slow movements (shuffling gait, soft/weak voice)
Hypokinesia	Absence of purposeful movements, reduced arm swing, mask-like expression
Tremor	Usually coarse or fine hand tremor seen when arms outstretched
Rigidity	Often cogwheel, less often leadpipe rigidity
Others	Drooling, constipation

Prevalence

The prevalence of parkinsonism in those receiving conventional antipsychotics may reach 75%. In those taking atypical drugs the prevalence of such symptoms is generally less than 20%.[9] Interestingly, the baseline for parkinsonism in schizophrenia is not zero and symptoms of parkinsonism are seen in around 15% of never-medicated people with schizophrenia.[10]

Pathophysiology

The parkinsonism seems to occur as a result of the relative balance of influences of dopamine and acetylcholine in the basal ganglia.[9] In Parkinson's disease dopaminergic neurones are destroyed and cholinergic innervation is allowed relative prominence. In antipsychotic-related parkinsonism, dopaminergic transmission is blocked by the antagonistic actions of these drugs at postsynaptic dopamine receptors.[9]

Treatment

Drug-induced parkinsonism is usually treated by switching to a drug less likely to be associated with such effects. Where switching antipsychotics is not practical, anticholinergic drugs such as benztropine are effective, but not without their own adverse effects.[2]

Tardive dyskinesia

TD generally occurs after long-term antipsychotic therapy.TD is a complex neurological syndrome that consists of hyperkinetic, involuntary movements, which are mainly choreoathetoid (but also dystonic) in nature.[11]

Clinical features

TD is commonly characterised by lip smacking and chewing, often with episodic tongue protrusion ('fly-catching') or pushing the tongue into the inner cheek or lip. Grimacing and other facial muscle movements can occur forming the buccolingual masticatory syndrome. Other abnormal movements which can appear include choreiform movements of the hands

('piano-playing'), pelvic-thrusting or rocking of the legs. In severe TD, there may be problems with speaking and eating as well as difficulty in breathing and swallowing.[11] Once developed, symptoms may be partly, or sometimes wholly, irreversible.[11] Although a person who develops TD is usually unaware of the movements, they are clearly noticed by others, and the condition has long been recognised as a severe social handicap.

Box 3: TD – symptoms[4]

General
Choreiform movements: rapid, jerking contractions
Athetoid movements: slow, sinuous muscular spasm
Rhythmic movements: repeated, purposeless movements
Specific examples
Tongue protrusion
Lip-smacking, lip-licking
Grimacing
Blepharospasm
Piano-playing or guitar finger dyskinesias
Neck-twisting (torticollis, retrocolis)
Shoulder-twisting
Trunk deformations (opisthotonos)

Prevalence

For patients receiving extended treatment with conventional antipsychotics, about 20% will be found to have TD at any time, and the probability per year of developing TD is about 5%.[12] A recent systematic review of 11 studies comparing the risk of TD between 5 different second generation antipsychotics with haloperidol, found the mean annual incidence of emergent TD in adults treated with atypical antipsychotics to be 0.8% compared with an incidence of 5.4% with haloperidol.[13]

Pathophysiology

A number of theories have been proposed to explain the development of TD with antipsychotics. One of the most prevailing hypotheses is that long-term dopamine blockade in the striatum by antipsychotic drugs leads to dopamine receptor hypersensitivity, which in turn leads to a loss of voluntary control over various aspects of motor movement.[11] It has also been proposed that TD may result from decreased Gamma-aminobutyric acid (GABA) function in the striatum induced by dopamine hypersensitivity in inhibitory dopaminergic neurones. It has also been postulated that TD arises as a result of over-stimulation of encephalin receptors or because of high activity of free radicals.[11]

Treatment

It is common practice to withdraw the offending antipsychotic and to substitute with another drug. The use of clozapine is best supported in this regard, but there is also evidence for quetiapine, olanzapine, risperidone and aripiprazole.[11] Switching or withdrawing antipsychotics is not always effective and so additional agents are often used. As anticholinergics may exacerbate TD, they should also be discontinued.[11]

Table 3: Possible treatments for TD[2]

Drug	Comments
Tetrabenazine	Only licensed treatment for TD in Australia. May cause depression, drowsiness & akathisia. 25-200mg/day.
Benzodiazepines	Widely used. Considered effective. Clonazepam 1-4 mg/day & diazepam 6-25mg/day
Propranalol	Open label studies only.40-120mg/day
Vitamin E	Many studies but efficacy inconclusive. Dose range 400-1600IU/day

Detecting and Monitoring of

Rating scales available for evaluating drug-induced movement disorders include: Barnes Akathisia Scale,[6] Simpson-Angus Scale (for Parkinsonism),[13] Abnormal Involuntary Movement Scale[14] for TD. Although these scales are specific to EPSE, they were devised to serve the needs of research, and whether they automatically transfer to routine practice has never been evaluated. The Glasgow Antipsychotics Side-Effect Scale (GASS),[15] although not specific to EPSE, may be a more practical option. It is patient-completed, relatively short (21 items for men and women), global in its coverage, and rates both the frequency and distress of each item.

Conclusion

The aim of this bulletin is to remind health professionals that EPSE remain a significant concern with the use of antipsychotic drugs. Although the risk of EPSE with atypical drugs is reduced compared with conventional antipsychotics, EPSE still occur with atypicals at specific doses. Clinicians should remain mindful for the possible development of EPSE when choosing an antipsychotic, and to ensure that patients are systematically monitored, preferably with the use of one of the recognised rating scales developed for this purpose.

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