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SIDE EFFECTS OF ANTIPSYCHOTICS

Antipsychotic medicines are the mainstay of treatment for psychotic symptoms for people with mental illness. All antipsychotic medicines have potential side effects, which vary from person to person. Side effects can include those related to metabolism, weight gain, extrapyramidal motor function (restlessness, trembling in the limbs), muscle stiffness, dizziness, increased sweating, unusually dry or watery mouth, eyesight problems, nausea, constipation, pain or irregularity in menstruation and issues with sexual function. There are important interactions antipsychotic medicines have with other medicines. There has been a recent focus on the inappropriate and overuse of antipsychotics, particularly for people with behavioural and psychological symptoms ofdementia (BPSD) or 'behaviours of concern'. Several problem areas for improvement have been identified:

- Multiple antipsychotic medicines
- Pro re nata (PRN or when required) medicines
- Monitoring the long-term side effects, including metabolic side effects

BPSD

It is estimated that BPSD affects up to 90% of all people with dementia over the course of their illness. BPSD is independently associated with poor outcomes, including distress among residents and caregivers, long-term hospitalisation, misuse of medication, and increased health care costs. Symptoms of BPSD can include:

- Apathy
- Verbal outbursts
- Sleep disturbances
- Wandering and pacing
- Socially inappropriate behaviour
- Repetitive behaviours
- Emotional withdrawal
- Incontinence
- Hallucinations
- Delusions

More serious symptoms of BPSD can include marked persistent agitation and aggression, acute psychiatric disturbance or psychosis.

Antipsychotics

Antipsychotics are generally described as first- or second generation. Older first-generation antipsychotics include chlorpromazine (Largactil) and haloperidol (Serenace). Second-generation antipsychotics include:

- Amisulpride (Solian)
- Aripiprazole (Abilify)
- Asenapine (Saphris)
- Clozapine (Clozaril)
- Olanzapine (Zyprexa)
- Paliperidone (Invega)
- Quetiapine (Seroquel)
- Risperidone (Risperdal)
- Ziprasidone (Zeldox)

Use of antipsychotics in people with BPSD should be limited to people showing intractable aggression and psychosis that has not responded to psychosocial interventions and who have low to moderate risk of stroke. Only a minority of residents with behavioural symptoms of dementia improve with antipsychotic treatment. For every five people with dementia only one will benefit from an antipsychotic.

Risperidone is the only oral antipsychotic approved by the Australian Therapeutic Goods Administration (TGA) for BPSD and listed on the PBS. Risperidone is to be used in people with dementia only of the Alzheimer type, who are unresponsive to non-pharmacological methods of treatment, and treatment duration is limited to twelve weeks. Commencing 1 January 2020 additional restrictions require approval from the Department of Human Services (DHS) to prescribe 'continuing' PBS subsidised treatment. Risperidone should be commenced at a dose of 0.25mg twice daily and increased if needed by 0.25mg every 2 or more days. Maximum dose is 2mg daily, including prn medication. Olanzapine is not approved by TGA for treatment of behavioural disturbance associated with dementia.

However, the Therapeutic Guidelines indicate olanzapine can be considered to control hallucinations, delusions or seriously disturbed behaviour at a starting dose of 2.5mg daily. Olanzapine may be increased if needed by 2.5mg every 2 or more days to a maximum of 10mg daily (including prn medication) in one or two

continued over

divided doses. Haloperidol is PBS-subsidised without restriction. Therapeutic Guidelines recommend low dose oxazepam (7.5mg one to three times daily) to relieve symptoms of severe anxiety and agitation. However, oxazepam should not be used for longer than 2 weeks, as all benzodiazepines can exacerbate cognitive impairment and increase the risk of falls. There is no convincing evidence that antiepileptic drugs such as gabapentin or pregabalin are helpful for BPSD.

Side effects

Adverse effects due to antipsychotics are common. The harms of antipsychotic use for BPSD are likely to outweigh any benefit, except for short-term use in residents with severe aggression and psychotic symptoms, unresponsive to non-drug approaches. Adverse effects of antipsychotics include:

- Sedation and confusion
- Cognitive decline
- Constipation
- Urinary retention
- Hypotension, postural hypotension
- Extrapyramidal effects including parkinsonism
- Increased risk of falls and hip fracture
- Transient ischaemic attacks (TIAs) and stroke
- Diabetes

Suggested monitoring for people taking antipsychotics long-term includes:

- Weight and waist circumference
- Blood pressure
- Fasting serum lipids
- Fasting blood glucose
- Electrocardiogram (ECG)
- Extrapyramidal symptoms
- Sedation
- Anticholinergic effects (dry mouth, blurred vision, urinary retention, constipation)

Metabolic effects

Metabolic disturbance is one of the most important concerns with long-term antipsychotic use. Fasting serum lipids andblood glucose should be reviewed every 12 months, and every 6 months for olanzapine. Clozapine, olanzapine, and quetiapine have been associated with increased blood glucose, weight gain and abnormal lipid levels. Olanzapine has the greatest risk to increase weight, waist circumference and fasting triglycerides, after an average of 9 months of treatment. Clozapine causes a similar degree of weight gain to olanzapine. Weight gain with risperidone and quetiapine is usually modest, and aripiprazole, ziprasidone and a misulpride cause the least weight gain. Risperidone and olanzapine cause greater weight gain than haloperidol. Clozapine and olanzapine are associated with an increased risk of type 2 diabetes. Drug-related obesity can precipitate diabetes in susceptible people; however, these medicines may also aggravate insulin resistance.

Mortality

The atypical antipsychotics increase the risk of death in people with dementia, in the order of 1 excess death per 100 people treated for 10-12 weeks.

Stroke

Use of antipsychotics in people with dementia is associated with an increased risk of cerebrovascular events including stroke. This increased risk may be due to postural hypotension, anticholinergic side effects, QT prolongation, platelet aggregation effects and venous thromboembolism (VTE). The risk of cerebrovascular adverse effects is highest in those with poorly controlled vascular risk factors (atrial fibrillation, hypertension or diabetes) or a history of previous stroke.

Extrapyramidal side effects

All antipsychotics can cause extrapyramidal side effects (EPSE) including rigidity, tremor, akathisia and abnormal involuntary movements. Involuntary muscular contractions or acute dystonia typically involve the muscles of the head and neck, and may appear after only a few doses. Akathisia is a sensation of inner restlessness, a compulsion to keep moving. 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. Tardive dyskinesia, rhythmic involuntary movements of the tongue, face and jaw, may develop after long-term use of antipsychotics, and may be irreversible. Risperidone and olanzapine have fewer extrapyramidal adverse effects than older antipsychotics such as haloperidol.

Anticholinergic effects

Anticholinergic adverse effects include dry mouth, blurred vision, urinary retention, constipation, tachycardia and confusional states.

References

Therapeutic Guidelines Ltd (eTG March 2018 edition)

NPS News Balancing benefits and harms of antipsychotic therapy, 2011.

Diabetes and antipsychotic drugs. Australian Prescriber, 2004. 1234