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DRUG BULLETIN

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# Management of Clozapine-Induced Side Effects

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- **Clozapine may be under-utilised due its adverse effect profile**
- **Many adverse effects resolve post-initiation**
- **Dose adjustments can result in relief for most adverse effects**
- **Adjunctive measures are available for many adverse effects**

## Introduction

Clozapine has been found to be superior to typical antipsychotics for treating both positive and negative symptoms in treatment–resistant schizophrenia(1). Despite its demonstrated efficacy in schizophrenia, widespread use of clozapine has been limited by the potential for adverse effects. Clozapine can cause reversible neutropenia, which may progress to a potentially fatal agranulocytosis. Other potentially serious adverse effects of clozapine include seizures, myocarditis and cardiomyopathy(2). Although clozapine shares a similar adverse effect profile to other antipsychotics, the incidence and severity of such effects may vary. Antimuscarinic effects, sedation and weight gain may be more prominent with clozapine(3). Additional adverse effects of clozapine include postural hypotension, hypersalivation, constipation, urinary incontinence, nausea and tachycardia. It has been estimated that up to 17 percent of patients cease clozapine therapy due to adverse effects(4).

This bulletin will review strategies to minimize the impact of the adverse effects of clozapine therapy on quality of life. Where data from the Australian Adverse Drug Reactions Advisory Committee (ADRAC) is presented; these reports are suspected reactions to clozapine reported from 1 November 1972 to 5 October 2005.

## Haematological Adverse Effects

### Agranulocytosis and Neutropenia

Neutropenia and agranulocytosis are serious adverse effects that may occur with clozapine therapy. Approximately 2.7% of patients treated with clozapine develop neutropenia and 0.7% of patients develop agranulocytosis(3). ADRAC has received 103 case reports of agranulocytosis, with one death and 534 reports of neutropenia including 3 deaths(5). These adverse effects are more likely to occur in the first 6 months of treatment, but may occur at any time(6).

A compulsory system of regular monitoring and recording of white blood cells and neutrophils serves as a safeguard against patients developing agranulocytosis. The following table details the management of patients according to haematological test results.

**Table 1: Haematological Monitoring**

| Status | WBC and neutrophil count result | Action |
|---|---|---|
| Green Range | WBC>3.5 x $10^9$/L and Neutrophils>2.0 x$10^9$/L | Continue clozapine |
| Amber Range | WBC 3.0-3.5 x$10^9$/L And/or Neutrophils 1.5-2.0 x$10^9$/L | Continue clozapine Commence twice weekly blood tests until a green range is obtained |
| Red Range | WBC<3.0 x$10^9$/L And/or Neutrophils< 1.5 x$10^9$/L | Stop clozapine Repeat blood tests daily until green range is obtained |

Patients whose blood samples fall in the red range are permanently ineligible for treatment with clozapine. Patients with a 'red range' status should be referred to a haematologist if the WBC and/or neutrophil counts continue to fall following discontinuation of clozapine. Granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor and antibiotics can be used to treat agranulocytosis if necessary(7).

### Eosinophilia

Clozapine-induced eosinophilia is usually benign but can be associated with myocarditis or eosinophilic colitis(4, 8). Overall, the incidence rate for eosinophilia has been estimated to be at 0.2%(7). The manufacturers recommend discontinuation of clozapine if the eosinophil count rises above 3.0 X $10^9$/L. Therapy may be recommenced only after the eosinophil count has fallen below 1.0X $10^9$/L(9).

## Cardiovascular Adverse Effects

### Myocarditis/Cardiomyopathy

ADRAC has received 193 case reports of clozapine-induced myocarditis, including 13 deaths(5). In 79% of patients who develop myocarditis, the symptoms develop within the first 6 weeks of clozapine treatment(10). Cardiomyopathy generally occurs later in treatment compared to myocarditis(11). Dilated cardiomyopathy may be due to acute myocarditis that was unrecognised in the early stages of therapy or a more chronic form of myocarditis(12). Although more rare than myocarditis, 131 cases of clozapine-induced cardiomyopathy including 6 deaths have been reported to ADRAC(5).

The following monitoring for cardiac adverse effects is recommended(9).

**Table 2 Cardiac Monitoring**

| Timeline | Test |
|---|---|
| Baseline | ECG<br>Troponin I or T and serum creatinine, or CK-MB |
| Day 7 | ECG<br>Troponun I or T or CK-MB<br>(Use same test as at baseline) |
| Day 14 | ECG<br>Troponin I or T or CK-MB<br>(Use same test as at baseline) |
| 6 months | Echocardiography |

Patients should also be monitored for any signs or symptoms of heart failure, such as tachypnoea, low or falling blood pressure, increased jugular venous pressure possibly associated with arrhythmias, fever or chest pain(9).

Patients with suspected myocarditis or cardiomyopathy should be referred to a cardiologist. Options for the management of myocarditis are limited. It has been reported that discontinuation of medication leads to resolution of symptoms(9). Treatment of myocarditis involves ceasing clozapine therapy and commencement on corticosteroids(10). Management of dilated cardiomyopathy is essentially the same as for congestive heart failure(13). Medication used may include a combination of angiotensin converting enzyme inhibitors, diuretics, digoxin, beta-blockers and anticoagulants(14). Patients developing clozapine-induced cardiomyopathy or myocarditis must not be re-exposed to clozapine(11).

### Tachycardia

Tachycardia due to clozapine occurs in 25% of patients, with a mean increase of 10 to 15 beats per minute(11, 15). Tachycardia is dose-dependent. Tolerance usually develops after 4-6 weeks of treatment(7). Patients that have persistent tachycardia at rest, especially during the first two months of treatment, should be closely observed for other signs or symptoms of myocarditis or cardiomyopathy(11). A lower dose of clozapine and slower upward titration can limit the occurrence of tachycardia(4). Pharmacological management consists of using a beta-blocker if necessary(4).

### Hypotension

Clozapine related hypotension is related to the alpha-adrenergic antagonism of clozapine. Postural hypotension is more likely to occur during the first days of clozapine therapy and can be accompanied by syncope(16). Clozapine has induced orthostatic hypotension severe enough to cause collapse and respiratory arrest(4). Most patients develop tolerance to hypotension after 4-6 weeks(4).

Hypotension can usually be managed by using a slow upward dose titration or by reducing the clozapine dose(4). Patients experiencing orthostatic hypotension should be advised to take measures to lessen the impact of postural hypotension such as taking time when standing up

and ensuring an adequate fluid intake. Use of support stockings and tilting the head of the bed at night are second-line management strategies(7). If non-pharmacological strategies fail, fludrocortisone or dihydroergotamine could be considered(7). There are two case reports of fludrocortisone being used successfully to ameliorate clozapine-induced hypotension. Fludrocortisone was well tolerated in both patients, although one patient required a lower dose because of emergent hypertension(17). Dihydroergotamine at doses of 10mg daily has been shown to prevent orthostatic hypotension in patients treated with antipsychotic medication(4). Dihydroergotamine is licensed for short-term or intermittent treatment of severe hypotension(2).

## Central Nervous System Adverse Effects

### Seizures

The risk of seizures among clozapine-treated patients increases with high doses, rapid dose titration, concurrent use of drugs that lower the seizure threshold and pre-existing seizure disorders(7). Doses over 600mg daily have been associated with a greater risk of seizures (4.4%) compared with doses of 300-599mg daily (2.7%) and doses below 300mg (1%)(18).

Seizures during clozapine therapy do not require drug discontinuation(18). If a patient experiences a seizure, brief interruption and/or lowering of dosage may be all that is required(7). Routine prophylactic anticonvulsant treatment is not currently recommended, although it can be considered for patients receiving greater than 600mg daily of clozapine, or if seizures have already occurred(19). If anticonvulsant therapy is indicated, sodium valproate is considered the drug of choice based on the type of seizures clozapine induces, adverse effect profile and interaction potential(20).

### Sedation

Sedation is a very common side effect of clozapine, with an overall incidence of 40%(2). Usually sedation occurs at the beginning of treatment and gradually decreases over 4-6 weeks(7). Management of sedation includes using the lowest effective dose, giving the majority of the dose at night and avoiding other drugs that cause central nervous system depression(21).

## Gastrointestinal Adverse Effects

### Constipation

Constipation occurs in 14 percent of patients treated with clozapine and can be severe(4). There have been six deaths reported to ADRAC due to constipation(5). ADRAC has received reports of colitis, ileus, paralytic ileus, intestinal obstruction, intestinal perforation, peritonitis, and gastrointestinal necrosis induced by clozapine(5). Constipation may persist throughout clozapine therapy(22).

Considering the potential for serious complications of constipation, it is advisable to ensure bowel habits are monitored and prophylaxis against constipation is provided(23). The following table details the management of clozapine-induced constipation(23).

**Table 3 Management of Constipation**

| | |
|---|---|
| Step 1 | **Increase exercise, fluid intake and dietary fibre**<br>Try for 2-4 weeks before initiating laxative therapy |
| Step 2 | **Bulk-forming laxatives (psyllium mucilloid, ispaghula bark)**<br>Agents of choice for chronic constipation. May be used in conjunction with other agents |
| Step 3 | **Stool softeners (docusate sodium)**<br>May be required for some patients with chronic constipation |
| Step 4 | **Osmotic laxatives (sorbitol, magnesium sulphate)**<br>Osmotic laxatives are more appropriate for long-term management of constipation than stimulants |
| Step 5 | **Stimulant laxatives (sennosides)**<br>For short-term use only, as long-term use can result in degenerative changes in colonic muscles and nerves(4). |
| Step 6 | **Suppositories or Enemas (glycerin suppositories, bisocodyl suppositories, microlax enema®)** |
| Step 7 | **Colonic Lavage (Golytely®, Glyco-Prep®, Glyco-Prep-C®)**<br>Avoid in rectal impaction |

For the relief of acute constipation, stimulant laxatives, suppositories and enemas may be used initially. Once resolved, management of chronic constipation should comprise of exercise, increased fluid intake, dietary fibre and any of steps of 2, 3 or 4(23).

### Nausea

Although antipsychotics have antiemetic effects due to their $D_2$-blocking properties, paradoxical nausea has been known to occur in clozapine-treated patients, usually later in treatment(16). Strategies to manage clozapine-induced nausea include using metoclopramide, antacids or $H_2$ blockers(7). Cimetidine is not recommended, as it can raise clozapine blood levels(2).

## Autonomic Nervous System Adverse Effects

### Hypersalivation

Clozapine induced hypersalivation can be socially embarrassing and potentially life threatening due to the risk of asphyxiation. The incidence of hypersalivation is estimated to be at 31%(15). Hypersalivation is particularly worse at night and during the early stages of therapy(24).

Non–pharmacological strategies that can be useful adjuncts include lowering the dose of clozapine and the use of sugar-free gum to increase the swallowing rate(24). A variety of pharmacological strategies have been employed to counteract hypersalivation, however there have been no large randomly controlled studies completed at this stage. The following agents have been effective in treating clozapine-induced hypersalivation in a few case reports; amitriptyline, benzhexol, benztropine, atropine, hyoscine hydrobromide, ipratropium bromide, terazosin, clonidine and botulinum toxin(24-30). Effective treatment is usually achieved with the use of amitriptyline at a dose of 25-50mg at night. There is a case report of amitriptyline being administered to four patients at a dose of 87-100mg and this resulted in either an improvement or cessation of hypersalivation in all patients(25). Hyoscine hydrobromide tablets sucked and swallowed three times a day is widely used in clinical practice, however, there are no publications supporting its efficacy(24). Caution is required when administering clozapine with other anticholinergic drugs(2).

### Nocturnal Enuresis

The incidence of nocturnal enuresis is about 1%, but it may be under-reported because of the embarrassing nature of this adverse effect(15). The pathophysiological cause requires investigation, as nocturnal enuresis can be due directly to the sedative nature of the medication, due to epileptic seizures presenting as nocturnal enuresis or due to diabetes mellitus(31). Nocturnal enuresis can occur at any time during therapy(31).

Patients should be advised to avoid fluids in the evening and to void before going to bed. Scheduled night awakenings to empty the bladder can be practised. If necessary, an enuresis alarm can be used(4). Pharmacological methods to manage nocturnal enuresis include desmopressin or oxybutynin. Oxybutynin has been used in doses ranging from 5mg at bedtime to 5mg three times a day(32). Desmopressin spray has been used at a dose of 10mcg in each nostril at bedtime(31). There has been a case report of hyponatraemia due to desmopressin in a clozapine-treated patient, which may have been due to ineffective fluid restriction just before and after administration of desmopressin dose(33). The cost of desmopressin relative to oxybutynin may prohibit its use.

## Metabolic Adverse Effects

### Weight Gain

Of the antipsychotics, those associated with the most weight gain are clozapine and olanzapine(34). A recent study of long-stay hospital studies showed that patients commenced on clozapine gained 7% of body weight over two years(35). Although body weight gain is more pronounced in the first 4-12 weeks of therapy, weight increase may also occur over a prolonged period of time(7).

There is insufficient evidence for pharmacological intervention for clozapine-induced weight gain(36). Clozapine-induced weight gain can be managed by informing patients of the potential for weight gain, dietary modification, increased physical activity and behavioural interventions(36). Drug treatment options for antipsychotic-induced weight gain was the subject of the October 2005 Drug Bulletin.

## Conclusion

The scope of this bulletin was to discuss the clinically significant adverse effects and their management. For a complete list of adverse effects of clozapine, please refer to the product information. Many of the side effects of clozapine are associated with antipsychotic therapy in general. There is a wide range of therapeutic benefits to clozapine compared to the associated risks. Appropriate management of clozapine side effects allows maximisation of the benefits of clozapine therapy.

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*References available on request*