

## Clozapine-induced hypersalivation

This bulletin is an update to a previously issued bulletin about clozapine-induced hypersalivation (vol 11 no 3, Oct 2013).

**There is a current UK shortage of hyoscine hydrobromide (Kwells) tablets** – this is due to a lack of raw ingredient and it is not clear when this shortage may be resolved. CPSU has exhausted its stocks.

In the meantime we have procured a supply of hyoscine from Australia however, as it is being imported, we don't have a firm date of delivery – it is expected to arrive within a matter of days and prescribers will be notified when we have stock available.

Please **do not start any new patients on hyoscine** until the imported version is available.

Prescribers will be notified by our dispensary staff if we are unable to fulfil a repeat prescription for hyoscine for any patients already prescribed it and they will be asked to make a decision about which alternative is most suitable. We hope the information in this bulletin will help inform the choice of alternative.

The information contained in this document includes the use of hyoscine tablets, as these are usually our first line treatment option for hypersalivation, however it is intended that the following information will allow prescribers to select alternative options that are suitable for their patients until hyoscine becomes available again.

### Suggested doses and methods of administration for the Trust's preferred options:

Priority of use	Drug	Method of administration	Dose	Administration	Secondary care cost for max dose/28 days
FIRST LINE	Hyoscine hydrobromide	Sublingual tablet *	300mcg daily. Increased if necessary to 900mcg daily.	Tablets must be sucked – <u>not swallowed whole</u> . Ensure correct use before dose increase. Do not increase dose rapidly.	£5.60
		Transdermal patch**	1mg/72 hours (equivalent to 1.5mg)	Apply to hairless area of skin behind ear. Wash hands well after application. Replace every 72 hours.	£17.28
SECOND LINE	Ipratropium bromide	Nasal spray 0.03% (21microgram/dose)	One or two sprays to be used intranasally or sublingually up to three times daily	Nasal spray can be sprayed under the tongue or nasally.	£5.88
	Trihexyphenidyl (Benzhexol)	Tablets	5 -15mg daily		£12.50
	Pirenzepine	Tablets	25 -100mg daily	Not licensed in the UK – available to import (eg IDIS World Medicines)	£36.11
THIRD LINE	Atropine sulphate	Mouthwash - using Atropine 1% <u>eye drops</u>	Add one or two drops to 10ml water or dissolve one tablet in 10ml water and <b>use as mouthwash</b> up to twice daily.	Mouthwash must be swished around mouth before swallowing. Solution has bitter taste. Requires the patient to be capable of following the preparation instructions.	£73.52
		or tablet			£51.50
		Tablets – used sublingually	600mcg up to twice daily.	Tablet disperses readily in the mouth. Bitter taste.	£51.50
<b>After discussion with pharmacy only (not for routine use due to very high cost):</b>					
	Glycopyrronium	Tablets	1 - 3mg TDS	Unlicensed. Discontinue after 4 weeks if no effect.	£1527.27

\*currently unavailable

\*\* remains AVAILABLE – may make a suitable alternative for patients who have responded to hyoscine orally.

## Community Patients:

If patients are not able to access second or third line options from primary care, please issue the dispensary with a hospital outpatient prescription and this medication will be sent out with the patient's next clozapine supply, unless you specify that you would like this to be sent as soon as possible.

## Background

Clozapine-induced hypersalivation (CIH) is a significant side effect, affecting about one-third of patients taking this drug. After sedation it is the second most common side effect of clozapine and can be a deeply stigmatising and unpleasant problem. It tends to appear early on in treatment and is often worse at night. In addition to sleep and social disturbances, it has been associated with significant health problems, such as aspiration pneumonia and is often a reason for treatment discontinuation.

The mechanism by which clozapine brings about this side effect is unclear, however several theories have been suggested. One theory involves muscarinic receptors (M3 and M4) which are present in salivary gland tissue. These receptors are thought to exert opposing effects on salivation: M3 blockade and M4 stimulation enhance saliva production. Clozapine has significant anti-muscarinic activity, and is an antagonist at M1, M3 and M5 receptors, however it is an agonist at M4 receptors. This could explain the paradoxical effect that it has on saliva production (normally anti-cholinergic drugs cause a dry mouth). Yet some authors have argued that salivary flow is not increased in CIH and have suggested that clozapine directly affects the swallowing reflex. Further studies have suggested a disruption in the circadian secretion of saliva.

Various treatment strategies have been put forward to manage this side effect. Non-pharmacological strategies, such as chewing gum during the day to encourage swallowing and placing a towel over the pillow at night to reduce soaking, may be useful but are often inadequate. Most of the treatments focus on reducing salivary output, usually through anti-cholinergic activity. The data available is mainly from small open label trials or case reports. There is only one RCT published on this subject. Many of the studies are limited because of the difficulty in measuring salivary output, especially when a patient is asleep.

## Anti-cholinergics

These drugs may enhance anti-cholinergic side effects, such as constipation, urinary retention and blurred vision and some may have cognitive side effects.

### **Hyoscine hydrobromide**

This is usually the first choice of treatment, despite no published trial data to support its oral use. It is available as tablets or a transdermal patch. Generally it is prescribed as 300mcg tablets nocte, increased if necessary to 300mcg three times daily. The tablets must be sucked or chewed for optimum efficacy. If they are swallowed whole, they may have limited effect. Alternatively, they could be dissolved in a small amount of water and rinsed around the mouth, like a mouthwash, before swallowing. The patch gradually releases hyoscine over a 72 hour period. A small study of 4 patients reported a dramatic improvement in CIH with the patch and one author suggested that it was effective in patients who did not respond to oral hyoscine.

### **Atropine sulphate**

There is limited literature to support the use of atropine eye drops given sublingually. This literature recommends that patients rinse their mouths with a solution prepared from 1 or 2 drops in 10ml water. It must be rinsed around the mouth for maximum topical absorption and effectiveness. Atropine is available in tablet form and is very soluble in water, however no studies have evaluated the efficacy of atropine tablets in CIH. The tablets can be held under the tongue until they disperse or they can be dissolved in water and rinsed like a mouthwash, then swallowed. Atropine has a bitter taste, which may make either option unpalatable. It is readily absorbed from the GI tract and from mucous membranes. The therapeutic effect of atropine is often brief, as it has a short half life (4 hours), which may predispose patients to morning rebound hypersalivation. It may also help some to have the atropine handy at the bedside if they wake during the night needing a further dose to tide them over until morning. Use of atropine eye drops as a mouthwash may not be suitable in patients who are confused or unable to follow the preparation instructions.

### **Trihexylphenidyl (Benzhexol)**

An open label study of 14 patients with clozapine induced nocturnal hypersalivation were treated with trihexylphenidyl. Three individuals showed no response to treatment, and the remaining 12 demonstrated a maximal 44% reduction in

nocturnal hypersalivation with a mean dose of 10.7mg. A case report using doses of 6mg per day in divided doses resulted in reduction of nocturnal hypersalivation and resolution of daytime hypersalivation. Doses of 5-15mg may be prescribed.

### **Pirenzepine**

This is a selective M1 and M4 muscarinic antagonist, which does not cross the blood brain barrier. An 8 week randomised double-blind, placebo-controlled, cross-over trial of 20 patients showed no significant therapeutic effect on hypersalivation with pirenzepine compared to placebo. Another 3 day open label study of 29 patients showed some improvement in hypersalivation with pirenzepine 50mg daily, although this study was limited in time and lack of objective measures. Finally one author has reported success in treating over 120 patients with CIH, using doses of pirenzepine of 25 to 100mg daily. Mild diarrhoea is a common side effect of this treatment. Pirenzepine has been discontinued in the UK, but can be imported from abroad using importing companies such as IDIS World Medicines.

### **Ipratropium bromide**

There is limited evidence (from non-RCT studies and case series) of a moderate benefit from using ipratropium in patients with CIH, however it has been noted that the effects can be short lived. The 0.03% nasal spray preparation was generally used. This can be administered either sublingually or intra nasally. It has minimal systemic absorption, which reduces the incidence of anticholinergic side effects. One or two sprays can be used up to three times a day. The only RCT conducted was small (n=20) and ipratropium was no better than placebo after 2 weeks.

### **Glycopyrronium**

Glycopyrronium tablets are available but are not licensed to treat hypersalivation associated with clozapine. It is slower in onset and produces less tachycardia than atropine or hyoscine. Benefits include a long duration of action and it doesn't cross the blood-brain barrier thus reducing central adverse effects (e.g. sedation, restlessness). However, published data are mainly limited to oral use in children/young adults with neurodevelopmental disabilities. In one small study in adult patients with Parkinson's disease, 39% responded to treatment with oral glycopyrronium. NICE concluded that there is moderate evidence that oral glycopyrronium reduces hypersalivation or drooling, but the RCTs do not provide evidence for the efficacy or safety of long-term use for treating adults, children and young people with hypersalivation.

### **Biperiden**

One case report described how biperiden, a centrally acting anticholinergic, at a dose of 6mg daily was effective at eliminating symptoms of CIH. A small (n=13) randomised cross-over trial of biperiden 2mg BD versus glycopyrronium 1mg BD showed that although hypersalivation was significantly improved at 4 weeks it was less so than with glycopyrronium and cognitive function was reduced. Biperiden is not available in the UK but can be imported.

### **Amitriptyline**

This tricyclic antidepressant has significant anticholinergic properties. One study reported its use in four patients to treat CIH at a dose range of 75-100mg/day. The study failed to include objective measures for hypersalivation, but reported that all four patients improved. The combination may increase the risk of orthostatic hypotension and possibly seizures.

## **Adrenoceptor agonists**

### **Terazosin (with and without benztropine)**

This drug is an alpha 1 receptor antagonist, as is clozapine, which makes this a controversial option. However its use in CIH has been assessed in one study involving 60 patients. The authors measured the efficacy of benztropine (1mg BD) and terazosin (2mg at bedtime) in combination or individually and concluded that the combination treatment was more effective. At the end of 12 weeks, they reported a 'resolution' of hypersalivation for 100% of those on combined treatment, compared to 67.7% on benztropine alone, 93.3% on terazosin alone and 0% on no treatment. The lack of objective measures of saliva limits these results. Common adverse events associated with terazosin include palpitations, nausea, peripheral oedema, dizziness and somnolence. Benztropine is no longer available in the UK but can be imported.

### **Clonidine and Lofexidine**

These drugs stimulate presynaptic alpha2 autoreceptors. There have been a few case reports that claimed success with each of these, however because of the associated side effects, they have limited value. Clonidine can cause significant postural hypotension and both have the potential to cause or worsen existing depressive or psychotic disorders.

## **Antipsychotics**

Augmentation of clozapine with other antipsychotics has been shown to be effective in treating hypersalivation. The mechanism for action is not known, although it is suggested that antipsychotics such as sulpiride and amisulpride may

reduce gastric and other mucosal secretions via central nervous system dopamine blockade. Furthermore, the addition of a second antipsychotic might allow the clozapine dose to be decreased, which could reduce CIH symptoms.

## Amisulpride

An RCT including 20 patients examined the effect of adding amisulpride (400mg daily) to clozapine, compared to placebo. The clozapine dose was not reduced. The authors reported a significant improvement in CIH, using a five point nocturnal hypersalivation rating scale (NHRS). Other case reports have shown how amisulpride augmentation allowed for the clozapine dose to be reduced, thereby improving the hypersalivation. In an open-label crossover study of amisulpride 400mg/day versus moclobemide 300mg/day (n=53) thirty-nine patients improved with moclobemide being more effective than amisulpride.

## Sulpiride

An open label trial of sulpiride augmentation to clozapine, involving 18 patients, resulted in significant reductions in sialorrhoea according to the 5 point NHRS. Clozapine doses were not reduced in this study.

## Quetiapine

A retrospective chart review (n=158) found that quetiapine was beneficial in some patients when added to a 25% reduction in clozapine dose.

## Botulinum toxin

Botulinum toxin injections into the parotid glands have been shown to be very effective in treating sialorrhoea in the context of various neurological disorders, such as Parkinson's disease and motor neuron disease. There is one case report of its use in CIH, detailing a good response to BTX injections lasting for more than 12 weeks.

For further information and advice please contact the Trust's  
Medicines Information Service by phone or email:



**01865 904365 (with answer-phone)**

**[med.info@oxfordhealth.nhs.uk](mailto:med.info@oxfordhealth.nhs.uk) (checked daily)**

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