DEPARTMENT OF PHARMACY

Guidance on clomipramine supply problems and therapeutic alternatives

BACKGROUND

- Clomipramine is made available in the UK as conventional release capsules (10mg, 25mg, 50mg) and modified release (m/r) 75mg tablets. The capsules are available in both generic and branded (Anafranil™) forms and the m/r tablet as a branded preparation only.
- Following the closure of the UK manufacturing facility, the manufacturer of Anafranil™ has announced that it has discontinued production of the conventional release capsules, that supplies of the 10mg and 50mg strengths would be expected to run out by January 2014 and of the 25mg strength by August 2014.
- Since that time, pharmaceutical wholesalers have predominantly been providing generic forms of the capsules.

Supply situation (at April 10th 2014)

- The supply situation for all strengths of clomipramine capsules deteriorated during March 2014.
- Supplies to the NTW pharmacy service have become intermittent.
- National wholesalers remain able to supply small amounts of the 10mg and 25mg capsules.
- Currently, wholesalers are unable to provide a date for the resumption of normal supply of all strengths.
- Until recently, supplies of clomipramine 75mg M/R tablets were unaffected. However, shortages of the capsules have led to some patients being switched to the m/r tablet. Increased demand for the latter formulation has led to stock levels becoming low amongst some suppliers; local branches of AAH remain in stock but have reported drawing upon stocks from other branches outside the NorthEast. Stocks of the m/r tablets may therefore become depleted if further switching from capsules to m/r tablets occurs. Although this preparation is ‘non-formulary’ within the NTW area, this restriction has been temporarily lifted until the ongoing clomipramine supply situation is clearer.
- NTW prescribers are asked to limit the duration of supply of clomipramine to a maximum of 14 days until further notice.

Clomipramine therapeutics and possible alternatives - general considerations

Clomipramine is a ‘dual action’ tricyclic antidepressant (TCA) which blocks the reuptake of both noradrenaline and serotonin. Clomipramine is a much more potent serotonin reuptake inhibitor than other TCAs and is therefore closer in

terms of its clinical effect to SSRIs. Clomipramine is licensed for the treatment of depression, phobic and obsessional states and is also used off-licence in the treatment of panic disorder². It is also licensed for adjunctive treatment of cataplexy associated with narcolepsy. Careful consideration should be given to the condition being treated when considering prescribing alternatives.

It is important that, wherever possible, clomipramine treatment should not be stopped abruptly.

NATIONAL GUIDANCE

A. Anxiety disorders

   NICE Guidance

   • Review the need for medication using the NICE guidelines for:

   Generalised Anxiety Disorder and Panic Disorder (with or without agoraphobia) in Adults (CG113)

   Obsessive Compulsive Disorder (OCD) and Body Dysmorphic Disorder (BDD) (CG31)

   Depression in Adults: The Treatment and Management of Depression in Adults (CG90)

   • If medication is required, offer the following treatments in combination with psychological treatments:

       Obsessive compulsive disorder (OCD) and body dysmorphic disorder (BDD):
       First line Offer an SSRI
       Second line An alternative SSRI.
       Other tricyclic antidepressants are not recommended, nor are SNRIs or tricyclic–related antidepressants.

B. Panic Disorder:

   NICE Guidance

   First Line Offer an SSRI
   Second Line If an SSRI is not suitable or there is not improvement after a 12-week course, and if further medication is appropriate, consider imipramine.

British Association of Psychopharmacology Guidance (March 2014)

BAP anxiety guidelines (see above) recommend that for the acute treatment of panic disorders the following are effective: all SSRIs, some TCAs (clomi-

² Summary of Product Characteristics (SPC) Clomipramine.
pramine, desipramine, imipramine, lofepramine) venlafaxine, reboxetine, some benzodiazepines (alprazolam, clonazepam, diazepam, lorazepam), some anticonvulsants (gabapentin, sodium valproate).

BAP guidance also states that when the initial treatment fails, to consider augmenting an SSRI with an antipsychotic, 5HT3 antagonist or with topiramate or lamotrigine (off-label indications).

Avoid prescribing propranolol, buspirone and buproprion

For longer term treatment, continue for at least 6 months for patients who have responded. Consider combining cognitive behavioural therapy with antidepressants or benzodiazepines (be mindful of risk of tolerance and dependence). If treatment fails consider increasing the dose if current dose is well tolerated; alternatively consider switching to or combining with another evidence based treatment.

C. Depression

NICE guidance (CG90)

<table>
<thead>
<tr>
<th>First Line</th>
<th>An SSRI</th>
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<tr>
<td>Second Line</td>
<td>A different SSRI or another different class of antidepressant (such as venlafaxine, mirtazapine, a TCA or an MAOI).</td>
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Do not use dosulepin due to its increased cardiac risk and toxicity in overdose.

For patients with treatment resistant depression, reviewing past treatment options and augmentation strategies such as lithium, an antipsychotic or the addition of another antidepressant such as mirtazapine can be considered.

Be mindful of side effects and drug interactions; for more information see the NICE guidelines (above) or seek pharmaceutical advice. For difficult to treat patients a second opinion or advice from the Regional Affective Disorders Service should be considered.

D. CKS guidelines for switching antidepressants:

1. When switching antidepressants, consider:
   - Any co-morbid conditions or potential drug interactions that may influence choice of drug.
   - Adverse effect profile — for example sedation, sexual adverse effects, weight gain.
   - Toxicity in overdose — if there is a history or likelihood of overdose, avoid venlafaxine and TCAs.

2. Abrupt withdrawal should generally be avoided when switching from one antidepressant to another.
3. When switching antidepressants, be aware of the need for gradual and modest increases of dose, interactions between antidepressants, and the risk of serotonin syndrome when combinations of serotonergic antidepressants are prescribed. Features of serotonin syndrome include confusion, delirium, shivering, sweating, changes in blood pressure, and myoclonus.

CKS have also produced guidelines regarding switching from clomipramine³:

When switching from clomipramine to:

A tricyclic antidepressant (TCA) — cross-taper cautiously

SSRI — withdraw (gradually reduce dose then stop), then start SSRI. Do not co-administer clomipramine and SSRI (increased risk of serotonin syndrome).

Duloxetine — withdraw (gradually reduce the dose then stop), and then start duloxetine at 30 mg once a day and increase very slowly.

Venlafaxine — withdraw (gradually reduce dose then stop), then start venlafaxine 37.5mg once a day. Do not co-administer venlafaxine and SSRI

See CKS guidance for more details³.

EXPERT COMMENTARY

If the patient is under secondary care supervision then alternative therapeutic options should first be discussed with the responsible consultant psychiatrist. If the patient is not under secondary care supervision then the following options may be considered. If there is any uncertainty about what to switch to or how to do it, then specialist advice should be sought. It is important to involve the patients (and the carers, as appropriate) in the discussion regarding any planned swap or change BEFORE making the change.

If other antidepressants have been tried and clomipramine needs to continue then consider switch to equivalent or nearest equivalent dose of MR preparation, if 75mg MR preparation is available (for example, 50mg or 100mg daily to 75mg once daily).

The most common use of clomipramine is in the treatment of obsessive compulsive disorder, where antidepressants with potent serotonin reuptake inhibitor action are most helpful. In such cases, the main alternative options are the SSRI, the most selective of these are citalopram (‘off-label indication) and escitalopram (non-formulary). Patients with refractory illnesses in whom clomipramine is being considered may require high doses.

Be aware of MHRA recommendations regarding the maximum daily doses of citalopram and escitalopram (see MHRA warning⁴).

Whilst citalopram and escitalopram are the most selective 5-HT reuptake inhibitors, the next most selective is sertraline, which is licensed in OCD. Paroxetine is the SSRI with the pharmacological profile nearest to clomipramine. When using paroxetine, be aware of the discontinuation reactions that can be particularly prominent if a patient has been taking high doses over a prolonged period.

If clomipramine is being used in the management of treatment-resistant depression, then in addition to the above, venlafaxine and duloxetine may be considered. While all of these are less 5-HT selective compared to clomipramine, this remains their most potent effect.

Other antidepressants that are useful in the treatment of OCD include fluoxetine and fluvoxamine. Fluvoxamine is however not widely used due to the significant risk of drug-drug interactions.

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MHRA Drug Safety Update Dec 2011  