ANXIOLYTICS & HYPNOTICS GUIDELINES

TREATMENT OF ANXIETY DISORDERS AND INSOMNIA

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Any enquiries regarding these guidelines or other medication related queries should be forwarded to the MIS (Medicines Information Service), pharmacy department, Prospect Park Hospital, on 0118 960 5075/5059, or your ward/locality pharmacist.
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Anxiety Disorders

These include generalised anxiety disorder (GAD), obsessive compulsive disorder (OCD), panic disorder, phobias and post traumatic stress disorder (PTSD).

General Treatment Principles

Benzodiazepines

- Benzodiazepines are indicated for the short-term relief (two to four weeks only) of anxiety that is severe, disabling, or causing the patient unacceptable distress, occurring alone or in association with insomnia or short-term psychosomatic, organic, or psychotic illness.

- The use of benzodiazepines to treat short-term ‘mild’ anxiety is inappropriate.

- Patients taking benzodiazepines may report a paradoxical increase in hostility and aggression. Adjustment of the dose (increase or decrease) usually attenuates the impulses. The effects range from talkativeness and excitement to anxiety, perceptual disorders and aggressive and antisocial behaviour.

  - Anxiolytic treatment should be limited to the lowest possible dose for the shortest possible time

  - NICE recommends that benzodiazepines should not be used to treat panic disorder, and should be used with care in post-traumatic stress disorder.

  - Other treatment methods should be commenced as soon as possible depending on diagnosis/underlying cause
e.g. relaxation, psychotherapy, treatment with antidepressants – see below

  - The long term use of any compound to deal with mild anxiety is generally not advised. The consequences of long term use are liable to outweigh the benefits of symptomatic relief. The decision for longer term treatment must be considered on an individual basis and only when the benefits of doing so outweigh the risks, such as in those with severely disabling anxiety.

  - Repeat prescriptions should be avoided in those with major personality problems whose difficulties are unlikely ever to resolve.

  - Benzodiazepines should be avoided, if possible, in those with a history of substance misuse.
# ANXIOLYTICS

*See individual disorders for details of first and second-line treatments

<table>
<thead>
<tr>
<th>First Line*</th>
<th>Non-first-line/restricted use</th>
<th>For secondary care initiation</th>
<th>Non-formulary</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRIs</td>
<td>Clomipramine</td>
<td>Clonazepam***</td>
<td>Duloxetine</td>
</tr>
<tr>
<td>Citalopram</td>
<td>Imipramine</td>
<td>Chlordiazepoxide</td>
<td></td>
</tr>
<tr>
<td>Escitalopram</td>
<td>Lofepramine</td>
<td>Augmentation with atypical Antipsychotics</td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Venlafaxine XL</td>
<td></td>
<td></td>
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<tr>
<td>Fluvoxamine</td>
<td>Moclobemide</td>
<td>Valproate</td>
<td></td>
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<tr>
<td>Paroxetine</td>
<td>Mirtazapine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sertraline</td>
<td>Propranolol</td>
<td>Hydroxyzine</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Buspirone</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Benzodiazepines</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diazepam</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Lorazepam</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oxazepam</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Pregabalin</strong></td>
<td></td>
</tr>
</tbody>
</table>

** Pregabalin is very expensive and should only be used 4th line (after failure of two SSRIs and venlafaxine).

*** clonazepam is only licensed in epilepsy; it is sometimes used (unlicensed) as an anxiolytic within Berkshire Healthcare NHS Foundation Trust. Only use for short duration.
### Antidepressants licensed for anxiety disorders

Anxiety disorders treatable with antidepressants are shown in the table below.

<table>
<thead>
<tr>
<th>Antidepressant</th>
<th>GAD</th>
<th>Panic Disorder</th>
<th>OCD</th>
<th>Social Phobias</th>
<th>PTSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td></td>
<td>✔️</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clomipramine</td>
<td></td>
<td></td>
<td>✔️</td>
<td>✔️</td>
<td></td>
</tr>
<tr>
<td>Escitalopram</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
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<td></td>
<td></td>
<td>✔️</td>
<td></td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✔️</td>
</tr>
<tr>
<td>Moclobemide</td>
<td></td>
<td></td>
<td></td>
<td>★</td>
<td></td>
</tr>
<tr>
<td>Paroxetine</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Sertraline</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td></td>
</tr>
<tr>
<td>Duloxetine</td>
<td></td>
<td>★</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venlafaxine IR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venlafaxine XL</td>
<td>✔️</td>
<td>✔️</td>
<td></td>
<td></td>
<td>✔️</td>
</tr>
</tbody>
</table>

**NB:** Dosage regimes for SSRIs and other antidepressants differ for anxiety disorders and depression – for correct dosages, refer to most current BNF.

SSRIs can worsen anxiety at the start of treatment.₆ For this reason, it is advisable to start at a low (sub-therapeutic) dose to minimise this, and titrate upwards. A short course of a benzodiazepine, usually diazepam, may be helpful during this period.
## Cost Implications

Costs for 28 days treatment at commonly used doses, from BNF March 2011

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Monthly Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>20mg/day</td>
<td>£1.30</td>
</tr>
<tr>
<td></td>
<td>30mg/day</td>
<td>£2.33 (10mg+20mg)</td>
</tr>
<tr>
<td></td>
<td>40mg/day</td>
<td>£1.37</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>150mg/day</td>
<td>£8.25</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>10mg/day</td>
<td>£14.91</td>
</tr>
<tr>
<td></td>
<td>20mg/day</td>
<td>£25.20</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>20mg/day</td>
<td>£1.77</td>
</tr>
<tr>
<td></td>
<td>40mg/day</td>
<td>£3.55</td>
</tr>
<tr>
<td></td>
<td>60mg/day</td>
<td>£50.80 (as 60mg capsule)</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>100mg/day</td>
<td>£10.89</td>
</tr>
<tr>
<td></td>
<td>150mg/day</td>
<td>£15.93</td>
</tr>
<tr>
<td></td>
<td>200mg/day</td>
<td>£21.78</td>
</tr>
<tr>
<td></td>
<td>300mg/day</td>
<td>£32.67</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>20mg/day</td>
<td>£2.13</td>
</tr>
<tr>
<td></td>
<td>30mg/day</td>
<td>£2.96</td>
</tr>
<tr>
<td></td>
<td>40mg/day</td>
<td>£4.27</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>150mg/day</td>
<td>£64.40 – as 75mg bd</td>
</tr>
<tr>
<td></td>
<td></td>
<td>£96.60 (as 50mg tds)</td>
</tr>
<tr>
<td></td>
<td>300mg/day</td>
<td>£64.40 (as 150mg bd)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>£96.60 (as 100mg tds)</td>
</tr>
<tr>
<td></td>
<td>450mg/day</td>
<td>£64.40 (as 225mg bd)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>£96.60 (as 150mg tds)</td>
</tr>
<tr>
<td></td>
<td>600mg/day</td>
<td>£64.40 (as 300mg bd)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>£96.60 (as 200mg tds)</td>
</tr>
<tr>
<td>Sertraline</td>
<td>50mg/day</td>
<td>£1.15</td>
</tr>
<tr>
<td></td>
<td>100mg/day</td>
<td>£1.53</td>
</tr>
<tr>
<td></td>
<td>150mg/day</td>
<td>£2.68</td>
</tr>
<tr>
<td></td>
<td>200mg/day</td>
<td>£3.06</td>
</tr>
<tr>
<td>Venlafaxine XL</td>
<td>75mg/day</td>
<td>£22.50</td>
</tr>
<tr>
<td></td>
<td>150mg/day</td>
<td>£37.51</td>
</tr>
<tr>
<td></td>
<td>225mg/day</td>
<td>£33.60 (from Drug Tariff)</td>
</tr>
</tbody>
</table>
Generalised Anxiety Disorder (GAD)

- Use an SSRI for first-line pharmacological treatment

- If this is ineffective, offer an alternative SSRI, or venlafaxine.

- With venlafaxine, practitioners should take into account the increased likelihood of patients stopping treatment because of side effects, withdrawal syndrome and toxicity in overdose. For more information on venlafaxine, see antidepressant prescribing guidelines

- Use pregabalin only where two SSRIs/venlafaxine are not tolerated, or are ineffective. When prescribing pregabalin, use twice-daily dosing, rather than three times daily (see cost table).

- Advise the patient that treatment periods of up to 12 weeks are needed to assess efficacy

- Review the effectiveness and side effects of the drug every 2–4 weeks during the first 3 months of treatment and every 3 months thereafter.

- If the drug is effective, advise the person to continue taking it for at least a year as the likelihood of relapse is high. Beyond this, an individualised approach should be adopted, depending on the needs and preferences of the patient.

Other treatments/augmentation strategies (see table below)

These have a much weaker evidence base and should not be used first-line. Specialist advice should usually be sought.

More details can be obtained from BHFT’s medicines information service on possible combinations.

There are no RCTs of mirtazapine for GAD.

Tricyclic antidepressants such as imipramine, and MAOIs do have an evidence base in GAD, but their use is often limited by side-effects, and in the case of MAOIs, by the low-tyramine diet restriction and treatment washout periods.
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antipsychotic</td>
<td>Area of research into atypical antipsychotic augmentation. Generally less risk of EPSE than older agents, which were previously widely used in GAD.</td>
<td>Very limited evidence – 4 trials included in NICE review (olanzapine&lt;sup&gt;10&lt;/sup&gt;, risperidone&lt;sup&gt;11,12&lt;/sup&gt; and ziprasidone&lt;sup&gt;13&lt;/sup&gt;) three of which were small. Limited benefit. High side-effect burden (risk of hyperglycaemia/diabetes/other metabolic effects) Not licensed for GAD.</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>Useful for somatic symptoms, e.g. tachycardia, sweating, tremor. Propranolol licensed for this indication at 40-120mg/day in 2-3 divided doses (but 30-60mg may be sufficient).</td>
<td>Limited role generally Licensed dose range may be too high for some patients and lead to cardiac symptoms Avoid abrupt withdrawal as rebound symptoms may arise. Withdraw over 1-2 weeks Potential for interaction with other drugs and cardiac symptoms. Avoid in asthma, hypotension or hypoglycaemia.</td>
</tr>
<tr>
<td>Buspirone</td>
<td>Considered to be as effective as the benzodiazepines, with a better side-effect profile. Licensed for this indication.</td>
<td>Lack of evidence, although more effective than placebo Nausea and dizziness may result in discontinuation Delayed onset of action (requires 4 weeks)</td>
</tr>
<tr>
<td>Hydroxyzine</td>
<td>Licensed for this indication.</td>
<td>Lack of evidence, although more effective than placebo More sedating than some alternatives</td>
</tr>
<tr>
<td>Moclobemide</td>
<td>Double-blind, parallel group studies exist for acute and maintenance treatment. Found to be as effective as fluoxetine and clomipramine. No dietary requirements.</td>
<td>Not licensed for GAD. Evidence base smaller than for many other antidepressants.</td>
</tr>
</tbody>
</table>
NICE Guidance on GAD from CG 113, January 2011

- For people with GAD and a comorbid depressive or other anxiety disorder: Treat the primary disorder first (that is, the one that is more severe and in which it is more likely that treatment will improve overall functioning)

- For people with GAD who misuse substances
  Be aware that:
  - substance misuse can be a complication of GAD
  - non-harmful substance use should not be a contraindication to the treatment of GAD
  - harmful and dependent substance misuse should be treated first) as this may lead to significant improvement in the symptoms of GAD.

- If a person with GAD chooses drug treatment, offer an SSRI. Consider offering sertraline first because it is the most cost-effective drug, but note that it is currently unlicensed for this indication. Informed consent should be obtained and documented.

- If sertraline is ineffective, offer an alternative SSRI or SNRI, taking into account the following factors:
  - Tendency to produce a withdrawal syndrome (especially with paroxetine and venlafaxine)
  - Side-effect profile and potential for drug interactions
  - The risk of suicide and likely toxicity in overdose (especially with venlafaxine)
  - The person’s prior experience of treatment with individual drugs (particularly adherence, effectiveness, side effects, experience of withdrawal syndrome and the person’s preference)

- If the person cannot tolerate SSRIs or SNRIs, consider offering pregabalin

- Do not offer a benzodiazepine for the treatment of GAD in primary or secondary care except as a short-term measure during crises.

- Do not offer an antipsychotic for the treatment of GAD in primary care

- Before prescribing any medication, discuss the treatment options and concerns the person has about taking medication. Explain fully the reasons for prescribing and provide information on:
  - The likely benefits of different treatments
  - The different propensities of each drug for side effects, withdrawal syndromes and drug interactions
  - The risk of activation with SSRIs and SNRIs, with symptoms such as increased anxiety, agitation and problems sleeping
  - The gradual development, over 1 week or more, of the full anxiolytic effect
  - The importance of taking medication as prescribed and the need to continue drug treatment after remission to avoid relapse
The stepped-care model

A stepped-care model (shown below) is used to organise the provision of services and to help people with GAD, their families, carers and practitioners to choose the most effective interventions. Follow the stepped-care model, offering the least intrusive, most effective intervention first.

<table>
<thead>
<tr>
<th>Focus of the intervention</th>
<th>Nature of the intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STEP 4</strong>: Complex treatment-refractory GAD and very marked functional impairment, such as self-neglect or a high risk of self-harm</td>
<td>Highly specialist treatment, such as complex drug and/or psychological treatment regimens; input from multi-agency teams, crisis services, day hospitals or inpatient care</td>
</tr>
<tr>
<td><strong>STEP 3</strong>: GAD with an inadequate response to step 2 interventions or marked functional impairment</td>
<td>Choice of a high-intensity psychological intervention (CBT/applied relaxation) or a drug treatment</td>
</tr>
<tr>
<td><strong>STEP 2</strong>: Diagnosed GAD that has not improved after education and active monitoring in primary care</td>
<td>Low-intensity psychological interventions: individual non-facilitated self-help*, individual guided self-help and psychoeducational groups</td>
</tr>
<tr>
<td><strong>STEP 1</strong>: All known and suspected presentations of GAD</td>
<td>Identification and assessment; education about GAD and treatment options; active monitoring</td>
</tr>
</tbody>
</table>

* A self-administered intervention intended to treat GAD involving written or electronic self-help materials (usually a book or workbook). It is similar to individual guided self-help but usually with minimal therapist contact, for example an occasional short telephone call of no more than 5 minutes.
Referral to secondary care

Consider referral to step 4 if the person with GAD has severe anxiety with marked functional impairment in conjunction with:

- a risk of self-harm or suicide

or

- significant comorbidity, such as substance misuse, personality disorder or complex physical health problems

or

- self-neglect

or

- an inadequate response to step 3 interventions.

Step 4 Treatments

- Inform people with GAD who have not been offered or have refused the interventions in steps 1–3 about the potential benefits of these interventions, and offer them any they have not tried.

- Consider offering combinations of psychological and drug treatments, combinations of antidepressants or augmentation of antidepressants with other drugs, but exercise caution and be aware that: evidence for the effectiveness of combination treatments is lacking and side effects and interactions are more likely when combining and augmenting antidepressants.

- Combination treatments should be undertaken only by practitioners with expertise in the psychological and drug treatment of complex, treatment-refractory anxiety disorders and after full discussion with the person about the likely advantages and disadvantages of the treatments suggested.
Panic disorder

- Offer an SSRI licensed for panic disorder\(^8\) (currently citalopram, escitalopram, paroxetine or sertraline)

- if a SSRI is unsuitable or if there is no improvement after a 12-week course, venlafaxine XL, imipramine or clomipramine may be considered. Clomipramine and imipramine are unlicensed for this indication, so informed consent should be obtained and documented.

- Benzodiazepines, sedating antihistamines or antipsychotics should not be prescribed

- Three open trials suggest that mirtazapine may be efficacious for the short-term treatment of panic disorder, and a double-blind parallel group study found it to be comparably efficacious to fluoxetine; however, all 4 studies used small samples\(^{17}\).

- Positive open trials and case series of valproate, vigabatrin and levetiracetam have been published, but lack more controlled evidence to substantiate the findings\(^{17}\).

- Review efficacy and side-effects within 2 weeks of starting treatment and again at 4, 6 and 12 weeks. After 12 weeks, review at 8-12 week intervals\(^8\).

- If there is improvement after 12 weeks, continue use for 6 months at optimal dose: then dose can be tapered. When stopping, reduce the dose gradually over an extended period\(^8\).

- Refer to specialist mental health services after failure of 2 interventions.

- Alternatives to drug therapy include psychological treatment (CBT) or self-help (bibliotherapy, support groups, exercise).
Obsessive Compulsive Disorder (OCD)

- First line treatment: SSRIs. Escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline are all licensed for OCD. Onset of effect is commonly delayed for up to 12 weeks.

- Trials of SSRIs in OCD have underscored the importance of using doses in the upper end of the dosing spectrum for this population. NICE advise that if there is an inadequate response to a standard SSRI dose and no significant side-effects at 4-6 weeks, then gradually increase the dose in line with the SPC.

- If effective, continue for at least 12 months to prevent relapse and allow for further improvement.

- Review continued use of the drug with the patient 12 months after remission. Consider:
  - The severity and duration of the initial illness
  - The number of previous episodes
  - The presence of residual symptoms
  - Concurrent psychosocial difficulties

- If continued beyond 12 months after remission, regularly review the need for continued treatment, agree this with the patient and record in the notes.

- Consider clomipramine when:
  - An adequate trial of at least one SSRI was ineffective, or
  - An SSRI was poorly tolerated, or
  - The patient prefers clomipramine, or
  - There has been a previous good response to clomipramine

- For people at significant risk of cardiovascular disease, carry out an ECG and a blood pressure measurement before prescribing clomipramine.

For those at significant risk of suicide, prescribe only small amounts because of its toxicity in overdose.

- If response to standard doses is inadequate and there are no significant side effects, consider a gradual dose increase in line with the SPC.

- Continue treatment for at least 12 months if effective.

- Drugs not generally recommended for OCD (without comorbidity)
  - Tricyclic antidepressants (except clomipramine)
  - Mirtazapine – small evidence base (one successful open label trial only supporting its use)
  - SNRIs – mixed results
  - MAOIs
  - Anxiolytics (except cautiously for short periods during early weeks of SSRI treatment)
- Antipsychotics (as monotherapy)

Other treatments

These are not intended for primary care initiation. Please contact medicines information for further details and to discuss individual cases. Possibilities include

- Antipsychotic augmentation. This is the most promising strategy, with most evidence behind it. Published trials are usually in patients who have not responded to SSRIs. Results are mixed, but there are positive studies of olanzapine, risperidone, quetiapine, aripiprazole and haloperidol. A meta-analysis\textsuperscript{23} concluded that augmentation with atypical antipsychotics could be a helpful strategy for treatment-resistant OCD. Benefits were most evident with risperidone, but evidence was inconclusive for both olanzapine and quetiapine. This was supported by a further meta-analysis\textsuperscript{24}.

- Other strategies, such as increasing the doses above BNF limits and combining clomipramine with an SSRI are areas of recent research, but are potentially hazardous. Please call medicines information with individual cases for consideration.
HYPNOTICS

General Treatment Principles

Prior to prescribing hypnotics, a thorough sleep history should be taken to determine type, length and pattern(s) of sleep. It may be useful to ask the patient to keep a complete sleep diary for two weeks. The causes, where possible, should be determined, and treated, as well as placing emphasis on sleep hygiene.

Possible causes for sleep disturbances include -

- psychiatric disorders e.g. depression, mania, anxiety
- physical problems e.g. thyroid, peptic ulceration, need to urinate, pain
- substance misuse
- drugs e.g. caffeine, illicit drugs, nocturnal anticholinergics, alcohol, nicotine, sympathomimetics, steroids, tranylcypromine.
- external factors e.g. noise, ward environment (ear plugs may be useful)
- excess daytime sleeping or ‘cat naps’.

Sleep Hygiene Measures

- Avoid excessive use of caffeine and alcohol, especially before bedtime. A hot milky drink may help.
- Avoid daytime napping.
- Increase daily exercise, but not in the evening.
- A warm bath can promote sleep.
- Use the bedroom only for sleeping.
- Establish a regular bedtime routine.
- Use anxiety management/relaxation techniques
- Make sure that the bed and bedroom are comfortable and not noisy, hot/cold, humid.
- Aromatherapy

If hypnotics are deemed necessary, the following points must be noted:-

- Use the lowest effective dose (always consider licensed indications, doses and duration of treatment (check most up to date edition of BNF or SPCs)
- They should only be prescribed for short periods of time; preferably one week, up to a maximum of 4 weeks
- Use intermittent dosing (alternate nights or less) if possible
- Avoid abrupt withdrawal if treatment has continued for over 2 weeks
- Avoid in addiction-prone and personality disordered individuals or those with respiratory disease or severe hepatic impairment
• Take care with the elderly, who will be prone to ataxia, confusion and falls. If essential use short-acting agents at reduced doses

• All hypnotics, including the ‘Z-hypnotics’, have the potential for causing tolerance, dependence and withdrawal symptoms. These risks should be outlined to the patient on treatment initiation

• Advise patients of the interaction with alcohol and other sedating drugs.

**Formulary**

<table>
<thead>
<tr>
<th>First Line*</th>
<th>Alternatives</th>
<th>Non-formulary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zopiclone</td>
<td>Temazepam*</td>
<td>Flurazepam</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>Oxazepam</td>
<td>Nitrazepam</td>
</tr>
<tr>
<td></td>
<td>Lormetazepam</td>
<td>Zaleplon</td>
</tr>
<tr>
<td></td>
<td>Loprazolam</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Promethazine**</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chloral Hydrate**</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chlormethiazole</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Melatonin (for CAMHS use only)</td>
<td></td>
</tr>
</tbody>
</table>

* This is a Controlled Drug but exempt from additional controlled drug prescribing requirements.
** denoted “less suitable for prescribing” by BNF
The Z Hypnotics

According to NICE there is a lack of compelling evidence to distinguish between the ‘Z-hypnotics’ -zopiclone, zolpidem and zaleplon, or shorter acting benzodiazepines\(^{25}\).

However, differences between the Z hypnotics do exist, e.g.

- Zolpidem is very quick acting (often within 15 minutes) and may be useful for initiating sleep\(^4\).

- Zopiclone has a slower onset, but longer duration (similar to some benzodiazepines).

- Zopiclone may possibly affect driving performance more than certain benzodiazepines and zaleplon.\(^{25, 26}\).

- Switching between treatments should only take place if adverse effects are experienced e.g. metallic taste from zopiclone.\(^{27}\) Switching hypnotics in the event of non response is not justified\(^{25}\).

- Z-hypnotics, in common with benzodiazepines, have the potential of causing tolerance and dependence.\(^{25, 28, 29}\). However, the dependence potential for zopiclone and zolpidem is probably much lower than with benzodiazepines\(^{15}\).

- Zopiclone and zolpidem are suitable first-line choices for the short term management of insomnia, based on efficacy,\(^30\) cost-effectiveness and usage within Berkshire Healthcare NHS Foundation Trust. Cost implications may vary in primary care and so will prescribing recommendations – GPs should consult with their PCT prescribing advisors for first line treatment choices.
Other Agents

Antihistamines are sedating and are sold as over-the-counter sleeping medications. However, there is limited evidence for their use.

Despite this, antihistamines are commonly used, possibly in an attempt to avoid dependence associated with other hypnotics.

It should be noted that some agents have a long half-life, and also a significantly longer time to onset of action, than newer agents.
Hangover Effects and Half-Lives

Hypnotics with short half-lives are better for patients who have difficulty dropping off to sleep, but tolerance and dependence may develop more quickly\textsuperscript{31}

A very short half-life limits a drug’s duration of action on sleep, and zaleplon and to some extent zolpidem are not particularly effective at maintaining sleep throughout the night\textsuperscript{32}.

Long-acting hypnotics may be useful where frequent or early morning waking is a problem. However hangover effects and loss of coordination are more likely to occur\textsuperscript{33}. This is a particular issue for the elderly, in whom the risks may outweigh the benefits.

The ease of waking and the propensity to daytime carryover (“hangover”) effects are determined by the duration of action – most typically defined by the elimination half-life of the drugs (see table) and the dose taken. Drugs with half-lives of more than 6h tend to leave sufficient residual drug in the brain to cause hangover in the morning\textsuperscript{32}. Whilst the Z-drugs were developed partly to address this, there can still sometimes be some hangover effects with zopiclone.

Individual factors seem important and some people are more susceptible to carry-over than others, probably due to individual differences either in the rate of drug clearance, which can vary by as much as twofold between subjects, or sensitivity to drug actions\textsuperscript{32}.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Hangover</th>
<th>Dependence Potential</th>
<th>Time to Onset (mins)</th>
<th>Adult Half-life (h)</th>
<th>Elderly Half-life (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loprazolam</td>
<td>*</td>
<td>*</td>
<td>?</td>
<td>10</td>
<td>24</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>*</td>
<td>*</td>
<td>?</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td>Temazepam</td>
<td>*</td>
<td>**</td>
<td>30-60</td>
<td>5-11</td>
<td>14+</td>
</tr>
<tr>
<td>Flurazepam</td>
<td>***</td>
<td>**</td>
<td>?</td>
<td>47-95</td>
<td>?</td>
</tr>
<tr>
<td>Nitrazepam</td>
<td>***</td>
<td>*</td>
<td>20-50</td>
<td>18-36</td>
<td>40+</td>
</tr>
<tr>
<td>Chloral Hydrate</td>
<td>*</td>
<td>*</td>
<td>?</td>
<td>7-10</td>
<td></td>
</tr>
<tr>
<td>Chlormethiazole</td>
<td>*</td>
<td>**</td>
<td>?</td>
<td>4-5</td>
<td></td>
</tr>
<tr>
<td>Promethazine</td>
<td>-</td>
<td>-</td>
<td>60-120</td>
<td>10-19</td>
<td>10-19</td>
</tr>
<tr>
<td>Zaleplon</td>
<td>-</td>
<td>-</td>
<td>30</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Zopiclone</td>
<td>*</td>
<td>*</td>
<td>15-30</td>
<td>3.5-6</td>
<td>8</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>-</td>
<td>-</td>
<td>7-27</td>
<td>2 (2-3)</td>
<td>Longer</td>
</tr>
<tr>
<td>Melatonin</td>
<td>-</td>
<td>-</td>
<td>?</td>
<td>3.5-4</td>
<td>3.5-4</td>
</tr>
</tbody>
</table>

*Indicates increased alertness and daytime carryover, **depicts decreased alertness and daytime carryover
Dependency

Benzodiazepine dependence is characterised by a strong need to continue the drug, a tendency to increase the dose, a psychological dependence on the effects of the drug and a characteristic abstinence syndrome.

Long term use and use of higher doses are associated with the risk of abuse, tolerance and dependency, as well as a possible increase in mortality. Tolerance and dependence may develop quicker with short acting benzodiazepines. If tolerance and dependence occur, withdrawal of treatment can be very difficult (additionally, benzodiazepine use may increase the risk of road traffic accidents and hip fractures in the elderly).

Dependence can be minimised by:
- using low doses
- using short courses of treatment (no more than one month)
- using intermittent doses where possible
- avoiding use in dependence-prone individuals/those with a history of drug misuse

Tolerance to the effects of hypnotics can develop within 3 to 14 days of continuous use. However, there is now evidence to suggest that dependence/tolerance is not inevitable, and there are studies supporting this for up to 1 year with zopiclone and zolpidem. Many patients continue happily on the same dose for years in clinical practice, and in a small minority continued use is beneficial.

Longer term use may be justified in the following:
- elderly patients well maintained and symptom free on low, unchanging doses
- chronic physical illness e.g. epilepsy, chronic, severe anxiety or panic disorder
- in those with a history or probability of relapse to substance misuse (including alcohol) when they are benzodiazepine free

Specialist help should be sought if withdrawal is necessary in:
- those with a history/risk of seizures
- elderly or frail individuals
- those with a history of substance misuse
- concomitant severe physical or mental illness
- long term (> 1 year) use and/or high doses (> 30mg per day diazepam or equivalent)
Withdrawal

A withdrawal syndrome may occur within a few hours or up to 3 weeks after stopping treatment (depending on the elimination half life of the benzodiazepine). Symptoms can occur to varying degrees, for varying lengths of time and are characterised as:-

- psychological: restlessness, agitation, panic, tension
- physical: dry mouth, sweating, tremor, headache, sleep disturbance, palpitations, lethargy
- mental: memory and concentration impairment, confusion, depression
- others: hypersensitivity to light and sound, anorexia
- severe and rare: convulsions, psychosis, delusions

Slow discontinuation of the drug reduces the risks of the above symptoms arising and/or reduces their severity.

1. For shorter-acting agents, substitute with an equivalent dose of diazepam (see table below). Diazepam has a long half-life and so the withdrawal symptoms may be less severe. If a large dose of diazepam is needed, divide throughout the day; smaller doses can be taken as a single dose at night.

2. Patients on high doses, or with a history of seizures or psychotic episodes during withdrawal, may be more safely managed as in-patients.

3. Full support from family and friends is essential, with regular review, and agreement of the regimen with the patient.

There is little information on withdrawal of the Z-hypnotics. As their dosage ranges are small, try halving the dose for a week; if successful, give on alternate days for a week then stop. Slower regimes may be necessary if this is poorly tolerated. The flow chart on the next page may be a useful guide.

Equivalent Doses (approximate guide only)

<table>
<thead>
<tr>
<th>Benzodiazepine</th>
<th>Equivalent Dose (range)</th>
<th>Half Life (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazepam</td>
<td>5mg</td>
<td>32 hours (21 – 50)</td>
</tr>
<tr>
<td>Chloridiazepoxide</td>
<td>15mg (10 - 25)</td>
<td>12 hours (6 – 30)</td>
</tr>
<tr>
<td>Loprazolam</td>
<td>0.5-1</td>
<td>10 hours (6-20)</td>
</tr>
<tr>
<td>Lormetazepam</td>
<td>0.5-1</td>
<td>10 hours</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>0.5mg (0.5 - 1)</td>
<td>12 hours (8 – 25)</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>15mg (10 - 40)</td>
<td>8 hours (5 – 15)</td>
</tr>
<tr>
<td>Temazepam</td>
<td>10mg (7.5 - 15)</td>
<td>5 – 11 hours</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>0.5mg (0.25 - 4)</td>
<td>19 – 60 hours</td>
</tr>
<tr>
<td>Nitrazepam</td>
<td>5mg(2.5-20mg)</td>
<td>18-36 (&gt;in elderly)</td>
</tr>
<tr>
<td>Chloral betaine</td>
<td>*</td>
<td>7 – 10 hours</td>
</tr>
<tr>
<td>Chlormethiazole</td>
<td>*</td>
<td>4 – 5 hours</td>
</tr>
<tr>
<td>Zopiclone</td>
<td>?7.5mg</td>
<td>3.5 – 6 hours (&gt;in elderly)</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>?10mg</td>
<td>2 hours (2 – 3)</td>
</tr>
</tbody>
</table>
Benzodiazepine Withdrawal Protocol

On benzodiazepine:-

Use within licence- (less than four weeks)?

- yes
  - Halve the dose for one week then stop.

- no
  - Medium-term use (up to six months) with no symptoms of dependence.

- yes
  - Reduce dose by \( \frac{1}{4} \) - assess after two weeks.

- no
  - Long-term use:

    - Significant withdrawal symptoms:
      - No withdrawal symptoms: reduce in three steps at two-weekly intervals.

    - Convert to equivalent dose of diazepam
      - This should be undertaken in steps

  Withdrawal period up to one year:
  - Reduce fortnightly by 2 - 2.5mg diazepam (depending on initial size of dose)
  - If significant withdrawal symptoms, delay next reduction and reduce size of steps (to 0.5mg if necessary).
  - If patient unwilling/unable to continue, review possible need for other treatments for anxiety/depression. Consider discussion with psychiatrist.

All patients:
Review six weeks after successful completion of detoxification - question treatment need for underlying mental health problem.
## Treatment in Special Patient Populations

<table>
<thead>
<tr>
<th>Condition/ Population</th>
<th>1&lt;sup&gt;st&lt;/sup&gt; Choice</th>
<th>2nd Choice</th>
<th>Avoid</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy</td>
<td>Low dose chlorpromazine Low dose amitriptyline Promethazine</td>
<td>long-acting benzos temazepam buspirone</td>
<td><strong>Avoid</strong> benzodiazepines in 1&lt;sup&gt;st&lt;/sup&gt; &amp; 3&lt;sup&gt;rd&lt;/sup&gt; trimester. Risk of neonatal withdrawal if used close to term V. little data on newer agents. <strong>Contact MI for most up to date information.</strong></td>
<td></td>
</tr>
<tr>
<td>Lactation</td>
<td>Lorazepam zolpidem</td>
<td>short-acting benzos temazepam</td>
<td>long-acting benzos buspirone zaleplon zopiclone</td>
<td>use lowest dose, monitor/observe infant for adverse effects <strong>Contact MI for most up to date information.</strong></td>
</tr>
<tr>
<td>Cardio-vascular Disease</td>
<td>Zopiclone zolpidem benzos (1)</td>
<td>buspirone</td>
<td>chloral (2) beta-blockers (depending on type of CV disease)</td>
<td>(1) Avoid in pulmonary insufficiency (2) contraindicated in severe disease</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>Zopiclone zolpidem benzos</td>
<td>beta-blockers chloral</td>
<td>buspirone (3)</td>
<td>(3) contra -indicated by manufacturers</td>
</tr>
<tr>
<td>Liver Disease</td>
<td>Low dose lorazepam, oxazepam, temazepam</td>
<td>Low dose zopiclone zolpidem</td>
<td>Long acting benzos chloral buspirone (c/i)</td>
<td><strong>AVOID</strong> sedative drugs in severe liver disease (can unmask hepatic encephalopathy and precipitate coma).</td>
</tr>
<tr>
<td>Renal Impairment</td>
<td>Zopiclone lorazepam</td>
<td>Other short acting benzos (4) zolpidem (4)</td>
<td>buspirone (c/i)</td>
<td>(4) dose dependent on CrCl Caution in severe impairment. <strong>Contact MI for most up to date information.</strong></td>
</tr>
<tr>
<td>Old Age</td>
<td>Lorazepam oxazepam zolpidem</td>
<td>Temazepam zopiclone</td>
<td>long-acting benzos e.g. nitrazepam</td>
<td>Use lower doses. NB: half lives can be increased</td>
</tr>
</tbody>
</table>

MI = Medicines Information service at Prospect Park Hospital  
Tel: 0118-960-5075, Monday – Friday 9am – 5pm  
Email: medicines.information@berkshire.nhs.uk
Unlicensed Use of Hypnotics & Anxiolytics

- Long term use i.e. longer than the drug’s licensed duration of treatment, is considered as an unlicensed use.

- Medication for unlicensed indications must be initiated by or on secondary care advice. A record must be made in the patient’s notes and a confirmation letter sent to the GP for continuation of care. This should include the reasons for initiating the unlicensed drug. Patient consent should be obtained where possible.

- The secondary care team should review the medication within eight weeks of treatment. A record must be made in the patient’s notes and a confirmation letter sent to the GP for continuation of care. This should include the reasons for initiating the unlicensed drug.

- **Remember** that the doctor prescribing the benzodiazepine holds responsibility for treatment.

- Problems with symptoms and side effects must be referred back to the consultant.

- Low dose sedating antidepressants, such as amitriptyline, trazodone and mirtazapine have been used to treat insomnia. Use of these agents to treat insomnia alone is **not recommended**, unless the insomnia is a component part of the depressive illness, in which case the dosages would be higher in order to treat the underlying depression.

- Herbal treatments have not been considered in these guidelines.

**NB:** Please note that clonazepam is only licensed for use in epilepsy, therefore the above recommendations apply to its use for other reasons.
References


5. SPCs for the following (www.emc.medicines.org.uk accessed 31/07/11)
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   Cipralex (escitalopram), Lundbeck Ltd, last updated on the eMC: 23/05/2011
   Anafranil (clomipramine), Novartis, last updated on the eMC: 15/12/2010
   Prozac (fluoxetine), Eli Lilly, last updated on the eMC: 14/04/2011
   Faverin (fluvoxamine), Abbott Healthcare, last updated on the eMC: 04/07/2011
   Manerix (moclobemide), Meda Pharmaceuticals, last updated on the eMC: 21/04/2010
   Seroxat (paroxetine), GlaxoSmithKline IK, last updated on the eMC: 06/07/2010
   Lustral (sertraline), Pfizer Ltd, last updated on the eMC: 05/08/2010
   Cymbalta (Duloxetine), Eli Lilly, last updated on the eMC: 11/02/2011
   Efexor XL (venlafaxine), Wyeth, last updated on the eMC: 10/01/2011
   Venlafaxine, Actavis UK Ltd, last updated on the eMC: 03/03/2011


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