Fact Sheet: Benzodiazepines - July 2019
SA Palliative Care Community Pharmacy Update

A joint initiative of South Australian Palliative Care Services

Psychoactive medicines are commonly used throughout the disease journey including the last days of life. This update is the first of three to discuss benzodiazepine and antipsychotic use in palliative care.

Clinical use
Benzodiazepines (BZD) promote the action of gamma-aminobutyric acid (GABA), the major inhibitory neurotransmitter of the nervous system.

- CNS effects include sedation, anxiolysis, amnesia and anti-seizure activity. At higher doses sedative effects increase causing hypnosis and eventually stupor.
- GABA pathways also exist peripherally accounting for hypotension and muscle relaxation.
- BZDs each interact slightly differently with GABA receptors resulting in varied clinical effects (see table). For example, the amnesic effect of midazolam during medical procedures is of benefit whereas this can be deleterious in a patient with delirium.

Regular use of BZDs can cause tolerance, mostly to the sedative effects and less to muscle relaxation.

Long term use of BZDs can cause physical and psychological dependence; discontinuation requires a gradual taper to avoid withdrawal symptoms. Dysphagia at end of life may require conversion to the subcutaneous equivalent.

Selecting the right BZD
Clinical effect, onset and duration of action along with patient factors should be considered when prescribing BZDs.

- Onset of action depends on the drug, formulation and route of administration.
- BZDs are rapidly distributed to the CNS and organs with high blood flow. Following the initial distribution phase some drugs (e.g. clonazepam) are redistributed into tissues including fat and accumulate with repeated dosing. In addition to this a long half-life may mean undesirable effects can take weeks to manifest with an unpredictable dose response.
- Hepatically cleared BZD have the potential for drug-drug interactions through CYP 450 and glucuronidation reactions, and must be used cautiously in hepatic impairment. Oxazepam is preferred in these circumstances.
- Renal impairment may increase the CNS effects of BZDs in part due to a reduction in active metabolite clearance.

BZDs should be used very cautiously in:
- Patients who are at higher risk of falls
- Patients with high-trait anxiety, alcohol misuse and borderline personality disorder are at higher risk of paradoxical arousal and agitation
- Patients who are using opioids as they are at higher risk for sedation and respiratory depression

Useful Resources
1. Therapeutic Reviews: Benzodiazepines AHFS 2014 (339kb pdf)
2. Benzodiazepine pharmacology and CNS mediated effects 2013
3. Benzodiazepine Review JPSM

With thanks to Lauren Cortis for her previous work

<table>
<thead>
<tr>
<th>Benzodiazepine</th>
<th>Approximate equiv doses</th>
<th>Sedation</th>
<th>Anxiolysis</th>
<th>Muscle relaxant</th>
<th>Anti-seizure</th>
<th>Duration of action</th>
<th>Onset of Action</th>
<th>Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonazepam</td>
<td>0.25-0.5mg PO*subcut</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>Long</td>
<td>PO intermediate</td>
<td>CYP 3A4</td>
</tr>
<tr>
<td>Diazepam</td>
<td>5mg PO</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>Long</td>
<td>PO rapid</td>
<td>CYP 2C19 3A4</td>
</tr>
<tr>
<td>Lorazepam#</td>
<td>0.5-1mg PO</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>Intermediate</td>
<td>PO rapid</td>
<td>CYP 3A4, 3A5</td>
</tr>
<tr>
<td>Midazolam</td>
<td>2.5mg subcut 5mg</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>Very Short</td>
<td>Subcut rapid</td>
<td>CYP 3A4, 3A5</td>
</tr>
<tr>
<td></td>
<td>Intrasal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Oxazepam#</td>
<td>30mg PO</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Short</td>
<td>PO rapid</td>
<td>Glucuronidation</td>
</tr>
<tr>
<td>Temazepam</td>
<td>10-20mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Short</td>
<td>PO intermediate</td>
<td>Glucuronidation</td>
</tr>
</tbody>
</table>

*clonazepam drops 0.1mg= 1 drop  * active metabolites  # preferred in hepatic disease

Table 1: Comparison of benzodiazepine drugs

This update is intended to provide practical up to date and factual information relating to pharmacy and medicines management in the setting of Palliative Care and is based on critical review of available evidence. Individual patient circumstances must be considered when applying this information. Please feel free to distribute this update further to interested colleagues.

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