

## Use of Anticonvulsants for Seizures in Palliative Care<sup>17,24</sup>

The most common indication for anticonvulsants in palliative care is for the treatment of seizures associated with brain metastases or primary brain tumours.

These patients may also require dexamethasone to reduce oedema around the tumour. The initial dose is usually in the region of 16mg daily in divided doses, but this is then reduced to the minimum dose possible to maintain control.

The therapeutic effect of dexamethasone may be markedly reduced by concurrent administration of phenytoin. There have also been inconsistent reports of dexamethasone causing plasma phenytoin levels to be either elevated or reduced.

### Choice of agent

<b>Oral therapy</b>	<ul style="list-style-type: none"> <li>• 1<sup>st</sup> line : <b>Sodium valproate</b> (unless hepatic impairment)</li> <li>• Alternative : <b>Phenytoin</b></li> </ul> <p><b>For further alternatives seek advice from neurologists</b></p> <ul style="list-style-type: none"> <li>• Short term use to gain control : <b>Clonazepam/Clobazam</b></li> </ul>
<b>For control of current prolonged fitting</b>	<ul style="list-style-type: none"> <li>• <b>Diazepam rectal</b> – 500mcg/kg (250mcg/kg elderly) repeated in 5-15 minutes if not settled</li> <li>• <b>Lorazepam iv</b> - 4mg slow iv injection</li> <li>• <b>Diazepam iv</b> - 10-20mg slow iv injection</li> <li>• <b>Clonazepam iv</b> – 1mg slow iv injection</li> </ul>
<b>Patient unable to swallow / terminal phase</b>	<p>Depending upon the patient's condition and circumstances</p> <ul style="list-style-type: none"> <li>• <b>Sodium valproate suppositories</b></li> <li>• <b>Clonazepam s/c infusion</b></li> <li>• <b>Midazolam s/c infusion</b></li> <li>• <b>Phenobarbitone s/c infusion</b> – if clonazepam/midazolam is ineffective</li> </ul>

### Summary of main agents

Anticonvulsant	Place in therapy and prescribing information
<b>Sodium valproate</b>	<p>Good first choice as broad spectrum and dose can be titrated reasonable quickly</p> <p><b>Advantages :</b></p> <ul style="list-style-type: none"> <li>❑ Therapeutic drug monitoring is not necessary, although may be useful if toxicity is suspected</li> </ul> <p><b>Disadvantages :</b></p> <ul style="list-style-type: none"> <li>❑ Should not be used in patients with hepatic impairment. Elevation of liver function tests is common, but is normally transient and dose related (but be aware that fatalities have occurred due to hepatic failure)</li> </ul> <p><b>Formulations :</b></p> <ul style="list-style-type: none"> <li>❑ Tablets : crushable 100mg, e/c 200mg, 500mg, chrono 200mg,300mg,500mg</li> <li>❑ Syrup : 200mg/5ml</li> <li>❑ Suppositories : 300mg – “unlicensed”. Use the same dose as orally</li> <li>❑ Intravenous : 400mg by iv injection or infusion</li> </ul> <p><b>Dosing :</b></p> <ul style="list-style-type: none"> <li>❑ Orally : 200mg- 300mg bd then increase dose by 300mg every 3 days to max 2.5g in 24 hrs</li> </ul>

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Anticonvulsant	Place in therapy and prescribing information
<p><i>Phenytoin</i></p>	<p>Often used by the neurosurgeons, probably because it can be administered intravenously.</p> <p><b>Advantages :</b></p> <ul style="list-style-type: none"> <li><input type="checkbox"/> Suitable for use in patients with hepatic impairment, but take care as the drug is metabolised hepatically</li> <li><input type="checkbox"/> Long half life and can therefore be administered as a single daily dose</li> </ul> <p><b>Disadvantages :</b></p> <ul style="list-style-type: none"> <li><input type="checkbox"/> May be poor tolerability in the long term with some patients – ataxia, may have impact on cognitive function and memory</li> <li><input type="checkbox"/> Complex non linear pharmacokinetics. Missed doses, changes in absorption or change in brand can affect plasma levels</li> <li><input type="checkbox"/> Many drug interactions including dexamethasone and other anticonvulsants</li> <li><input type="checkbox"/> Needs therapeutic drug monitoring               <ul style="list-style-type: none"> <li><input type="checkbox"/> Therapeutic Range : 10-20mg/l</li> <li><input type="checkbox"/> Steady state : 7-10 days (but may be up to 5 weeks with higher doses as phenytoin inhibits its own metabolism)</li> </ul> </li> </ul> <p><b>Formulations :</b></p> <ul style="list-style-type: none"> <li><input type="checkbox"/> Capsules : 25mg,50mg,100mg and tablets – prescribe by brand name</li> <li><input type="checkbox"/> Suspension : 30mg/5ml –(100mg capsule is equivalent to 90mg suspension)</li> </ul> <p><b>Dosing :</b></p> <ul style="list-style-type: none"> <li><input type="checkbox"/> Oral : Initially 150-300mg daily and then increase the dose at a minimum interval of 7-10 days with therapeutic drug monitoring. Care as non linear kinetics (small increments in dose may produce large rises in the plasma concentration) As a guide :               <ul style="list-style-type: none"> <li><input type="checkbox"/> Increase by 100mg if steady state level &lt;7mcg/ml</li> <li><input type="checkbox"/> Increase by 50mg if steady state level &gt;7 - &lt;12 mcg/ml</li> <li><input type="checkbox"/> Increase by 30mg if steady state level &gt;12 mcg/ml</li> </ul> </li> </ul>
<p><i>Clonazepam/ Clobazam</i></p>	<p>Both agents can be used orally as an adjunct treatment for short term use to gain control. Choice is prescriber preference but clobazam is thought to be less sedating than clonazepam. Clonazepam only as subcutaneous infusion over 24 hrs in the terminal phase</p> <p><b>Advantages :</b></p> <ul style="list-style-type: none"> <li><input type="checkbox"/> Clonazepam s/c infusion is smaller volume than midazolam and less sedating. Compatible with haloperidol, hyoscine hydrobromide and diamorphine</li> </ul> <p><b>Disadvantages :</b></p> <ul style="list-style-type: none"> <li><input type="checkbox"/> Long term use is limited by tolerance and loss of efficacy without dose titration</li> <li><input type="checkbox"/> Approximately 50% of patients develop drowsiness</li> </ul> <p><b>Formulations :</b></p> <ul style="list-style-type: none"> <li><input type="checkbox"/> Tablets : Clonazepam 500mcg and 2mg (both cross scored), Clobazam 10mg</li> <li><input type="checkbox"/> Injection : Clonazepam 1mg/ml active drug + 1ml water for injection as diluent</li> </ul> <p><b>Dosing Clonazepam:</b></p> <ul style="list-style-type: none"> <li><input type="checkbox"/> Orally : 500mcg - 1mg ON increasing every 3- 5 days up to 2-4mg in 2 divided doses (occasionally higher maintenance dose of 4-8mg may be required)</li> <li><input type="checkbox"/> S/C infusion : 2-4mg (max 8mg) / per 24 hours (<b>unlicensed</b>)</li> <li><input type="checkbox"/> Slow iv injection : 1mg (can also be given as an infusion)</li> </ul> <p><b>Dosing Clobazam :</b></p> <ul style="list-style-type: none"> <li><input type="checkbox"/> Orally : 5-10 mg with a maximum of 30mg daily</li> </ul>

<b>Midazolam</b>	<p>Used as a subcutaneous infusion over 24 hrs in the terminal phase</p> <p><b>Advantages :</b></p> <ul style="list-style-type: none"> <li><input type="checkbox"/> Rapid onset of action</li> <li><input type="checkbox"/> Compatible in a s/c infusion with diamorphine, cyclizine, haloperidol, hyoscine hydrobromide</li> </ul> <p><b>Disadvantages :</b></p> <ul style="list-style-type: none"> <li><input type="checkbox"/> May be limited by the volume in the syringe driver</li> <li><input type="checkbox"/> More sedating than clonazepam (which may be a disadvantage)</li> </ul> <p><b>Formulations :</b></p> <ul style="list-style-type: none"> <li><input type="checkbox"/> Injection 10mg/2ml and 10mg/5ml</li> </ul> <p><b>Dosing :</b> S/C infusion <b>Start low 10 to 20mg/ 24hours &amp; titrate up. Prn dose 5-10mg</b> <b>Maxm dose 60mg/ per 24 hours (unlicensed for route)</b> If not controlling fits use clonazepam or phenobarbitone</p>
<b>Diazepam</b>	<p>Main use is rectally to control recurrent prolonged seizures</p> <p><b>Formulations :</b></p> <ul style="list-style-type: none"> <li><input type="checkbox"/> Injection 10mg/2ml</li> <li><input type="checkbox"/> Rectal tubes 2.5mg, 5mg, 10mg</li> <li><input type="checkbox"/> Orally – tablets 2mg,5mg, 10mg and liquid 2mg/5ml, 5mg/5ml</li> </ul>
<b>Lorazepam</b>	<p>Main indication is the initial treatment of prolonged /repeated seizures</p> <p><b>Formulations :</b></p> <ul style="list-style-type: none"> <li><input type="checkbox"/> Injection 4mg/ml. Best given IV. (can be diluted with a further 1ml of normal saline or water for injection before administration)</li> <li><input type="checkbox"/> Orally - tablets 1mg, 2.5mg,</li> </ul>
<b>Phenobarbitone</b>	<p>Used as a subcutaneous infusion over 24 hrs in the terminal phase if patients are refractory to midazolam/ clonazepam.</p> <p><b>Advantages :</b></p> <ul style="list-style-type: none"> <li><input type="checkbox"/> May be effective when other agents have failed</li> </ul> <p><b>Disadvantages :</b></p> <ul style="list-style-type: none"> <li><input type="checkbox"/> Incompatible with most other drugs in a syringe driver – infuse in separate syringe</li> </ul> <p><b>Formulations :</b></p> <ul style="list-style-type: none"> <li><input type="checkbox"/> Injection 200mg/mL</li> </ul> <p><b>Dosing :</b></p> <ul style="list-style-type: none"> <li><input type="checkbox"/> S/C infusion – 200mg-600mg / per 24 hours <b>(unlicensed)</b></li> <li><input type="checkbox"/> <b>S/C bolus are painful therefore are best avoided.</b> If prn doses are needed give by intramuscular (im) injection 50 to 100mg.</li> </ul>
<b>Other agents</b>	<p>Many other agents are available which may have a role and can be used as adjunct or as monotherapy in difficult to control patients. Seek specialist advice from the Neurology Department</p>
<b>Carbamazepine</b>	<p>Limited by slow dose titration - poorly tolerated on initiation. Risk of blood dyscrasias</p>
<b>Gabapentin</b>	<p>Limited by large doses required</p>
<b>Levetiracetam</b>	<p>Potent agent</p>
<b>Oxcarbazepine</b>	<p>May be suitable for patients who cannot tolerate carbamazepine Therapeutic dosage problem of hyponatraemia</p>
<b>Lamotrigine</b>	<p>Slow dose titration to reduce the risk of rash</p>

## Benzodiazepines – half life

Clobazam	10-50 hrs (mean 20 hrs)
Clonazepam	18-45 hrs (mean 29 hrs)
Diazepam	20-100 hrs (mean 30hrs ) metabolite 30-200 hrs
Lorazepam	8-25 hrs (mean 15 hrs)
Midazolam	2-3 hrs

(Ref Therapeutic Drugs C. Dollery 1999 Churchill Livingstone)