Therapeutic Reviews

Series Co-Editors: Andrew Wilcock, DM, FRCP, and Robert Twycross, DM, FRCP

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Anti-epileptic Drugs *AHFS 28:12*

Paul Howard, BMedSci, MRCP, Robert Twycross, DM, FRCP, John Shuster, MD, Mary Mihalyo, BS, PharmD, RPh, Jan Rémi, MD, and Andrew Wilcock, DM, FRCP
Duchess of Kent House (P.H.), Reading, United Kingdom; Oxford University (R.T.), Oxford, United Kingdom; Vanderbilt University (J.S.), Nashville, Tennessee, USA; Mylan School of Pharmacy (M.M.), Duquesne University, Pittsburgh, Pennsylvania, USA; University of Munich (J.R.), Munich, Germany; and University of Nottingham (A.W.), Nottingham, United Kingdom

Indications: (Licensed indications vary; see individual drug PI for details.) Epilepsy, neuropathic pain, mania, anxiety, sweats and hot flashes, refractory hiccup, terminal agitation, restless legs syndrome, spasticity, pruritus.

Pharmacology

Anti-epileptic drugs are structurally and functionally diverse. The relationship between clinical activity and mode of action is not fully understood. Further, clinically relevant differences exist among anti-epileptics acting in similar ways, and additional actions contribute to the beneficial and/or undesirable effects of some. Choice of drug thus remains partly empirical.[1] Actions of anti-epileptics include:

- membrane stabilization:
  - ▸ sodium channel blockers
- reduced neurotransmitter release:
  - ▸ N/P/Q-type calcium channel blockers (α2δ ligands)
  - ▸ SV2A ligands
- increased GABA-mediated inhibition:
  - ▸ GABAmimetics (Table 1 and Fig. 1).

Membrane stabilizers

Generally, membrane stabilizers reduce excitability by blocking sodium channels. However, those which do so through potassium channel activation are in development (see below).

Sodium channels are present in high densities at sites which initiate action potentials, e.g., sensory nerve endings, and in lower densities along the remainder of the neuron to propagate the action potential. Neuronal damage can lead to the accumulation of sodium channels, e.g., through impaired transport or enhanced production, resulting in neuronal hyperexcitability and foci of ectopic action potential

Address correspondence to: Andrew Wilcock, DM, FRCP, Hayward House Macmillan Specialist Palliative Care Unit, Nottingham University Hospitals NHS Trust, Nottingham NG5 1PB, United Kingdom. E-mail: andrew.wilcock@nottingham.ac.uk

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Table 1
Mechanisms of Action of Anti-epileptics[1–8]

	Membrane Stabilizers		*↓ Neurotransmitter Release*		*GABAmimetics*		*Other Actions*	
	Na^+ Channel Blocker	K^+ Channel Activator	Ca^{2+} Channel Blocker (N, P/Q-type)	↓ Vesicle Release (SV2A)	↑ $GABA_A$ Receptor Activation	Altered GABA Re-uptake and Breakdown	Ca^{2+} Channel Blocker (T-type)	NMDA-Receptor-Channel Blocker
Benzodiazepines					++			
Carbamazepine	++							
Ethosuximide							++	
Felbamate					+			+
Gabapentin		+	++					
Lacosamide	++							
Lamotrigine	++		++					
Levetiracetam				++				
Oxcarbazepine	++	+						
Phenobarbital					++			
Phenytoin, fosphenytoin	++							
Pregabalin			++					
Tiagabine						++[b]		
Topiramate	++				++			
Valproic acid	+[a]					+[a,b]	+[a]	+[a]
Vigabatrin						++[b]		
Zonisamide	++		++				++	

Key: ++ = predominant action, + = putative or non-predominant action.
[a]Although many anti-epileptics have more than one mode of action, valproic acid in particular is thought to have no predominant mode of action, helping to explain its broad spectrum of activity.
[b]Tiagabine and vigabatrin inhibit GABA reuptake and breakdown (via GABA transaminase), respectively. Valproic acid affects both synthesis and re-uptake/breakdown of GABA in selected brain regions.

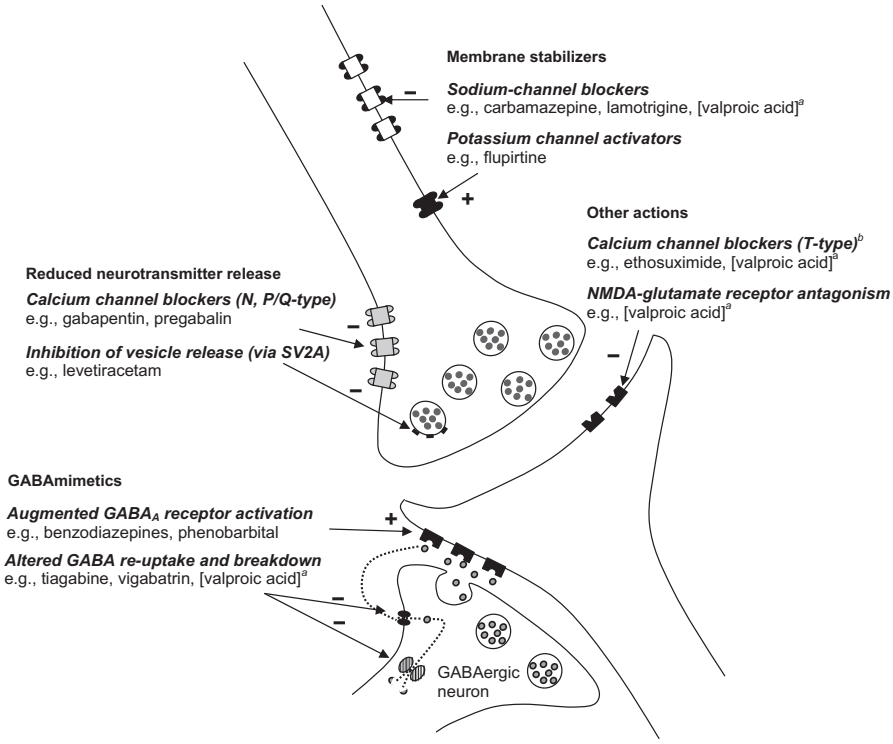

Fig. 1. Mechanisms of action of anti-epileptics and related drugs.[1–7,9] Brackets indicate a contributory, but not predominant, action of the anti-epileptic. [a]Although many anti-epileptics have more than one mode of action, valproic acid in particular is thought to have no single predominant action. [b]T-type calcium channels are responsible for thalamic burst firing (implicated in absence seizures); they are also found in some nociceptors, where they may influence firing thresholds (see text).

generation.[10] In conjunction with other effects of nerve injury, and depending on the site of the damage, this may contribute to the development of neuropathic pain (or seizures).

Several classes of drugs used in neuropathic pain act as sodium channel blockers:

- some anti-epileptics, e.g., carbamazepine, oxcarbazepine[11]
- local anesthetics, e.g., lidocaine[12]
- class 1 anti-arrhythmics, e.g., flecainide.[13]

Important clinical differences exist among these drugs because of the variation in their duration of channel blockade and other effects beyond sodium channels.

Potential future developments in membrane stabilizing drugs for pain management include:

- subtype-selective sodium channel blockers, e.g., $Na_v1.7$ (see Pharmacogenetics and pharmacokinetics)
- drugs with reduced CNS penetration and thus fewer central undesirable effects
- potassium channel activators which stabilize the membrane by hyperpolarization; this is the probable analgesic mechanism of flupirtine (not U.S. or U.K.).[9]

Neurotransmitter release inhibitors: α2δ and SV2A ligands

Gabapentin and pregabalin bind to the α2δ type 1 and 2 regulatory subunits of pre-synaptic (N, P/Q-type) voltage-gated calcium channels, reducing the calcium influx responsible for triggering neurotransmitter release.[14,15] Calcium channel α2δ subunits in the forebrain/brainstem play a role in pain processing and descending pain inhibitory pathways[16,17] and are upregulated in the spinal dorsal horn by inflammation and neuropathic pain.[18,19]

Gabapentin and pregabalin primarily cause the redistribution of calcium channels away from the cell surface, rather than blocking them directly. Effects on sodium and potassium channels also have been shown.[7,20] Despite being GABA analogues, neither gabapentin nor pregabalin is GABAmimetic.[14] They are unrelated to the L-type calcium channel blockers, nifedipine, diltiazem and verapamil.

Levetiracetam binds to synaptic vesicle protein SV2A, and is presumed to interfere with the release of the neurotransmitter stored within the vesicle.[2,21]

GABAmimetics

GABAmimetic anti-epileptics either affect GABA metabolism (synthesis, re-uptake, or breakdown, e.g., vigabatrin, tiagabine, valproate) or act directly on $GABA_A$ receptors (e.g., benzodiazepines and barbiturates). In contrast to other GABAmimetics, valproic acid's GABAmimetic effect is selective (particularly for the midbrain) and involves several mechanisms (altered synthesis, release, re-uptake, and degradation).[6]

Other actions

Some anti-epileptics have additional effects. For example, valproic acid, in addition to being a membrane stabilizer (sodium channel blocker) and a GABAmimetic, also blocks NMDA receptor-channels and T-type calcium channels, and impacts on dopamine and serotonin transmission.[6] The NMDA receptor-channel is an established analgesic target.[22] T-type calcium channels may have a role in neuropathic pain,[23] the burst firing responsible for absence seizures[1] and in regulating pain excitation thresholds in a "T-rich" subset of peripheral nociceptors.[3]

Pharmacogenetics and pharmacokinetics

Genetic variations in anti-epileptic targets have been identified (e.g., sodium and potassium channels, the $GABA_A$ receptor complex). Some cause inherited epilepsy, but there is no straightforward link between the affected channel/receptor and either the epilepsy type or optimal choice of anti-epileptic.[24,25] A polymorphism in the gene (SCN1A) encoding the sodium channel α-subunit has been linked to carbamazepine-resistant epilepsy.[26] In relation to pain, inherited abnormalities of the $Na_v1.7$ subtype sodium channel have resulted in a reduced function (e.g., congenital insensitivity to pain)[27] or an enhanced function (e.g., primary erythromelalgia).[28]

The pharmacokinetics of anti-epileptics are summarized in Table 2. Although absorption is generally unaffected by increasing age, the volume of distribution may change (reduced albumin, total body water and lean:fat mass ratio) and elimination rates slow (altered metabolism, renal function and volume of distribution).[29]

A number of anti-epileptic drugs exhibit significant pharmacokinetic drug interactions through hepatic enzyme induction or inhibition (see below).

Genetic factors affect both pharmacokinetics and the risk of undesirable effects. Two poor metabolizer CYP2C9 alleles (which occur in 10–20% of Caucasians, 10% of Japanese, and 1–5% of Asians and Africans) reduce the mean effective daily phenytoin dose by 20–40%.[25] Human leukocyte antigen (HLA) genes are associated with the risk of Stevens-Johnson syndrome in patients taking carbamazepine or phenytoin.[38,39] The FDA recommends testing HLA B*1502 status before carbamazepine or phenytoin is started in people of Chinese, Malaysian, Indonesian, Filipino, Taiwanese, or Thai origin.[40,41]

Cautions

Safety concerns with vigabatrin (visual field deficits) and felbamate (aplastic anemia and hepatic failure) limit their use to refractory epilepsy under specialist supervision when all other measures have failed.

Driving

Legislation varies between countries; both the underlying condition (e.g., seizures) and effects of the medication (e.g., drowsiness) require consideration.[22,42]

Skin rashes and cross-reactive hypersensitivity

In relation to skin rashes, cross-reactive hypersensitivity may occur with various anti-epileptics:[43]

- carbamazepine: increased risk of skin rash if rash has occurred with a previous anti-epileptic (particularly phenytoin, phenobarbital, or oxcarbazepine) or TCA; use alternative if possible

Table 2
Pharmacokinetic Details of Selected Anti-epileptics[29–37]

Drug	*Bioavailability PO (%)*	*T_{max} (h)*	*Plasma Binding (%)*	*Plasma Half-life (h)*	*Fate*
Carbamazepine	80	4–8	75	8–24	CYP3A4, CYP2C8[a]
Clonazepam	≥80	1–4	80–90	30–40	CYP3A
Diazepam	≥80	1–3	95–98	24–48 48–120[b]	CYP2C19, CYP3A4[a]
Gabapentin	60[c]	1–4	0	6	Excreted unchanged
Lacosamide	≥95	0.5–4	<15	13	Multiple pathways[a] (40% excreted unchanged)
Lamotrigine	98	1–4	55	15–30 8–20[a] 30–90[e]	Glucuronidation
Levetiracetam	≥95	1–2	<10	6–8	Non-hepatic hydrolysis (70% excreted unchanged)
Oxcarbazepine[f]	≥95	1–3 3–8[f]	65 40[f]	1–5 7–20[f]	Cytosolic keto-reduction to MHD,[f] which then undergoes glucuronidation[a]
Phenobarbital	≥90	2–12	50	72–144	CYP2C9 (25% excreted unchanged)
Phenytoin	90–95	4–8	90	10–70[c]	CYP2C9
Pregabalin	>90	1	0	5–9[g]	Excreted unchanged
Tiagabine	≥90	1–2	96	4–13 2–5[d]	CYP3A4
Topiramate	≥80	1–4	13	20–30 8–15[d]	Multiple pathways (>60% excreted unchanged)
Valproic acid	95	1–2[h]	90	9–18 5–12[d]	Multiple pathways[a]
Vigabatrin	80–90	1–2	0	6	Excreted unchanged
Zonisamide	≥50	1–4	50	50–70 25–35[d]	CYP3A4 (15–30% excreted unchanged)

[a]Metabolites biologically active.
[b]Nordiazepam, active metabolite.
[c]Dose or plasma concentration dependent.
[d]With concurrent enzyme-inducers.
[e]With concurrent valproic acid.
[f]Monohydroxycarbazepine, active metabolite of oxcarbazepine (a pro-drug).
[g]>2 days in severe renal impairment and hemodialysis patients.
[h]3–5h for e/c tablets, 5–10 h for m/r tablets.

- phenytoin: increased risk of skin rash if rash has occurred with a previous anti-epileptic (particularly carbamazepine or phenobarbital); use alternative if possible
- oxcarbazepine: 25–30% risk of cross-reactivity if previous reaction to carbamazepine
- zonisamide: avoid if hypersensitive to sulphonamides
- lamotrigine: increased risk in children, if rash has occurred with a previous anti-epileptic, rapidly titrated and/or receiving concurrent valproic acid.

Hepatic impairment

With the exception of gabapentin, pregabalin, and vigabatrin, the manufacturers advise caution with all the anti-epileptics listed in Table 2 (i.e., lower initial doses, slower titration, and careful monitoring). Specific advice is given for levetiracetam (halve the dose in severe hepatic impairment because of probable concurrent renal impairment), lacosamide (usual dose with mild–moderate impairment, no data with severe impairment), lamotrigine (see PI), oxcarbazepine (usual dose with mild–moderate impairment, no data with severe impairment), phenytoin (monitor plasma concentration), tiagabine (reduce dose if mild, avoid if severe), and zonisamide (avoid if possible).

Although previous or concurrent hepatic disease increases the risk of valproic acid and carbamazepine-related hepatic failure (see below), there is no specific information available about the risks with hepatic metastases. However, these do not generally affect the hepatic metabolism of drugs unless there is concurrent cirrhosis.[44,45] When used in this situation, careful monitoring is required.

Renal impairment

With the exception of phenytoin and tiagabine, the manufacturers advise caution with all the anti-epileptics listed in Table 2 (i.e., lower initial doses, slower titration and careful monitoring). Specific advice on dose adjustment is available for gabapentin (see PI), lacosamide (maximum dose 250 mg/day if creatinine clearance <30 ml/min; dose unchanged if >30 ml/min), levetiracetam (see PI), and pregabalin (see PI). There have been occasional reports of renal failure with pregabalin, which improved when it was stopped.

Females of child-bearing age

Enquire about oral contraceptives if using an enzyme-inducing anti-epileptic and counsel accordingly. Specialist advice should be sought, e.g., before trying to conceive because of the risk of teratogenicity and, when pregnant, in order to avoid the use of benzodiazepines or phenobarbital around the time of delivery because of the risk of floppy infant syndrome.

Suicide

Anti-epileptic drugs are associated with suicidal thoughts or behavior in 1/500 patients from the start of treatment onwards. Based on current evidence, it appears to be a class effect, independent of the indication for use.[46] Thus, look for underlying psychiatric comorbidities, assess suicidal risk, and advise patients to report any mood disturbance or suicidal thoughts.[47,48]

Additional cautions with specific anti-epileptics

- atrioventricular block (carbamazepine, lacosamide and oxcarbazepine may cause complete block)
- previous bone marrow suppression (carbamazepine, possible increased risk of bone marrow toxicity)
- heart failure (oxcarbazepine and pregabalin, reported to cause fluid retention; monitor weight and plasma sodium)

Drug Interactions

Phenobarbital, carbamazepine and phenytoin cause numerous interactions through hepatic enzyme induction, see individual PI for details. Conversely, gabapentin, levetiracetam, and pregabalin have few clinically significant pharmacokinetic interactions.

Undesirable Effects

Despite their diverse actions and structures, anti-epileptics share many undesirable effects.[49,50]

All anti-epileptics cause psychotropic and CNS depressant effects including drowsiness, ataxia, cognitive impairment, agitation, diplopia, and dizziness. Cognitive impairment is worst with phenobarbital and

least with newer anti-epileptics and valproic acid.[33,51] Anti-epileptics cause suicidal ideation in 1/500 patients (see Cautions).

All anti-epileptics can cause personality change, behavioral disturbance, and aggression. Levetiracetam is most commonly implicated (≤15% in some RCTs).[52,53] The risk can be minimized by screening for a past history of aggression and using a cautious rate of dose titration.[54] Switching to an alternative anti-epileptic may be required. Pyridoxine supplementation has improved behavioral disturbance in children taking levetiracetam.[55,56]

Most cause hematological derangements. These are often asymptomatic and may not require discontinuation of the drug (see PIs for specific advice). Severe derangement (e.g., aplastic anemia and agranulocytosis) also is reported particularly with felbamate (limiting its use) and carbamazepine (where symptoms of bone marrow suppression and blood counts should be monitored), but also with many newer anti-epileptics. Folate deficiency occurs with enzyme-inducers (e.g., phenytoin).

Biochemical derangements (particularly of LFTs) are also common but are generally asymptomatic. Rarely, hepatic failure is seen with many anti-epileptics, particularly felbamate (also limiting its use) and carbamazepine (where symptoms of hepatic disease and LFTs should be monitored). The incidence compared with newer anti-epileptics is unknown. Pancreatitis affects 1:3,000 users of valproic acid.[57] It also occurs with many newer anti-epileptics but the incidence compared with valproic acid is unknown. Valproic acid also causes hyperammonenia (LFTs can be normal); discontinuation is not required unless symptomatic, e.g., vomiting, ataxia, drowsiness.

Transient rashes are particularly associated with lamotrigine, carbamazepine and oxcarbazepine. Risk factors include rashes with previous anti-epileptics, higher starting doses and rapid titration (and, with lamotrigine, childhood and concurrent valproic acid). Severe rashes such as Stevens-Johnson syndrome are reported with all anti-epileptics, but most commonly with lamotrigine (affecting 1:1,000 adults). An HLA type is known to predispose specific groups to carbamazepine- and phenytoin-related Stevens-Johnson syndrome (see above).

Undesirable effects seen with particular anti-epileptics include: urolithiasis (topiramate and zonisamide); and coarse facies, acne, hirsutism, and gingival hypertrophy (phenytoin).

Use of Anti-epileptics in Palliative Care

Particularly when prescribing more than one anti-epileptic, it is important to consider:
- pharmacokinetic drug−drug interactions (see below)
- seizure type (generalized seizures may be precipitated by carbamazepine, oxcarbazepine, gabapentin, tiagabine and vigabatrin)[58]
- additive cognitive impairment.

Neuropathic pain

Gabapentin, pregabalin, carbamazepine, and valproic acid are used for central and peripheral neuropathic pain. Their efficacy and tolerability appear comparable to each other and to alternatives (e.g., antidepressants), as judged by NNT and NNH,[59−61] although there have been few direct comparisons.

Gabapentin and pregabalin are first-line options. Both are beneficial in various non-cancer neuropathic pains.[61,62] Pregabalin's twice daily administration is a possible advantage, although it is more expensive and is no more effective than gabapentin. Gabapentin is also effective for cancer-related neuropathic pain, although the benefit in an RCT was small.[63,64] Gabapentin appeared to act more quickly and with less sedation than carbamazepine in relation to neuropathic pain in Guillain-Barre syndrome, but neither was used optimally (dose regimens were fixed).[65]

Valproic acid is used in some centers as an alternative first choice when a smaller tablet load or once daily regimen is required, particularly if a TCA cannot be used. Benefit is reported for cancer-related neuropathic pain,[66,67] but the results of RCTs in non-cancer pain are conflicting;[68−71] thus EFNS and IASP guidelines do not recommend its use first line.[61,62] It appears to be well tolerated in both cancer series and RCTs; rates of discontinuation because of adverse events are low (3−5%)[68−71] compared with trials of gabapentin (8−19%)[57,60] and pregabalin (8−32%)[72−78] in similar populations.

Carbamazepine is a first-line treatment for trigeminal neuralgia. It has been used off-label for other neuropathic pains despite few supporting RCTs.[79] Phenytoin is also effective, at least in the short term.[80] However, both require slow titration and particular care with regard to drug interactions. Other membrane stabilizers, particularly lacosamide, lamotrigine, oxcarbazepine and topiramate also have been used, but benefit has been inconsistent or of uncertain clinical relevance. Nonetheless, they are sometimes used for patients failing to respond to more usual approaches, e.g., gabapentin or pregabalin in combination with an antidepressant and an opioid.[61]

Clonazepam is reported to improve both cancer-related and non-cancer neuropathic pain.[81–84] Its concurrent anxiolytic and muscle-relaxant properties have led to its use for selected palliative care patients despite the absence of supporting RCTs.

Alternatives to anti-epileptics include antidepressants and opioids, which are also often used in combination. The efficacy of gabapentin was similar to TCAs in two RCTs although, in one, TCAs caused more dry mouth, constipation and postural hypotension.[85,86] Combined use was superior to either treatment alone.[87] Morphine was as effective as TCAs,[88] whereas the combination of morphine and gabapentin was superior to either treatment alone.[89] An open-label trial in cancer pain with a neuropathic component also found this combination to be superior to morphine alone.[90]

Combinations of ≥2 anti-epileptics are used less commonly. Undesirable effects may be increased and alternative options (e.g., antidepressants, opioids, ketamine, and nerve blocks) are often more appropriate. Where a second anti-epileptic drug is added, the first is generally withdrawn, although examples of combined use are reported. Improvements in efficacy and tolerability have been described in 11 patients with multiple sclerosis whose trigeminal neuralgia had been unsatisfactorily controlled by carbamazepine ± lamotrigine. The addition of gabapentin brought relief in 10 patients. The former were reduced to the minimal effective dose, with improved overall tolerability, but could not be withdrawn completely in any patient, suggesting that both anti-epileptics were contributing to overall relief.[91]

Epilepsy

Overtreatment with anti-epileptic drugs is common. Seek specialist advice where the diagnosis of seizures or the dose or choice of anti-epileptic drug is in doubt.

Initiating Treatment

In palliative care, an anti-epileptic is generally commenced after a first seizure because the persisting underlying cause (e.g., cerebral tumor, multiple sclerosis) makes further seizures probable. In other settings, this risk is lower and an anti-epileptic is often withheld unless a second seizure occurs.[92] Focal lesions cause seizures of partial onset ± secondary generalization. Because the partial onset is not always evident, this can lead to them being incorrectly diagnosed as generalized seizures. However, true generalized convulsive seizures are generally evident within the first two decades of life.

Choice of anti-epileptic is guided by seizure type, potential for drug interactions, co-morbidities, and the simplicity of the regimen (Box A). Because of the risk of teratogenicity with some anti-epileptics, obtain specialist advice when treating women of childbearing age. Enzyme-inducing anti-epileptics can interfere with chemotherapy, although the clinical relevance is unknown.[93] Valproic acid, levetiracetam, gabapentin, carbamazepine and phenytoin are among the anti-epileptics examined in trials and case series for seizures secondary to cerebral tumors.[94–97]

Anti-epileptics are better tolerated if commenced at lower than recommended doses.[98] Doses can be increased if seizures persist. However, the likelihood of additional benefit from a dose increment generally diminishes once higher doses are reached. In one observational study, 90% of those responding to a first-line anti-epileptic required:

- valproic acid ≤1,500 mg/24 h
- lamotrigine ≤300 mg/24 h
- carbamazepine ≤800 mg/24 h.[99]

Few patients responded to increases above these doses.[99] In non-responders, a change of anti-epileptic is indicated.

Box A. Anti-epileptics for seizures in palliative care[95,96,100]

First-line alternatives

Oxcarbazepine

Fewer drug interactions than phenytoin and carbamazepine; effective doses achieved more quickly than with lamotrigine and carbamazepine.

Valproic acid[a]

Can be titrated rapidly, IV if necessary.

Second-line

Switch to another first-line choice, or prescribe

Levetiracetam

[a]Despite abnormal in vitro hemostasis, valproic acid has not been shown to increase neurosurgical bleeding complications,[101,102] but some surgeons advise caution; discuss with surgeons before starting if neurosurgery is planned.

Switching vs. Combining Anti-epileptics for Epilepsy

If the first choice treatment fails, add a second anti-epileptic (Box A). When the second one is at an adequate or maximally tolerated dose, the first one is slowly withdrawn (see below).[103] Long-term combination therapy is generally avoided unless two trials of monotherapy have proved ineffective because:

- there is an increased likelihood of drug interactions
- toxicity may be enhanced
- evidence of benefit compared with monotherapy is limited.[98,104]

Combinations are guided by the same considerations as those for choosing first- and second-line anti-epileptics. Many successful combinations have been reported,[104,105] but the relative benefits of such combinations have not been established. Studies of older anti-epileptics indicate probable benefit in combining GABAmimetics with sodium channel blockers or possibly with other GABAmimetics, but not in using two sodium channel blockers together.[106] Despite this, combinations of sodium channel blockers are among those used by epileptologists.[104] Combining valproic acid and lamotrigine increases the risk of skin reactions.

Do not combine three or more anti-epileptics except on specialist advice; additional benefit is rare.[98]

Prophylaxis in Patients With Cerebral Tumors

Although about 20% of patients diagnosed with cerebral tumors will experience seizures, the risk is not reduced by prophylactic anti-epileptics. Subtherapeutic levels, a potential explanation in some trials, does not adequately account for this lack of effect. Thus, anti-epileptics should not generally be commenced in the absence of a history of seizures.[92,107] Peri-neurosurgical use is an exception, but anti-epileptics should generally be slowly tapered after one week.[107]

Convulsive Status Epilepticus

Fig. 2 is modified from NICE guidance in the U.K.[108] Hypoglycemia should be excluded in all patients. If alcoholism or severely impaired nutrition is suspected, give thiamine 250 mg IV. Phenobarbital has been given preference over phenytoin because it is more likely to be immediately available in many palliative care units.

Lorazepam is the benzodiazepine of choice in the control of status epilepticus[109] but, if unavailable, midazolam 10 mg is an alternative. If venous access cannot be obtained, give midazolam 10 mg buccally or SC (off-label routes of administration), or diazepam 10–20 mg PR.[110]

Fosphenytoin is a pro-drug of phenytoin (1.5 mg of the former is equivalent to 1 mg of the latter). The dose is expressed as phenytoin sodium equivalent (PE). It can be given more rapidly than phenytoin. Ideally, heart rate, blood pressure, and respiratory function should be monitored during and for

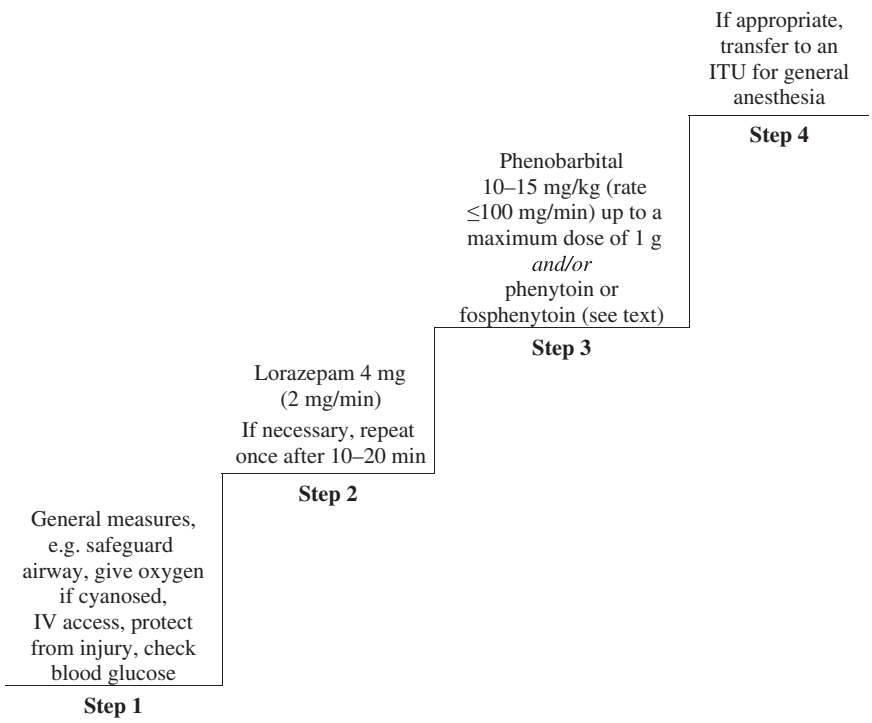

Fig. 2. Management and IV drug treatment of status epilepticus in adults. See text for more detail.

30 min after the administration of fosphenytoin 15−20 mg(PE)/kg (50−100 mg(PE)/min). IV phenytoin sodium 15 mg/kg up to a maximum total dose of 1 g (≤50 mg/min; dilute 500 mg with 50 mL 0.9% saline) can be used instead, preferably with ECG monitoring.

IV valproic acid is an alternative second-line treatment which carries a lower risk of cardiorespiratory depression.[111]

Non-convulsive Status Epilepticus (NCSE)

NCSE is characterised by seizure activity on an EEG but without associated tonic-clonic activity. Presentations include delirium or coma.[112] In one report, NCSE was diagnosed in 5% of patients admitted to a palliative care unit; of these, half responded to treatment with anti-epileptics.[113] Treatment is less urgent than for convulsive status epilepticus (Box A).

Terminal agitation

Phenobarbital is sometimes used in the management of intractable agitation in patients who are imminently dying.[114]

Mania

Valproic acid is generally added only when the response to an antipsychotic and a benzodiazepine is inadequate, but is an alternative first-line therapy particularly when previously effective. Carbamazepine and lamotrigine are second-line options.[115,116]

Anxiety

Benefit is reported in various anxiety disorders,[117] but the best supporting evidence exists for pregabalin in generalized anxiety disorder. Efficacy is similar to lorazepam, alprazolam, and venlafaxine. Pregabalin has a faster rate of onset than venlafaxine, and causes less nausea. It has a similar rate of onset to lorazapam and alprazolam, and causes less drowsiness but more dizziness.[118] It is also effective for social phobia.[119] RCTs also show some benefit with gabapentin,[120,121] tiagabine,[122] and lamotrigine.[123]

However, anti-epileptics are not commonly used in these settings and indirect comparison suggests that they are less effective than SSRIs.[124]

Sweats and hot flashes

Gabapentin is effective for hot flashes resulting from menopause or the treatment of breast cancer.[125,126] Although efficacy was comparable with venlafaxine in an open-label cross-over study, twice as many patients preferred the latter.[127] Benefit is also reported in idiopathic sweating in cancer.[128]

Refractory hiccup

Gabapentin is reported to be effective for hiccup.[129–131]

Restless legs syndrome

Anti-epileptic drugs, along with dopaminergics (D_2 agonists or L-dopa) and some opioids are effective for restless legs syndrome.[132] Benefit is reported with pregabalin, gabapentin enacarbil and gabapentin, with the latter as effective as ropinirole (a D_2 agonist).[133–136] Valproic acid and carbamazepine are possible alternatives.[137]

Spasticity

Although they have not been directly compared, gabapentin has been used as an alternative to baclofen.[138]

Pruritus

The use of gabapentin for neuropathic itch is an extrapolation from its use in neuropathic pain.[139] There are reports of benefit in uremic itch[140] and intractable idiopathic itch.[141,142]

Stopping Anti-epileptics

Withdrawal of treatment for epilepsy is a specialist area of practice best supervised by a neurologist.

Recommendations vary regarding the rate at which it is safe to withdraw a particular anti-epileptic. For example, abrupt cessation of long-term GABAmimetics (e.g., benzodiazepines or barbiturates) should be avoided because rebound seizures may be precipitated, *even when used for indications other than epilepsy.* On the other hand, both gabapentin and pregabalin can be stopped progressively over one to two weeks.

Traditionally, a gradual tapering of the dose over a period of months has been recommended (Table 3). However, few RCTs have compared gradual versus abrupt cessation[143] and some centers successfully withdraw anti-epileptics over shorter periods, e.g., GABAmimetics over four weeks and other anti-epileptics over ≤1 week.

In adults, the risk of relapse of pre-existing epilepsy on stopping treatment is 40–50%.[145] Caution also should be exercised when switching to an alternative anti-epileptic drug. The first drug should *not* be withdrawn until the new drug has been titrated up to an anticipated effective dose.

For patients who are imminently dying (i.e., death expected within a few days) and who can no longer swallow medication, consider substituting SC midazolam or SC phenobarbital. However, some anti-

Table 3
Recommended Monthly Reductions of Selected Anti-epileptics[144]

Drug[a]	*Reduction*
Carbamazepine	100 mg
Clobazam (not U.S.)	10 mg
Clonazepam	0.5 mg
Ethosuximide	250 mg
Lamotrigine	25 mg
Levetiracetam	1,000 mg[b]
Phenobarbital	15 mg
Phenytoin	50 mg
Topiramate	25 mg
Valproic acid	250 mg
Vigabatrin	500 mg

[a]Gabapentin and pregabalin can be stopped progressively over 1–2 weeks.
[b]Data from PI.

epileptics have a long half-life (Table 2) and, in a moribund patient, might continue to be effective for 2–3 days after the last PO dose.

Abbreviations/Key

Ca^{2+}	Calcium
CNS	Central nervous system
CYP	Cytochrome P450
D_2	Dopamine-2 receptor
ECG	Electrocardiogram
EEG	Electroencephalogram
EFNS	European Federation of Neurological Societies
GABA	Gamma-amino butyric acid
HLA	Human leukocyte antigen
IASP	International Association for the Study of Pain
IT	Intrathecal
ITU	Intensive therapy unit
IV	Intravenous
K^+	Potassium
LFT	Liver function test
m/r	Modified release
Na^+	Sodium
NCSE	Non-convulsive status epilepticus
NICE	National Institute for Health and Clinical Excellence
NMDA	N-Methyl-D-aspartate receptor
NNH	Number needed to harm
NNT	Number needed to treat
RCT	Randomized controlled trial
SC	Subcutaneous
SSRI	Serotonin specific re-uptake inhibitor
SV2A	Synaptic vesicle protein 2A
TCA	Tricyclic antidepressant

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