Anticonvulsants: an overview of use in old age psychiatry

Anticonvulsants are being widely used in psychogeriatric practice for their non-epileptic proprieties despite limited research specific to older adults. **Drs Murali Krishna** and **Haripriya Kamireddy** review the evidence base for anticonvulsants commonly used in psychiatric disorders, focusing particularly on issues specific to older adults, offering a helpful guide and general overview of available options.

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Historically, agents introduced for the treatment of epilepsy have been widely used by psychiatrists in the management of elderly patients with both functional and organic mental illness. In addition, endocrinologists, neurologists and pain specialists use them to treat conditions like diabetic neuropathy, cluster headaches, migraine, neuropathic pain and chronic pain syndrome. Thus, anticonvulsant drugs are widely used beyond treating epilepsy, so that the name 'antiepileptic drug' (AED) is a misnomer.

The exact pharmacological properties responsible for their non-epileptic action are not certain. Essentially, anticonvulsants act on neurotransmitter pathways and it is possible their psychotherapeutic actions are mediated through stabilising effects on neuronal membranes. Therefore, they are more accurately considered as neuromodulatory drugs. Due to their effect on mood they are also termed as 'thymoleptics'. They can be classified as older or typical (eg, valproate, carbamazepine) and newer or atypical agents (eg, lamotrigine and gabapentin). Names of commonly prescribed anticonvulsant drugs are listed in *Table 1*. The newer ones appear to have relatively simpler pharmacokinetics and limited drug interactions compared to the older agents, which had numerous problems ranging from inconvenient dosing schedules to frequent side effects and common drug interactions.

Table 1. Classification of anticonvulsant drugs

Typical	Atypical
Phenytoin	Lamotrigine
Barbiturates	Gabapentin
Valproate	Topiramate
Carbamazepine	Levetiracetam
Vigabatrin	Oxcarbazepine

Anticonvulsant drugs are gradually gaining ground in psychiatry.

Valproate

Thirty-five years since its introduction into clinical use, valproate has become the 'most frequently prescribed antiepileptic in the world'[1]. This is mainly because of relatively lesser side effects and drug interactions compared with carbamazepine. Sodium valproate is the soluble sodium salt of valproic acid, a poorly soluble branched chain carboxylic acid. Valproate is available in three forms of which Epilim® is prescribed more often merely for the ease of intake, as it can be administered once daily. Valproate semisodium is a mixture of sodium valproate and valproic acid.

Mechanism of action

Despite extensive research, its precise mode of

action has not yet been fully understood. In view of its wide spectrum of activity, it is clear that its pharmacological effects involve a variety of mechanisms[2].

Indications

It is commonly used in the management of bipolar affective disorder, in particular acute mania and mixed episodes. Licensed in the UK as monotherapy for acute mania[2], one study suggested that valproate is superior to placebo in treating acute mania and mixed affective states[3]. Another study showed it to be as effective as lithium in acute mania independently of a prior responsiveness to lithium[4]. In addition, it is recommended as the first-line treatment with lithium in patients with rapid cycling disorder. The drug may also have aprophylactic role in prevention of mania and mixed episodes[5].

Although promising, further data are required before definitive statements can be made about the use of valproate in managing mood symptoms in schizoaffective disorder, but it is increasingly being used for treatment of behavioural and psychological disturbance in dementia. Even though some studies describe favourable effects of valproate in agitation, explosiveness, sexually inappropriate behaviour and impulsivity, a *Cochrane Review* published in 2005 found methodological flaws in the existing studies[6]. It is also used in treatment of neuropathic pain and migraine.

Dosage

The recommended daily dose of valproate is between 500mg to a maximum of 2500mg, with usual maintenance dose of 20–30mg/kg[7]. It is initiated at a lower dose and titrated slowly while monitoring side effects. Valproate semisodium and other valproate preparations do not have same dose equivalence, with higher bioavailability with valproate semisodium. Dosage requirements for patients with affective disorder have not been adequately characterised, but elderly patients may need lower doses than younger ones.

Side effects

In lower doses, valproate is generally well tolerated by the elderly. Nausea, sedation, gastric irritation, diarrhoea, increased appetite, weight gain, tremors, hyperammonaemia and transient hair loss with curly regrowth are some of the side effects. It can rarely lead to pancytopenia, hepatic dysfunction and pancreatitis[7].

Drug interactions

The metabolism of valproate is complex and is mediated via the microsomal cytochrome P450 system and mitochondrial B oxidation. It is considered a relatively safe drug with minimal drug interaction. It is known to interact with aspirin, warfarin, erythromycin, cimetidine, fluoxetine, tricylic antidepressants, lamotrigine and phenobarbitone.

Monitoring

There is little correlation between blood levels and therapeutic monitoring, so routine blood level monitoring is of limited use but may help in cases of poor response or compliance[2]. Serious toxicity is rare and careful supervision initially will guard against major problems (eg, liver toxicity)[8]. Monitoring liver functions and full blood count (FBC) before the therapy and during first six months is recommended.

Carbamazepine

Carbamazepine is a tricyclic compound closely related structurally to imipramine. It was introduced as a highly effective anticonvulsant in 1960 and appears to have a similar profile to valproate. Though it is licensed for the prophylaxis of bipolar illness, it is not used frequently in the elderly due to its numerous side effects and drug interactions.

Mechanism of action

The action of carbamazepine is probably mediated via the adenylate cyclase and phosphoinositol second messenger system[2].

Indications

Despite being widely prescribed for patients with bipolar affective disorder, only a few clinical studies support the use of carbamazepine in the elderly. The efficacy of carbamazepine in patients with acute mania has been supported by five randomised controlled trials (RCTs)[9]. Carbamazepine is more beneficial than lithium in patients with mixed affective state, but less efficacious than lithium in classical bipolar disorder. It is perceived wisdom that it is more effective than lithium in rapid cycling manic depressive illness, even though only some evidence supports this view[10].

Limited evidence suggests that carbamazepine may be effective in treatment resistant mania and can be considered if lithium is ineffective[11]. The

Table 2. Carbamazepine side effects[7]

Nausea and vomiting
Headache
Ataxia
Visual disturbance
Photosensitivity
Erythematous rash (transient)
Leucopenia and other blood dyscrasias
Arthralgia
Hepatic impairment
Cardiac conduction disturbances
Hyponatremia
Oedema.

combination of lithium and carbamazepine may have superior effect as compared with monotherapy with either drug.

The evidence base for the efficacy of carbamazepine in prophylaxis of bipolar disorder is extremely limited. There have been no specific placebo controlled studies of carbamazepine monotherapy in short-term treatment in bipolar depression, but three small RCTs suggest it has a modest antidepressant effect at best. Limited data suggest it is more potent when used in combination with lithium for treatment of acute bipolar depression[12]. The efficacy of antidepressants and other mood stabilisers is augmented by carbamazepine and thus is of benefit as an adjunctive treatment of refractory unipolar depression[10]. Several case reports suggest it can decrease agitation and aggression in schizophrenia[13], but a recent *Cochrane Review* found no significant benefit in schizophrenia. Carbamazepine may be as effective as lithium in maintenance management of schizoaffective disorder.

Similar to valproate, carbamazepine has been used in the management of agitated and aggressive behaviour[14]. Even though the evidence base is rather weak, it tends to favour the use of carbamazepine in elderly patients despite its greater propensity for adverse effects. A pilot randomised trial of carbamazepine for behavioural symptoms in treatment resistant patients with Alzheimer's disease showed modest clinical benefit[15]. It is the most widely studied anticonvulsant for neuropathic pain and three RCTs showed that it has significant response in patients with trigeminal neuralgia[16]. In addition, a crossover study showed that 30 per cent of patients with diabetic neuropathy had significant improvement in pain relief compared to placebo[16].

Dosage

Carbamazepine is usually initiated at a dose less than 200mg/day in the elderly and titrated slowly over one to two weeks. The usual maintenance dose is 400–1600mg/day[10] and the accepted range of serum level is six–10ug/ml. It is rather slowly and erratically absorbed and has a short half-life, further reduced by its autoenzyme inducing effect. Hence sustained release preparations should be preferred for long-term usage. The elimination half-life of carbamazepine increases linearly with age, so a dose reduction is needed in the elderly.

Side effects

Carbamazepine has potentially serious side effects and the tolerance is poor. Published studies report a high drop-out rate. Side effects are more common at the start of therapy and often subside after a few days. Side effects (*Table 2*) are varied and include central nervous system, liver and GIT side effects along with blood dyscrasias. The elderly patients may develop cardiac arrhythmias or confusional states. Unlike valproate, it is not associated with weight gain.

Drug interactions

Carbamazepine is a potent inducer of hepatic cytochrome P450 enzymes and hence lowers the levels of concomitant medication that depend on cytochrome P450 systems like most antidepressants, antipsychotics, benzodiazepines, anticholinesterase inhibitors, methadone, levothyroxine, theophylline, oestrogen and other steroids.

Monitoring

Baseline FBC, liver function and coagulation tests must be determined before commencing therapy. Serum carbamazepine levels must be checked every six months in well stabilised patients[7].

Lamotrigine

Lamotrigine is a new anticonvulsant drug from the phenyltriazine class used in the treatment of resistant partial seizures. It appears to be the most promising of newer anticonvulsants with respect to mood disorders and has attracted special interest. It now occupies an important place in the treatment of major affective disorders, something that is set to increase.

Mechanism of action

The therapeutic effect of lamotrigine may be mediated via blockade of sodium channels and by

inhibiting the release of excitatory amino acids[13] and calcium channels in presynaptic neurons.

Indications

It has been observed to possess moderate efficacy in depression, mixed states and hypomania. It appears to lack antimanic properties and the need for slow titration precludes reliance on its use in acute mania[17].

Two controlled studies have established its mood stabilising properties in bipolar disorder and present evidence suggests it is an effective prophylactic for patients with bipolar I disorder[18]. Yet, even though most of the available studies suggest lamotrigine is effective in rapid cycling bipolar disorder[18], studies are underway to clarify its efficacy. Several case studies and case series support its use as adjunctive therapy in cases of refractory bipolar disorder[19]. It has shown to be an effective and well-tolerated antidepressant in bipolar depression as a monotherapy or as adjunctive[19], but unlike other antidepressants, lamotrigine does not induce mania or hypomania[20]. In refractory unipolar depression, its efficacy is reasonably well researched and it is considered as a second-line of treatment[21].

Recent studies have shown that lamotrigine is beneficial in the management of behavioural symptoms like aggression and impulsivity, even in the absence of diagnosable mood disorders[17]. There is some evidence to suggest it is an effective adjunctive with clozapine in treatment resistant schizophrenia[17] and a potentially effective treatment in schizoaffective disorder[22].

In the treatment of anxiety disorders, it was found to be better than placebo on measures of intrusive thoughts, avoidance or numbing symptoms. Significant evidence suggests lamotrigine is effective in alleviating neuropathic pain and the extent of analgesia produced is similar to gabapentin[23]. Though older people seem to handle lamotrigine similarly to younger ones, there is little experience of using it for the treatment of psychiatric disorders in the elderly.

Dosage

Lamotrigine should be titrated slowly, starting with a low dose of 25mg/day to a maximum of 300–400mg/day in divided doses. Its metabolism is inhibited by valproate so even slower titration and lower final doses are required in patients already on that drug[2]. As carbamazepine induces metabolism of lamotrigine, relatively higher doses may be required.

Side effects

Skin rash is the most concerning adverse effect, which may progress to Stevens Johnson syndrome or very rarely to toxic epidermal necrolysis[19]. Hence, in the absence of a clearly identifiable aetiology for the rash, lamotrigine must be discontinued if the patient develops rash of any kind regardless of the severity. The risk is reduced by slow titration[2]. Other side effects include dizziness, tremor, headache and nausea. Body weight remains relatively stable with long-term use.

Drug interactions

Blood levels of lamotrigine is increased by valproate and decreased by phenytoin, carbamazepine, phenobarbitone, oxcarbazepine, and primidone[10,11]. No specific monitoring is recommended.

Gabapentin

First introduced in 1990, gabapentin is a novel anticonvulsant, as it possesses a wide therapeutic index with a favourable side effect profile and benign drug interactions[2].

Mechanism of action

Though gabapentin is a cyclohexane derivative of GABA, the mechanism of action is still uncertain. Gabapentin is not metabolised, has no known pharmacokinetic interaction with other anticonvulsants and is excreted unchanged in the urine.

Indications

Several open trials suggest the evidence of gabapentin in management of mania. But this finding has not been consistently replicated in RCTs – in two trials gabapentin was not superior to placebo in the treatment of mania[8], but in other open trials, it has been shown to be effective and well tolerated, both as a monotherapy and adjunctive therapy in bipolar depression[18,24]. There is limited evidence for treating rapid cycling disorder with gabapentin and studies are underway to evaluate its prophylactic value in bipolar disorder. A preliminary study by Schaffer and Schaffer has showed positive response to treatment with gabapentin as adjunctive therapy in refractory bipolar disorder[19]. In a randomised double blind controlled study, gabapentin demonstrated a statistically significant reduction in

symptoms of social phobia[20]. It may have anxiolytic properties in more severely ill patients with panic disorder[25]. In addition, gabapentin has been used successfully to reduce aggression and agitation in dementia[13].

In open trials it has been reported to be effective in the management of neuropathic pain in diabetic neuropathy, multiple sclerosis, migraine, post-herpetic neuralgia and reflex sympathetic dystrophy[26].

Dosage

Gabapentin is usually started at 300mg once daily at bedtime and then increased every three to five days as clinically indicated to 600–3600mg/day[7].

Side effects

Side effects of gabapentin include diarrhoea, dry mouth, dyspepsia and increased infections (including urinary and respiratory tract). Depression, hallucinations and psychosis are rare, but Stevens Johnson syndrome is a recognised adverse event[7]. No monitoring is necessary except for pre-treatment renal function test[27].

Topiramate

Topiramate is a sulphamate substituted carbohydrate and licensed for adjunctive treatment of partial seizures.

Mechanism of action

It acts by potentiating GABA inhibition, blocking glutamate at non-NMDA receptors, and blocking of sodium and calcium channels[20].

Indications

Preliminary reports showed encouraging results in acute mania but current evidence suggests there is limited scope for its use[28]. A limited number of open label studies have supported its use in rapid cycling disorder. There is some evidence for mood stabilising properties in some patients with bipolar disorder, including those who are treatment resistant, but there is no clear indication

Key points

- Anticonvulsants are being widely used in psychogeriatric practice for their non-epileptic properties.
- There are no clear guidelines for prescribing and monitoring for anticonvulsants being used for psychiatric reasons.
- The exact pharmacological properties responsible for such benefits are not certain.
- Nonetheless their complex drug interactions and wide range of side effects make it essential to regularly review older adults on anticonvulsants.
- There is limited research on use of anticonvulsants in psychiatry specific to older adults.

for its use in unipolar depression. The evidence of its efficacy in this condition is entirely based on case series and reports[28]. Limited evidence suggests the usefulness of topiramate in post traumatic stress disorder in the treatment of nightmares, flashbacks and intrusions[28]. The evidence supporting the analgesic action in neuropathic pain is mostly anecdotal and an RCT failed to support the use of topiramate for trigeminal neuralgia[28].

Side effects

Side effects of topiramate include appetite suppression, weight loss, paraesthesias, nausea and constipation. Patients must be monitored for signs of visual disturbance[7].

Conclusion

Anticonvulsants are being widely used in psychogeriatic practice for their non-epileptic properties despite limited research specific to older adults. There are no clear guidelines for prescribing and monitoring anticonvulsants when being used for psychiatric reasons, though there are some guidelines by the National Institute for Health and Clinical Excellence (NICE)[29] on their use in bipolar disorder (see article on page 43 for more detail).

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References

1. Perucca E. Pharmacological and therapeutic properties of valproate – a summary after 35 years of clinical experience. *CNS Drugs* 2002; **16**(10): 695–714
2. Anderson I, Reid IC. Mood stabilisers: Lithium and anticonvulsants. Fundamentals of clinical psychopharmacology. Second edition. Taylor and Francis. 87–91
3. Bowden CL. Role of newer medication for bipolar disorder. *Journal of Clinical Psychopharmacology* 1996; **16**: 55
4. Bowden CL, Brugger AM, Swann A, *et al*. Efficacy of divalproex vs lithium and placebo in the treatment of mania. The Depakote Mania Study Group. *Journal of American Medical Association* 1994; **271**(12)
5. Calabrese JR, Markovitz PJ, Kimmet SE, *et al*. Spectrum of efficacy of valproate in 78 rapid cycling bipolar patients. *Journal of Clinical Psychopharmacology* 1992; **12**: 53–56
6. Lonergan ET. Luxenberg. Valproate preparations for agitation in dementia. Cochrane database of systematic reviews 2004. Issue 2
7. Antiepileptics. BNF. sec 4.8 September 2005, 237–48
8. Bazire S. Treatment options epilepsy. Psychotropic drug directory 2005: 76–83
9. Keck PE, McElroy SL. Antiepileptic drugs for bipolar disorder. Are there any clear winners? *Current Psychiatry* 2002; **1**(1)
10. Bipolar Disorder. The Maudsley Prescribing guidelines.8th edition, Taylor and Francis. 107–34
11. Goodwin GM. Evidence-based guidelines for treating bipolar disorder: recommendations from the British Association for Psychopharmacology. *Journal of Psychopharmacology* 2003; **17**(2): 149–73
12. Malhi GS, Mitchell PB, Salim S. Bipolar depression – Management options. *CNS Drugs* 2003; **17**(1): 9–25
13. Alao AO. The Frontiers of mood stabilisers in psychiatry. *Psychiatric Times* 2002; Vol XIX(5)
14. Davidson HE. Pharmacological management of aggression in elderly patients with dementia. *Consult Pharma* 1998; **13**(Suppl A): 17–23
15. Tariot PN. Efficacy and tolerability of carbamazepine for agitation and aggression in dementia. *The American Journal of Psychiatry* 1998; **155**(1): 54–61
16. Bashford GM. The use of anticonvulsants for neuropathic pain. *Australian Prescriber* 1999; **22**: 140–1
17. Ovsiew F. Antiepileptic drugs in psychiatry. *Journal of Neurology Neurosurgery and Psychiatry* 2004; **75**: 1212, 1655–61
18. Bowden CL, Calabrese JR, Sachs G, *et al*. A Placebo-Controlled 18-Month Trial of Lamotrigine and Lithium Maintenance Treatment in Recently Manic or Hypomanic Patients With Bipolar I Disorder. *Arch Gen Psychiatry* 2003; **60**: 392–400
19. Macdonald KJ, Young LT. Newer antiepileptic drugs in bipolar disorder: Rationale for use and role in therapy. *CNS Drug* 2002; **16**(8): 549–62
20. Aston H, Young AH. GABA-ergic drugs: exit stage left, enter stage right: *Journal of Psychopharmacology* 2003; **17**(2): 174–78
21. Bowden C.The efficacy of lamotrigine in rapid cycling and non–rapid cycling patients with bipolar disorder. *Biological Psychiatry*; **45**(8): 953–58
22. Erfuth A, Wladen J, Gruze H. Lamotrigine in the treatment of schizoaffective disorder. *Neuopsychobiology* 1998; **38**: 204–5
23 McCleane G. Pharmacological management of neuropathic pain. *CNS Drugs* 2003; **17**(14): 1031–43
24. Altshiler L, Keck PE, McElroy SL, *et al*. Gabapentin in acute treatment of refractory bipolar disorder. *Bipolar disorder*; **1**: 61–5
25. Pande AC, Pollack MH, Crockatt J, *et al*. Placebo controlled study of gabapentin treatment. *Journal of Clinical Psychopharmacology* 2000; **20**(4); 467–71
26. Clark MR. Pharmacological treatments for chronic non-malignant pain. *International Review of Psychiatry* 2000 (Publisher: Routledge, part of the Taylor & Francis Group); **12**(2): 148–56
27. Schachter S. Medscape. Neurology Treatment Updates, "Critical Issues in the Use of Antiepileptic Drugs" CME March 17, 2000
28. Arnone D. Review of the use of topiramate for treatment of psychiatric disorders. *Annals of General Psychiatry* 2005; **4**: 5
29. NICE clinical guideline.Bipolar Disorder. The management of bipolar disorder in adults, children and adolescents, in primary and secondary care. July 2006. CG038