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Selecting an Antidepressant for Use in a Patient with Epilepsy

Safety Considerations

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Summary

Depression is a common and disabling condition and is especially disabling for patients who also have epilepsy. Antidepressants, particularly the tricyclic antidepressants are well known to be associated with seizure activity, but this is a very neglected area of research. Most of the data on the proconvulsive effects of antidepressants come from either work in animal models or from research into the effects of antidepressants in overdose. Both of these situations may tell us little about the behaviour of antidepressants in patients with epilepsy. The selective serotonin [5-hydroxytryptamine; 5-HT] reuptake inhibitors have a low seizure propensity, are well tolerated in overdose and have a favourable adverse effect profile, making them suitable as first line treatments for depression in patients with epilepsy. Other antidepressants, e.g. trazodone, moclobemide, mirtazepine, are also likely to have minimal proconvulsive effects, but adverse effects, interactions with other drugs, especially anticonvulsants, or the lack of clinical data may make their use less attractive. Although this review has focused on these clinically important issues it is clear that considerably more research needs to be undertaken on the seizure propensity and clinical efficacy of antidepressants in patients with epilepsy.

Epilepsy, the 'tendency to recurrent seizures', has a point prevalence of 0.5%[1] and a lifetime prevalence of 3.5%.[2] It is most frequently idiopathic or familial, but may have a number of other aetiologies. In addition, several types of epileptic seizures have been defined by the International League Against Epilepsy,[3] but this classification does not mention psychiatric criteria. This is surprising, since epilepsy is linked with several psychiatric syndromes, particularly depression, which may be important in determining prognosis and quality of life.[2]

When a depressive disorder occurs in a patient with epilepsy, it should be treated. This review aims to examine which groups of antidepressants are most appropriate in this context.

1. Mechanisms of Seizures

The mechanisms whereby seizures are produced in epilepsy are not entirely clear. Most of the experimental work has concentrated on the effects of excitatory and inhibitory neurotransmitters, together with the role of calcium.[2] The γ-aminobutyric $acid_A$ ($GABA_A$) receptor is thought to be responsible for mediating CNS neuronal inhibition, while the rapid influx of calcium into neurons is one of a number of mechanisms that play an important role in the induction and generalisation of seizures. However, the mechanisms responsible for drug-induced seizures remain to be clarified,[2] and a better understanding may lead to the development of improved anticonvulsants and antidepressant drugs.

2. Prevalence of Depression in Patients with Epilepsy

A significant number of patients with epilepsy also have clinical depression, the prevalence varying from 11 to 22%, depending on diagnostic criteria used.[4,5] This may increase to 32% when anticonvulsants are withdrawn, since these drugs [e.g. valproic acid (sodium valproate), carbamazepine] may be effective in the treatment of, particularly treatment-resistant, mood disorders.[6]

However, the term *depression* covers a variety of different morbid mood states (e.g. single depressive episode, recurrent depressive episode, brief depressive episode, bipolar affective disorder – depressed type) but these subtypes have not been extensively studied in patients with epilepsy. It is also important to distinguish between *symptoms* of depression and depressive *disorder*. Patients may develop symptoms of depression (e.g. following a seizure) but, under these circumstances, pharmacological treatment would not be indicated. For drug treatment to be considered, patients should have depression that meets recognised criteria for a depressive disorder (e.g. those given in the International Classification of Diseases, 10th Edition[7]). In addition, and most importantly, suicide rates may be 5 times higher in patients with epilepsy compared with the general population,[8] while the risk in those with temporal lobe epilepsy may be even higher.[2] It is thus important to treat depression in patients with epilepsy.

Although it is a common clinical observation that patients with well-controlled epilepsy do not appear to have an increased seizure risk when prescribed an antidepressant, no studies have been undertaken to investigate this phenomenon. However, if a seizure does occur shortly after commencing an antidepressant, this would suggest a causal link. Under such circumstances, it would be prudent to stop the antidepressant, then, after a suitable period (5 times the half-life of the antidepressant), to try a different drug. It might also be worthwhile checking serum anticonvulsant concentrations, which can also be affected by antidepressants.

3. Pharmacological Treatment of Depression

The main groups of antidepressant drugs are monocyclic antidepressants, tricyclic antidepressants (TCAs), tetracyclic/heterocyclic antidepressants, monoamine oxidase inhibitors (MAOIs), reversible inhibitors of monoamine oxidase (MAO) type A (RIMAs), selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitors (SSRIs), serotonin and noradrenaline (norepinephrine) reuptake inhibitors (SNRIs) and lithium.

Antidepressants increase the availability of the monoamines noradrenaline and serotonin in the synaptic cleft, which subsequently leads to alteration in receptor densities, including the down-regulation of postsynaptic β-noradrenergic and 5-HT_2 receptors.[9] Antidepressants differ in their selectivity for this process; for example, TCAs tend to increase the availability of noradrenaline and serotonin, whereas the SSRIs increase the availability only of serotonin.

4. Effect of Antidepressants on Seizure Threshold

Antidepressants may exert proconvulsive effects by antagonising the actions of GABA. Compounds that *completely* reverse the effects of GABA include viloxazine, while those that *partially* reverse the effects of GABA include mianserin, doxepin and tranylcypromine. Drugs that *do not* reverse the inhibitory effects of GABA include TCAs (e.g. amitriptyline, clomipramine, desipramine and imipramine), SSRIs (e.g. fluoxetine and fluvoxamine), MAOIs (e.g. phenelzine) and trazodone.[10]

At therapeutic dosages, seizures are a rare, but serious, complication of antidepressant therapy.[11] This may result from a direct neurotoxic effect of the drug or its metabolite(s) or from interactions with other drugs. However, it is difficult to compare the rate of seizure activity induced by different antidepressants, since studies vary enormously with regard to methodology and study design, the number of patients included, dosage of medication, plasma drug concentrations, duration of treatment, the presence of other risk factors and concomitant medication.[12]

The majority of studies have been undertaken in animals; only a few clinical studies have specifically examined the relationship between seizure threshold and psychotropic drugs. Interpretation is also difficult because the doses given to animals are often very large and much greater than would be considered 'therapeutic'. In addition, most of the work in humans has concentrated on the proconvulsive effects of antidepressants in overdose. Work in this area is further complicated because some antidepressants have a variable effect on seizure threshold, depending on the duration of treatment; the best example of such a drug is lithium.[13]

An excellent review of the effect of antidepressants on seizure activity has been published.[12] Antidepressants may also influence seizure activity by their interaction with anticonvulsants (table I).[14]

5. Cytochrome P450 Hepatic Isoenzymes

The cytochrome P450 (CYP) oxidative hepatic isoenzymes are one of the largest groups of drug-metabolising enzymes. Most psychotropic drugs, with the exception of lithium, are metabolised to some degree by one or more of the CYP enzymes.[15] There are 4 CYP families: CYP1, CYP2, CYP3 and CYP4, and each of these families is further subdivided, for example, CYP2D. Individual enzymes are designated by a number, for example, CYP2D6. A further number is added for genetic polymorphisms, for example, CYP2C19. Table II provides some indication as to which drugs are metabolised by a particular enzyme, and thus some indication about possible interactions.

6. Antidepressant Classes in Patients with Epilepsy

6.1 Monocyclic, Tricyclic, Heterocyclic and Related Antidepressants

Seizures have been reported in patients treated with tricyclic antidepressants for depression, both with and without a past history of epilepsy,[16,17] at both therapeutic and toxic doses. Rasmussen and Johnson[18] reported the following incidence of seizures in patients taking antidepressants at therapeutic dosages: imipramine 0.3%, amitriptyline 0.3%, mianserin 0.6% and clomipramine 1.0%; the incidence in patients taking paroxetine was 0.1%. Other studies have also reported rates of 0.3 to 0.6% with imipramine.[12]

At therapeutic dosages, maprotiline is reported to be more likely to induce seizure activity com-

Table I. Interactions between commonly used anticonvulsants and antidepressants[13]

Anticonvulsant	Interactions with antidepressants
Carbamazepine	Plasma concentrations increased by fluoxetine, fluvoxamine, viloxazine and monoamine oxidase inhibitors Reduces plasma concentrations of tricyclic antidepressants and mianserin Lithium is frequently combined with carbamazepine, but neurotoxicity may occur. Early symptoms include nausea, vomiting, diarrhoea, tremor, dry mouth, fatigue. As concentrations increase to toxic levels, symptoms and signs include ataxia, poor co-ordination, slurred speech, confusion, seizures and coma. Stop lithium if toxic concentration is found and adjust dose after checking blood concentration if mild/early symptoms No significant interactions reported with sertraline and venlafaxine Toxicity reported in combination with nefazodone
Ethosuximide	Antagonism (reduced seizure threshold); specific antidepressants not identified
Gabapentin	Nothing specified
Lamotrigine	Nothing specified
Phenobarbital (phenobarbitone)	Antagonism of anticonvulsant effect with antidepressants. Plasma concentrations of mianserin, paroxetine and tricyclic antidepressants reduced
Phenytoin	Plasma concentrations increased by fluoxetine, fluvoxamine, viloxazine and imipramine Reduces plasma concentrations of mianserin, paroxetine and tricyclic antidepressants Lithium neurotoxicity may occur (see above) No interaction with sertraline or nefazodone reported
Valproic acid (sodium valproate)	Antagonism of anticonvulsant effect with antidepressants Clomipramine concentrations may increase when combined with valproic acid Fluvoxamine may increase valproate concentrations by 50% No significant interaction with paroxetine reported
Vigabatrin	Nothing specified

pared with other antidepressants.[11] Moderately high seizure rates have also been reported with mianserin; in one clinical trial of mianserin involving 6100 patients with depression, the incidence of seizures was 0.4%.[19]

Doxepin[20] and MAOIs[11] have, for many years, been considered to be the least proconvulsive antidepressants. However, SSRIs are associated with a lower incidence of seizures at therapeutic doses compared with TCAs (section 6.2).[21]

Markowitz and Brown[11] reported that maprotiline and amoxapine were associated with a much higher incidence of seizures at therapeutic dosages compared with other TCAs. Amfebutamone (bupropion), a unique monocyclic antidepressant, is also well known to cause seizures at high therapeutic dosages and in acute overdose;[22] in addition, when taken in overdose, amfebutamone may produce recurrent seizures.[22]

Patients taking an antidepressant may be more likely to have a seizure if they have pre-existing brain damage. Wroblewski et al.[17] retrospectively examined the case histories of 68 brain-injured patients; the incidence of seizures in those receiving TCAs was 19%.

The proconvulsive effects of various antidepressants have also been examined in rats with congenital petit mal–like seizures. Imipramine, desipramine, amitriptyline, maprotiline, mianserin and trazodone produced convulsions, but very high doses were used.[23] Since these data were from rats, the results must be treated with caution.

Foulke and Albertson[24] examined a series of 102 patients who had taken an overdose of a TCA and found a seizure prevalence of 9%. Studies involving animals have revealed a similar prevalence for convulsions.[25] James and Kearns[26] reported a seizure prevalence of 15.6% following overdose with TCAs and, in a similar study of TCA toxicity, Liebelt et al.[27] found a seizure prevalence of 20%. Taboulet et al.[28] reported a lower prevalence (6.2%) in their sample of 388 patients, but Ellison and Pentel[29] observed a seizure rate of 83% in patients admitted to hospital with TCA toxicity. These rates are very difficult to compare because of the wide range of drugs involved, variations in

dosage and duration of treatment, the presence of concomitant medication and alcohol (ethanol) and a wide range of risk factors and criteria for seizures. However, Buckley et al.[30] suggested that dothiepin is twice as likely to induce a seizure after overdose, compared with other TCAs. Seizure risk is also high after overdose with amoxapine and maprotiline.[12]

6.2 Selective Serotonin Reuptake Inhibitors

Despite the enormous amount of interest being generated by the SSRIs, it is surprising that very few data are available in relation to the use of these drugs in patients with epilepsy. However, in overdose, these drugs may occasionally cause convulsions.[31] Early clinical studies suggested that the SSRIs were not associated with seizures,[32] but more recent work has indicated that seizures may occasionally occur following overdose, for instance, with fluoxetine.[33-35] Fluvoxamine has been reported to be associated with a higher prevalence of seizures compared with other SSRIs in overdose, but the evidence for this is poor.

Krijzer et al.[36] examined the proconvulsive effects of several different antidepressants by comparing the effect of intravenous antidepressants in animal models. Antidepressants were ranked by their proconvulsive effects; in decreasing order these were: amitriptyline, mianserin, imipramine, desipramine, viloxazine, maprotiline and fluvoxamine. Furthermore, Harmant et al.[37] examined fluvoxamine in dosages of 50 to 200 mg/day for at least 4 weeks in 35 patients with epilepsy. There was no change in the number of seizures, and electroencephalogram (EEG) monitoring indicated that fluvoxamine was not epileptogenic.

Rasmussen and Johnson[18] reported a 0.1% incidence of seizures in patients taking paroxetine, lower than the incidence with imipramine (0.3%), amitriptyline (0.3%), mianserin (0.6%) or clomipramine (1.0%). In addition, no seizures have been reported with paroxetine following overdose. Sedgwick et al.[38] examined the EEG in 23 depressed patients before and after 4 weeks of treatment with paroxetine 30 mg/day; no significant differences were observed between the paroxetine and placebo groups. Citalopram also

Table II. Potential cytochrome P450 (CYP)–associated drug interactions between antidepressants and anticonvulsants[14]

CYP isoenzyme	Drugs metabolised by the enzyme	Drugs that inhibit the activity of the enzyme	Drugs that induce the activity of the enzyme
CYP1A2	Amitriptyline Clomipramine Fluvoxamine Imipramine	Paroxetine Sertraline	
CYP2C9	Hexobarbital (hexobarbitone) Phenytoin TCAs	Sertraline	Barbiturates
CYP2C19	Clomipramine Imipramine Moclobemide	Fluoxetine Fluvoxamine Sertraline	
CYP2D6	TCAs Fluoxetine Paroxetine Maprotiline Nefazodone Venlafaxine	Fluvoxamine Norfluoxetine Sertraline	
CYP3A4	Amfebutamone (bupropion) Sertraline TCAs Venlafaxine Carbamazepine	Fluvoxamine Nefazodone Norfluoxetine Sertraline	Barbiturates Carbamazepine Phenytoin

Abbreviation: TCAs = tricyclic antidepressants.

has no effect on EEG activity.[39] There have been no specific studies examining the clinical efficacy of sertraline in patients with epilepsy.

Interestingly, although SSRIs do not appear to decrease the seizure threshold, there is some evidence that SSRIs increase the seizure duration once a seizure has commenced.[40-42]

6.3 Monoamine Oxidase Inhibitors

MAOIs[11] were one of the first types of antidepressants to be recommended for the treatment of depression in patients with epilepsy. There is evidence from work with 'epilepsy-prone rats' that noradrenaline is able to suppress convulsions and that this effect is enhanced by the coadministration of MAOIs.[43] In addition, both type A and type B MAO inhibitory activity increases after moderate seizures,[44] suggesting that MAOIs may be moderately protective against further seizure activity.

Moclobemide, a RIMA, is efficacious, well tolerated and associated with a low incidence of seizures in patients with depression.[45] Although moclobemide is likely to be effective and well tolerated in patients with epilepsy, confirmatory data are still awaited.

6.4 Lithium

Lithium appears to reduce the seizure threshold,[46] but there are no data on patients with epilepsy being treated with lithium. At supratherapeutic dosages, lithium is known to be neurotoxic and to induce seizures.[47] The majority of reports have described transient seizures, but there have been reports of persistent seizure activity in patients with lithium intoxication.[48]

Most of the work in animals suggests that lithium reduces the seizure threshold after prolonged treatment,[49] and severe brain oedema may occur if a patient has a seizure whilst taking lithium, i.e. if lithium is already in the system.[50] However, Holden[51] has reported that lithium in therapeutic dosages has no observable effects on the EEG or seizure threshold in humans.

6.5 Miscellaneous

There are no known reports examining the effects of tryptophan in epilepsy. However, serotonin does not seem to play an important part in the genesis of seizure activity,[53] and it is unlikely that tryptophan would be proconvulsive at therapeutic dosages.

Trazodone (a serotonin agonist) is not proconvulsive and is considered suitable for patients with epilepsy.[53] Heterocyclic antidepressants, such as mianserin, have a relatively low incidence of seizures compared with TCAs at therapeutic dosages[12,19] in patients with brain damage,[17] and following overdose.[28]

Venlafaxine (an SNRI) and nefazodone (SSRI-related) are 2 relatively new antidepressants and, as yet, there have been no published reports of seizures associated with these drugs at therapeutic plasma concentrations or following overdose. Reboxetine (an SNRI) and mirtazepine [a dual-action noradrenergic and specific serotonergic antidepressant (NaSSa)] have been shown to be efficacious in the treatment of depression, and are associated with a low incidence of seizures.[54,55]

Anticonvulsants such as carbamazepine and valproic acid are extensively used in the treatment of patients with bipolar affective disorder,[56] and may also be of value in the treatment of unipolar depression. The more recently introduced anticonvulsants, gabapentin and lamotrigine, are currently generating considerable interest in the treatment of mood disorders too.

7. Electroconvulsive Therapy

Following the administration of a single electroconvulsive shock, a marked rise in the seizure threshold has been observed in animals.[57] The increase in seizure threshold has also been demonstrated after seizures induced by drugs that antagonise GABA function, but not in seizures induced via a non-GABAergic mechanism [for example, by strychnine (a glycine antagonist) or quipazine (a serotonin agonist)]. These findings suggest that

there is an increase in GABA function in animals that have experienced a convulsion.

In a detailed review, Post et al.[58] commented on the anticonvulsant properties of electroconvulsive therapy (ECT). The mechanism is not entirely clear, but one hypothesis is that ECT stimulates the production of an 'endogenous anticonvulsant'. In a review of this subject, Sackeim et al.[59] noted that the anticonvulsant effects of ECT are cumulative, with a progressive increase in seizure threshold, a progressive decrease in seizure duration, a reduction in neurometabolic rate and blood flow, and enhanced transmission of inhibitory neurotransmitters and peptides.

ECT is a well-tolerated treatment and in our opinion it is worth considering in patients with epilepsy who have severe depression. However, as far as we are aware, no studies have specifically examined the clinical efficacy, tolerability and safety of ECT in depressed patients with epilepsy.

8. Choosing an Antidepressant for a Patient with Epilepsy

In general, very little specific information is available about the use of antidepressants in epilepsy, but from the preceding discussion, it would seem appropriate to choose one that did not antagonise GABAergic mechanisms. Series[60] has reiterated that maprotiline and amoxapine are particularly epileptogenic and should be avoided. Trazodone, SSRIs and MAOIs are considerably less epileptogenic.

More recently, Duncan and Taylor[53] published a short review examining the treatment of depression in patients with epilepsy. They concluded that fluoxetine, paroxetine, sertraline or trazodone should be used as first-line treatments. They did not recommend fluvoxamine, although they note that the seizure rate in patients with depression taking therapeutic dosages of fluvoxamine is the same as with fluoxetine. In addition, there is considerable evidence that fluvoxamine is considerably less proconvulsive than many antidepressants.[38] Although MAOIs are not proconvulsive, they should not be used as a first-line treatment because of the potential adverse interaction with certain foods and drugs.

It is likely that there will be a positive correlation between seizure activity and the oral dosage of an antidepressant. Whichever antidepressant is chosen, patients should be commenced on a low dosage, and this should be gradually increased until a therapeutic dose has been achieved. In addition, since antidepressants may interact with anticonvulsants, plasma concentrations of the latter should be carefully monitored, particularly during the early phase of treatment.

9. Conclusions

Most studies investigating the relationship between antidepressants and seizure activity have examined the effects of antidepressants in overdose, making it difficult to extrapolate the findings to patients with epilepsy in general. Few studies have specifically examined the proconvulsive effects of antidepressants in patients with epilepsy.

Patients with epilepsy may be at increased risk of seizure activity following treatment with antidepressants. Before commencing an antidepressant, such patients should receive a thorough psychiatric examination and any risk factors for seizures should be identified. In addition, consideration must be given to the interaction between antidepressants and concomitant medication, including anticonvulsants.

The ideal antidepressant would be one that was efficacious with few adverse effects (especially sedation), did not antagonise GABAergic mechanisms or interfere with plasma anticonvulsant concentrations. Fluoxetine, fluvoxamine, paroxetine, sertraline, trazodone and MAOIs satisfy many of these criteria and are suitable choices for the treatment of depression in patients with epilepsy, but the final choice, particularly of the SSRIs, will depend on which anticonvulsant is being prescribed. Trazodone is also very sedating, which may significantly exacerbate the sedative effects of some anticonvulsants. The newer antidepressants, venlafaxine and nefazodone, also appear to have few interactions with anticonvulsants, but data are still

awaited on citalopram, moclobemide, reboxetine and mirtazapine. Venlafaxine and nefazodone should also be considered as first-line treatments; trazodone or moclobemide may be used if these are unsuccessful.

However, the data available on the treatment of depression in epilepsy is very limited and further work in this area is needed.

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