

Which is the safest antidepressant to use in epilepsy?

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Seizures are a serious adverse effect of many antidepressants: most, if not all, tricyclics (TCAs) lower the seizure threshold, some atypicals (e.g. maprotiline) are known to cause convulsions and seizures have been reported to occur with all selective serotonin reuptake inhibitors (SSRIs). Opinions vary on which is the safest antidepressant to use in epilepsy.

To date there have been no double-blind trials performed to determine differences between seizure rates for two drugs or between drug and control groups. A trial of this sort would obviously be very useful. However, as seizure incidence is very low (generally between 0.2% and 4%), large sample populations (up to 9000) would be required to show significant differences.

When comparing the results of published studies available, methodological problems become apparent. Many of the early estimates of seizure incidence were based on case reports where there were many influencing variables and poor definitions for what constituted a convulsive event. Patients were also often taking concomitant central nervous system medication which may have affected seizure threshold or, through inhibition of antidepressant metabolism, caused higher TCA plasma levels. Newer antidepressants have undergone clinical trials with improved methodology and with systematic reporting of adverse events. Nevertheless, even these do not allow accurate comparisons to be made. It is also difficult to assess seizure incidence simply by

referring to Committee of Safety of Medicines reports as details are often sparse and reporting rates are highly variable.

Imipramine is the most extensively studied tricyclic antidepressant. A meta-analysis of 98 studies performed between 1955 and 1966 found a seizure rate of 0.1% for imipramine at doses less than 200 mg/day and a rate of 0.6% at doses greater than 200 mg/day (Peck *et al*, 1983). An upper confidence limit of 1.1% was calculated for this latter group, suggesting a range of 0.0–1.1% for seizure risk with imipramine depending on the dose given. Other studies suggest a seizure incidence between 0.1% and 4% (Rosenstein *et al*, 1993), thus indicating some of the difficulties involved in estimating risk.

Seizure risk is certainly increased following overdose with antidepressants (Frommer *et al*, 1987). This suggests a dose-dependent relationship between antidepressant drugs and seizures. Seizure risk also appears to be higher for amoxapine and maprotiline (in overdose – 24.5% and 12.2% respectively) than for other antidepressant drugs (Wedin *et al*, 1986). Interestingly, in the same study, a seizure frequency of 0% was found following overdose with trazodone. The increased risk seen with maprotiline and amoxapine has been confirmed in clinical practice (Edwards, 1979; Jabbari *et al*, 1985).

During clinical trials with fluoxetine, approximately 0.2% of patients exposed to the drug developed seizures or events which were possibly seizures (Physician's Desk Reference, 1992). Patients who had overdosed, received greater than 60 mg/day or who had a pre-existing seizure disorder were excluded from these figures. Seizure risk with paroxetine and sertraline appears to be similar (De Jonge & Swinkels, 1992). Because of early reported incidents of convulsions with fluvoxamine (19 in 10,401 pts, Edwards *et al*, 1994) (i.e. 0.2%), its data sheet initially recommended that fluvoxamine should be

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avoided in epilepsy. This has recently changed: caution is now advised. The study quoted here includes a majority of patients on very low doses of fluvoxamine (<100 mg/day); seizure incidence may be higher when therapeutic doses are used.

Although comparison of the potential seizure risks for different antidepressant drugs remains difficult, at least one author has felt able to assign relative seizure risks to certain antidepressant drugs. Rosenstein *et al* (1993) stated that the incidence of seizures is lowest for fluoxetine, fluvoxamine, sertraline, trazodone and MAOIs, whereas tricyclics, maprotiline and amoxapine have a higher risk.

In a further review (Showron & Stimmel, 1992), it was concluded that maprotiline, amoxapine and clomipramine should be avoided in epileptic patients and that fluoxetine and trazodone may be somewhat safer than the tricyclic antidepressants.

In summary it would seem that, as MAOIs are not agents of first choice, fluoxetine, paroxetine, sertraline or trazodone should be prescribed to patients with epilepsy suffering from depression. Furthermore, these agents should be started at a low dose and increased cautiously as seizure risk may be increased with rapid dose escalation (Toone & Fenton, 1977). As these drugs may interfere with serum anticonvulsant levels, careful monitoring is recommended. There is some evidence that trazodone and sertraline may be less likely to interact with anticonvulsants. Consideration should also be given to

increasing the dose of anticonvulsant when starting an antidepressant.

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