<table>
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<tr>
<th>Study</th>
<th>Sources Summary</th>
<th>Summary (continued)</th>
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<tr>
<td>Pisani 2002</td>
<td>Not described</td>
<td>Size of the problem: the epidemiological approach and its limits&lt;br&gt;Smaller sample sizes gave higher seizure incidences&lt;br&gt;Predisposing factors&lt;br&gt;-acquired seizurogenic conditions&lt;br&gt;-epilepsy&lt;br&gt;-brain damage&lt;br&gt;-febrile convulsions&lt;br&gt;-general illness&lt;br&gt;-individual inherited seizure threshold&lt;br&gt;-drug related factors&lt;br&gt;-intrinsic seizurogenic potential&lt;br&gt;-high dose / overdose&lt;br&gt;-rapid dose escalation&lt;br&gt;-drug combinations&lt;br&gt;The various epidemiological studies have different drawbacks, which make interpretation of data difficult, and sometimes misleading.&lt;br&gt;Notwithstanding the limitations, the epidemiological approach has led to the following general conclusions&lt;br&gt;-the incidence of psychotropic drug-triggered seizures is higher than the incidence of unprovoked seizures in the general population&lt;br&gt;-the phenomenon is a strictly dose-related effect&lt;br&gt;Patient related factors: relevance of predisposing conditions (continued)&lt;br&gt;Significance of pre-existing EEG activity&lt;br&gt;One study found 2% of unselected individuals without epilepsy had EEG “epileptiform” discharges; most had risk from&lt;br&gt;-congenital or perinatal acquired brain damage&lt;br&gt;-mental retardation&lt;br&gt;-biochemical disorder&lt;br&gt;-other organic pathology&lt;br&gt;-14.1% subsequently developed epilepsy&lt;br&gt;Pharmacology study of single IV bolus of imipramine and amitriptyline&lt;br&gt;-cause activation and aggravation of epileptiform discharges only in patients with epilepsy&lt;br&gt;-especially in patients with already exhibiting EEG alterations&lt;br&gt;Similar data for other antidepressants&lt;br&gt;-trimipramine&lt;br&gt;-maprotiline&lt;br&gt;-lithium&lt;br&gt;-antipsychotics&lt;br&gt;Sleep deprivation also activates epileptiform discharges&lt;br&gt;Psychotropic drugs may induce activation or aggravation of epileptiform discharges almost exclusively in patients with pre-existing EEG abnormalities and/or history of epilepsy&lt;br&gt;-such EEG discharges have to be considered clinically relevant in heralding an epileptic seizure only in patients with additional seizurogenic conditions&lt;br&gt;Acquired seizure conditions&lt;br&gt;History of epilepsy in patient and/or family&lt;br&gt;Neurological abnormalities&lt;br&gt;-brain injury&lt;br&gt;-blood-brain barrier abnormality&lt;br&gt;-angioma cavernous&lt;br&gt;Cerebral arteriosclerosis&lt;br&gt;Being elderly (not defined)&lt;br&gt;Reduced drug clearance&lt;br&gt;Preexisting EEG alterations&lt;br&gt;General physical illness&lt;br&gt;-malignant hypertension leading to hypertensive encephalopathy</td>
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<td>Italy</td>
<td>Clinical Review</td>
<td>Purpose&lt;br&gt;To review the effect of psychotropic drugs on seizure threshold in patients with epilepsy and&lt;br&gt;the various clinical and therapeutic aspects, particularly in vulnerable patients, giving priority to practical medical aspects.</td>
<td>Study&lt;br&gt;Search methodology / Databases searched&lt;br&gt;Not described&lt;br&gt;Inclusion criteria&lt;br&gt;Patients with epilepsy&lt;br&gt;Use of psychotropic drugs&lt;br&gt;Meta analysis&lt;br&gt;Prospective study&lt;br&gt;Postmarketing surveillance&lt;br&gt;Retrospective premarketing analysis&lt;br&gt;Comparison with placebo&lt;br&gt;Exclusion criteria&lt;br&gt;Not described&lt;br&gt;Evaluation Methods for Included Studies&lt;br&gt;Not described&lt;br&gt;Summary&lt;br&gt;Size of the problem: the epidemiological approach and its limits&lt;br&gt;Chlorpromazine introduced in 1952; 1 year later generalized tonic-clonic seizures attributed to this drug&lt;br&gt;Imipramine introduced in 1958; relationship to seizures reported soon after&lt;br&gt;-additional support for this association for imipramine and other TCAs shown in EEG studies of patients both with and without epilepsy&lt;br&gt;Incidence of seizures during antidepressant therapy&lt;br&gt;-range 0.1% to 0.6%&lt;br&gt;-&lt;0.1% for amitriptyline (exception)&lt;br&gt;-risk of epileptic seizures during antidepressant therapy may be about 7-fold greater&lt;br&gt;Less data on antipsychotic drugs&lt;br&gt;-1967 study with phenothiazines compounds (4.5 years) = overall incidence of seizures = 1.2%&lt;br&gt;-1994 study of clozapine = 1.3% incidence&lt;br&gt;-50 to 60% variability in seizure incidence in studies of antidepressants and antipsychotics&lt;br&gt;-influenced by trial design&lt;br&gt;-differences in sample size&lt;br&gt;-inclusion or exclusion of patients with predisposing factors for seizure&lt;br&gt;-inclusion of patients on widely different daily doses&lt;br&gt;-differences in duration of observation</td>
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Summary (continued)

**Drug-related factors**

**Experimental data**

Clinical trials have failed to rank psychotropic drugs on a scale with a progressive rate of seizurogenic potential.

Animal studies revealed:
- compounds varied from each other in the degree to which they increased spikes.
- the effect was strictly dose related.
- imipramine and haloperidol showed the highest activating effect.
- amitriptyline was able to inhibit spike activity at lower concentrations.
- protriptyline and trimipramine did not exhibit any activating effect and were able to reduce spikes.

**Effects of psychotropic drugs on spontaneous EEG activity**

Literature in this field is "immense".

Review comments limited to general psychotropic EEG findings commonly seen in clinical practice.
- many drugs, even belonging to different classes, share similar EEG features.
- differentiation is impossible.

Drugs that induce slowing of background activity with increased amounts or voltage of theta activity and (lesser extent) delta activity (alpha rhythm and beta activity simultaneously diminish):
- TCAs
- MAOIs
- lithium
- phenothiazines
- butyrophenones

Lithium may cause EEG changes even at therapeutic serum concentrations.

Anxiolytic and hypnotic agents induce or enhance beta activity.

Clozapine frequently induces EEG changes even at low doses.
- usually associated with high serum concentrations.

Olanzapine induces less pronounced EEG abnormalities but unspecific EEG abnormalities have been observed more frequently than with other antipsychotics.

All observed EEG activities induced by psychotropic drugs are usually unspecific and are rarely followed by a seizure unless additional facilitating factors intervene.

Summary (continued)

**Drug-related factors (continued)**

**Clinical findings**

**High risk for seizures**

**Antidepressants** (~10% at high doses):
- Bupropion
- Clomipramine
- Maprotiline

**Antipsychotics** (associated with potent sedative effects):
- Chlorpromazine
- Clozapine (cumulative risk 10%)
- possibly olanzapine

**Intermediate to low risk for seizures**

**Antidepressants**
- MAOIs
- Mirtazapine
- Nefazodone
- various TCAs
- various SSRIs
- Doxepin
- Trazodone
- Venlafaxine

**Antipsychotics** (associated with lower sedative, more extrapyramidal effects):
- Fluphenazine
- Haloperidol
- Quetiapine
- Risperidone
- Thoridazine
- Trifluoperazine

**Drug dose, plasma drug concentrations and rate of upward dosage titration**

Drug dose is a crucial factor in triggering seizures.

Promazine study (Kurtzke 1957):
- <900 mg/d = zero seizures
- >900 mg/d = 29% patients with ≥1 seizure

Antidepressant overdose study (Frommer 1987):
- seizure incidence = 8.4%
- overdose at very high dose = up to 40% (3 studies)

Clozapine study (% seizures):
- <300 mg/d = 1%
- 300 to 599 mg/d = 2.5%
- >599 mg/d = 4.5%

Bupropion study:
- ≤450 mg/d = zero seizures
- 500 to 700 mg/d = 0.85% seizures

Drug interactions may have detrimental effects on seizure control.
- the number of drug interactions documented in the literature is very large.
- drug interactions represent one of the most important reasons for monotherapy as a more advantageous approach.

**Antiepileptic effects of psychotropic drugs and paradoxical convulsant effects of antiepileptic drugs: is there a link?**

**Antiepileptic effects of psychotropic drugs**

Psychosis, depression and other psychiatric disorders are common in persons with epilepsy.
- availability of psychotropic agents displaying a simultaneous antiepileptic action would be a therapeutic advantage.

**Drug combinations**

Most psychotropic and especially antiepileptic drug cause mutual pharmacokinetic interactions with possible marked changes in blood concentrations of either one or both compounds and consequent modification of the expected clinical response.

Imipramine, nortriptyline and viloxazine increase plasma concentrations of:
- phenytoin
- carbamazepine
- phenobarbital

Toxic effect also observed between fluoxetine and:
- carbamazepine
- phenytoin

Phenytoin, carbamazepine, phenobarbital and primidone may stimulate elimination (thus decreased plasma drug concentration, possible reduction in efficacy and possible formation of toxic metabolites):
- nortriptyline
- clomipramine
- protriptyline (and others)

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**Drug dose, plasma drug concentrations and rate of upward dosage titration (continued)**

Few studies include information on plasma concentrations of psychotropic drugs.

Rate of dose escalation, amount of dose administration during titration and duration of treatment have not been thoroughly investigated.

Sudden increase in drug dose and/or rapid dose escalation are usually indicated as seizure risk factors.

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### Summary (continued)

**Antiepileptic effects of psychotropic drugs and paradoxical convulsant effects of antiepileptic drugs: is there a link?**
- Use of psychotropic drugs may indicate that they produce favorable effects on seizures as a consequence of an amelioration of the mental state.
- Other observations suggest a specific anticonvulsant action of some psychotropic drugs.

Imipramine (Millichap 1965; and subsequent studies)
- Low doses reduced frequency of seizures.
- However, studies involved small numbers of patients so must be interpreted cautiously.

Animal studies
- Imipramine has a biphasic effect on brain excitability with anticonvulsant effects occurring at lower doses and convulsant effects at higher doses.

On the whole, human observations and animal data support the possibility and some drugs that primarily exert a psychotropic action may also exhibit a concomitant antiseizure effect.

**Paradoxical convulsant effect of antiepileptic drugs**
- Carbamazepine has been most frequently involved in seizure aggravation.

Valproic acid may cause seizures in overdose and to exacerbate epileptic seizures in the context of hepatotoxicity or toxic encephalopathy.

**Do psychotropic and antiepileptic drugs share some common mechanisms?**
- Specific literature scanty; matter of speculation.

Antidepressants may trigger seizures because of their local anesthetic or their antihistaminic/antimuscarinic action rather than because of their known property of blocking noradrenaline or serotonin reuptake.

Increasing serotonergic transmission is associated with anticonvulsant action in animal models of epilepsy and in humans.

Recently demonstrated that carbamazepine increases the release of serotonin and that depletion of serotonin greatly decreases anticonvulsant effects.

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**Conclusion:** Although there is sufficient evidence that psychotropic drugs may lower seizure threshold, published literature date have also suggested that an appropriate psychotropic therapy may not only improve the mental state in patients with epilepsy, but also exert antiepileptic effects through a specific action. Further scientific research is warranted to clarify all aspects characterizing the complex link between seizure threshold and psychotropic drugs.

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<td>Additional mechanisms may be mediated by the GABA system: - GABA has a well-established role in the antiepileptic effect of some anticonvulsants, - may also have an important function in the pathogenesis of mood disorders, - concomitant implementation of both effects in electroshock therapy, - increase seizure threshold, - therapeutic effect on refractory depression. However, there is no convincing experimental evidence in favor of a given mechanism coupling both actions; thus the issue remains speculative.</td>
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| Use of psychotropic drugs in patients with epilepsy may be more problematic due to complex pharmacokinetic and/or pharmacodynamic interactions between antiepileptic and psychotropic drugs. Abnormal seizure threshold of the patient. Psychotropic medication use in patients with epilepsy may also have beneficial effects. The lack of direct comparisons among compounds and important differences in methodology of investigations performed make any conclusions only tentative and to be interpreted cautiously. |