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Effects of Psychotropic Drugs on Seizure Threshold

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Abstract

Psychotropic drugs, especially antidepressants and antipsychotics, may give rise to some concern in clinical practice because of their known ability to reduce seizure threshold and to provoke epileptic seizures. Although the phenomenon has been described with almost all the available compounds, neither its real magnitude nor the seizurogenic potential of individual drugs have been clearly established so far. In large investigations, seizure incidence rates have been reported to range from ~0.1 to ~1.5% in patients treated with therapeutic doses of most commonly used antidepressants and antipsychotics (incidence of the first unprovoked seizure in the general population is 0.07 to 0.09%). In patients who have taken an overdose, the seizure risk rises markedly, achieving values of ~4 to ~30%. This large variability, probably due to methodological differences among studies, makes data confusing and difficult to interpret. Agreement, however, converges on the following: seizures triggered by psychotropic drugs are a dose-dependent adverse effect; maprotiline and clomipramine among antidepressants

and chlorpromazine and clozapine among antipsychotics that have a relatively high seizurogenic potential; phenelzine, tranylcypromine, fluoxetine, paroxetine, sertraline, venlafaxine and trazodone among antidepressants and fluphenazine, haloperidol, pimozide and risperidone among antipsychotics that exhibit a relatively low risk. Apart from drug-related factors, seizure precipitation during psychotropic drug medication is greatly influenced by the individual's inherited seizure threshold and, particularly, by the presence of seizurogenic conditions (such as history of epilepsy, brain damage, etc.). Pending identification of compounds with less or no effect on seizure threshold and formulation of definite therapeutic guidelines especially for patients at risk for seizures, the problem may be minimised through careful evaluation of the possible presence of seizurogenic conditions and simplification of the therapeutic scheme (low starting doses/slow dose escalation, maintenance of the minimal effective dose, avoidance of complex drug combinations, etc.). Although there is sufficient evidence that psychotropic drugs may lower seizure threshold, published literature data 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 characterising the complex link between seizure threshold and psychotropic drugs.

One of the most common concerns with the use of psychotropic drugs is their potential for provoking epileptic seizures. This involves mainly antidepressants and antipsychotics. However, the problem has also been described with mood stabilisers and benzodiazepines. Physicians may find themselves having to face the problem in different clinical situations, either in patients with psychiatric disorders or in patients with epilepsy and concomitant psychiatric disorders. In patients with psychiatric disorders, occurrence of a seizure may present within the context of a clearly defined pathological entity, such as neuroleptic malignant syndrome, or even as one of the generic signs of drug toxicity, such as that associated with antidepressant overdosage in cases of suicide attempts. Similarly, the phenomenon may complicate, for example, the treatment of patients who require high dosages of psychotropic drugs and/or who are undergoing complex multidrug therapy because of the severity of the psychiatric disorder. In clinical practice, it may also happen that doses considered therapeutically low are sufficient to trigger an epileptic seizure in particularly vulnerable patients, for example those with an abnormally low, genetically determined seizure threshold. The problem may cause even greater concern when psychotropic medication is required in patients with diagnosed epilepsy and concomitant psychiatric disorders. Psychiatric comorbidity with epilepsy is common.[1] Depression, for example, has been found to affect up to about 50% of patients with epilepsy,[2,3] and the risk of suicide in patients with epilepsy has been found to be four to five times greater than that of the general healthy population.[4] Another condition that is frequently observed, especially in paediatric patients, is that characterised by epileptic seizures, learning disorders and behavioural disorders. This triad of symptoms is typical of perinatal encephalopathies and, because of its particular severity, often requires aggressive multidrug medication.

Based on the above analysis, correct knowledge of the effect of psychotropic drugs on seizure threshold, and awareness of the various clinical and therapeutic aspects associated with it are essential to minimise the risk of seizures. This is particularly important for vulnerable patients. This review deals with this specific therapeutic area, giving priority to practical medical aspects. Experimental data, however, and very particular topics are also briefly pre-

sented with the aim of facilitating full comprehension of the complexity inherent in the matter.

1. Size of the Problem: the Epidemiological Approach and its Limits

Occurrence of epileptic seizures and, more rarely, status epilepticus has been described with almost all conventional and recently introduced psychotropic drugs. The phenomenon was recognised soon after introduction of the first psychoactive compounds. Chlorpromazine was introduced into clinical practice in 1952, and as early as 1 year later generalised tonic-clonic seizures were attributed to the drug.[5] Similarly, soon after the introduction of imipramine onto the market in 1958, a number of case reports suggested a relationship between that drug and occurrence of epileptic seizures.[6-8] Additional support for this association came from studies demonstrating an 'activating' effect of imipramine and other tricyclic antidepressants (TCAs) on the electroencephalogram (EEG) of patients both with and without epilepsy.[9-13] During the same period, data from studies performed on animals reinforced this belief. One of the classic studies performed on baboons, for example, demonstrated that haloperidol at doses of 0.6 to 1.2 mg/kg produced

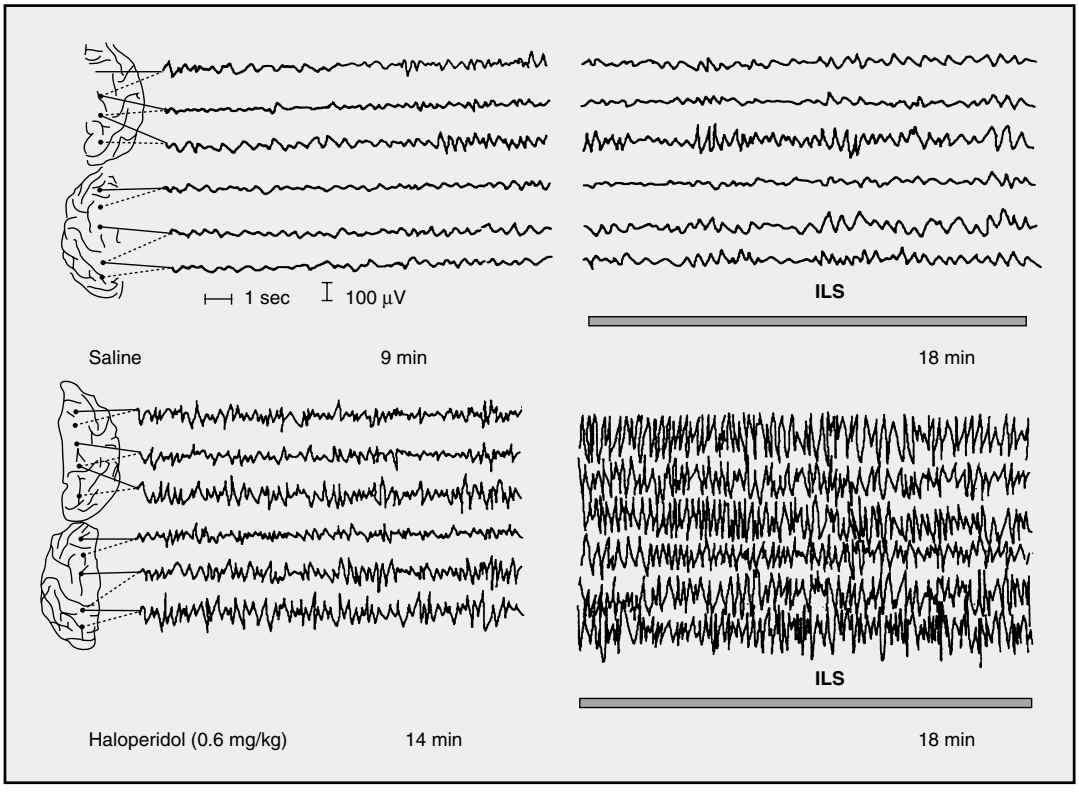

Fig. 1. Electroencephalogram records from a baboon: above, electrical activity, eyes open, 9 min (left) and during intermittent photic stimulation (ILS) 18 min (right) after intravenous saline injection; below, left, enhancement of spontaneous spike and wave activity, eyes half-closed, 14 min and, right, sustained paroxysmal discharge during ILS, 18 min after intravenous haloperidol injection. In both conditions, spikes were accompanied by eyelid myoclonus (reprinted from European Journal of Pharmacology, volume 32, Meldrum B, Anlezark G, Trimble M. Drugs modifying dopaminergic activity and behaviour, the EEG and epilepsy in papio papio. 203-213; 1975, with permission from Elsevier Science).[14]

Table I. Seizure incidence with antidepressants and antipsychotics[a] as reported by some of the largest and most representative studies

Drug	Seizure incidence (%)	Patient population (no.)	Drug dose (mg/day)	Reference
Antidepressant				
Imipramine	0.10	2986	≤200	16
	0.60	958	>200	16
Amitriptyline	0.00	1037	<200	16
	0.06	1811	≥200	16
	0.10	7000	Wide range	17
Clomipramine	0.50	4160	Wide range	18
Maprotiline	0.40	6100	Wide range	19
Fluoxetine	0.20	6000	20-60	20
Fluvoxamine	0.20	10 401	<100	21
Antipsychotic				
Chlorpromazine	0.50	859[b]	<1000	22
	9.00	859[b]	>1000	22
Clozapine	1.00	1418	<300	23
	4.40	1418	≥600	23
	1.30	5629	Wide range	24

a Incidence of the first unprovoked seizure in the general population = 0.07 to 0.09%.[15]

b Patients were receiving phenothiazine compounds, mostly chlorpromazine.

an increased incidence of spontaneous EEG spikes and waves and a great enhancement of paroxysmal EEG activity during photic stimulation (figure 1).[14]

On these grounds, clinical investigations were carried out on large populations of patients to establish the magnitude of this important drug adverse effect. Table I illustrates the results of some of the largest and most representative studies regarding antidepressants and antipsychotics.

In these studies, the incidence of seizures during antidepressant therapy ranged from 0.1 to 0.6%, except for the value of <0.1% reported for amitriptyline[16] (table I). If one considers that the annual incidence of a first unprovoked seizure in the general population is 0.07 to 0.09%,[15] one has to conclude that the risk of epileptic seizures during antidepressant therapy may be about 7-fold greater. The literature regarding antipsychotic drugs is scantier and most reports are based on insufficient numbers of patients to give reliable information. One of the earliest and largest investigations is the study of Logothetis,[22] who in 1967 reviewed the literature concerning the spontaneous occurrence of epileptic seizures in 859 patients without epilepsy treated with phenothiazine compounds, most with chlorpromazine, over a period of 4.5 years. The overall incidence of seizures was 1.2%. A similar value (1.3%) has been found with the newer antipsychotic clozapine in a population of 5629 patients[24] (table I). Seizures have been reported during therapeutic use of most other antipsychotics, including the more recent compounds olanzapine, risperidone and quetiapine.[25,26] Some antipsychotic agents, however, seem to exhibit less or no seizurogenic activity. Although a reliable conclusion cannot be drawn because of the small number of patients investigated, no seizures occurred in 18 patients given fluphenazine at a very high dosage (1200 mg/day)[27] and in 15 patients who overdosed with risperidone.[28]

Reviewing all the published antidepressant and antipsychotic data, a 50 to 60% variability in seizure incidence has been reported.[29,30] This wide range makes any comparison of data valueless. In particular, it is difficult on this basis to assess the real magnitude of the phenomenon in clinical practice. Methodological differences among studies may partly explain such a discrepancy: different sample size of the populations investigated; inclusion or exclusion of patients with predisposing factors;

differences in trial design; inclusion of patients on very different daily drug dosages; and differences in duration of observation.

One of the most important sources of variability in this kind of investigation is the sample size of the population investigated and, often, the number of patients studied is far from that theoretically calculated to achieve sufficient statistical power.[18,31] In fact, studies with relatively small samples of patients (in the order of hundreds) gave seizure incidence values higher than those reported in table I: for example, 1.5 to 4.0% for imipramine [6,7,32-34] and 3.5% for clomipramine.[35] This aspect is more evident when comparing some data on maprotiline. Seizure rates have been reported to be 0.02% in a population of about 17 000 patients,[35] 3.3% in a sample size of about 150 patients[19] and 15.6% in a group of 69 patients.[36] Similarly, in a study including a total number of approximately 8000 patients,[16] the estimated seizure risk for imipramine was approximately 10-fold higher than that for amitriptyline (table I). Conversely, a seizure incidence of 2% was observed in a sample of 200 patients receiving amitriptyline and no seizures occurred in another group of 200 patients receiving imipramine.[37]

Inclusion or exclusion of patients with predisposing risk factors may also greatly influence the results of epidemiological studies. These factors include, for example, history of epilepsy, brain injury, learning disabilities, dementia or concomitant intake of additional drugs which modify seizure threshold (see also section 2.3). Figure 2 and table II illustrate the most frequently reported factors and conditions which facilitate the occurrence of seizures during psychotropic drug medication. In some studies, for example, patients with a previous history of epilepsy were excluded;[16,22] in others, the inclusion criteria were not clearly specified and even patients with a history of epilepsy, or taking additional psychotropic drugs, were included.[19,38]

Differences in the trial design may also account for variability of results. Thus, available data were obtained through meta-analysis,[16] prospective studies by single groups of investigators,[17,22] post-marketing surveillance,[24] retrospective premarketing analysis,[23] comparisons with placebo-treated groups,[48] or, most frequently, without any control group.

Drug dosage is another confounding factor in comparing the various studies and has to be taken into careful consideration when drawing conclusions. Table I clearly illustrates how the seizure rate changes as a function of the daily dosage. With imipramine, for example, the incidence of seizures was 0.1% at daily doses of ≤200mg and rose to 0.6% at doses of >200mg. Similarly, with amitriptyline at ≥200mg the incidence was 0.06%, whereas

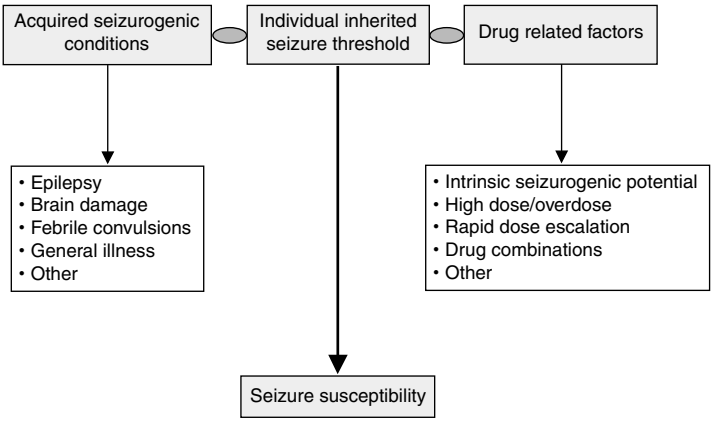

Fig. 2. Patient- and drug-related factors determining seizure susceptibility during psychotropic drug medication.

Table II. Patient-related predisposing conditions for psychotropic-triggered seizures

Condition	References
History of epilepsy (including febrile convulsions) in the patient and/or their family	19, 22, 37-41
Neurological abnormalities[a]	22, 26, 42-44
Cerebral arteriosclerosis	7
Being elderly	45
Reduced drug clearance	26, 46
Pre-existing electroencephalogram alterations	39, 47
General physical illness (e.g. malignant hypertension leading to hypertensive encephalopathy)	22, 41

a Including brain injury, blood-brain barrier abnormality, angioma cavernous.

no seizures were observed in patients taking <200mg. Antipsychotics show similar variability, as is evident from table I for chlorpromazine and clozapine. The clearest evidence on the crucial role played by drug dose in generating large differences in incidence rates of seizures comes from data regarding overdosed patients. In this case, the risk is much higher than that observed in patients receiving therapeutic doses, and incidence values range from ~4 to >30%.[6,16-18,37,42,49-54] The role of drug dosage in triggering seizures is discussed in more detail in section 3.2.

Assessment of seizure risk is also affected by the duration of observation.[29] However, systematic analysis of the incidence of new cases during a given time interval over prolonged treatment, for example with proportional hazards analysis, has seldom been done. Rare examples are those concerning clomipramine and bupropion, the annual cumulative risk of which has been estimated to be 1.45 and 1.4%, respectively.[18]

Apart from the specific factors discussed above, other factors have to be considered as possible sources of variability in the production of data, namely an erroneous diagnosis of epileptic seizure and an erroneous causal connection between a seizure and the administered drug.

In summary, the various epidemiological studies have different drawbacks, which make interpretation of data difficult and, sometimes, misleading. In particular, further investigations, prospective and more homogeneous in methodology, are needed to establish the real extent of seizures induced by psychotropic drugs in clinical practice, especially with regard to individual classes of drugs and individual compounds.[18,29]

Notwithstanding the above-mentioned limitations, the epidemiological approach has led to the following general conclusions: the incidence of psychotropic drug-triggered seizures is higher than the incidence of unprovoked seizures in the general population; the phenomenon is a strictly dose-related adverse effect.

2. Patient-Related Factors: Relevance of Predisposing Conditions

The individual propensity to develop seizures may be regarded as the result of two distinct factors: the individual inherited seizure threshold and the presence of seizurogenic conditions experienced by a given patient during his or her life. Combination of the two factors, further complicated by additional interference of drug-related factors (figure 2), may easily account for the extreme difficulty in anticipating the occurrence of an epileptic seizure. Hence, a deep knowledge of all possible variables involved, which in other words means a careful evaluation of the basal clinical condition of the patient, is essential to minimise the risk of seizures during psychotropic drug therapy.

2.1 Individual Inherited Seizure Threshold

The concept of a physiological range of neuronal excitability which is genetically determined and characterises each individual is an intuitive and universally accepted condition. This individual attribution is, like many other conditions in medicine and biology, a theoretical assumption, since specific quantitative data have not yet been produced in humans to typify this range of excitability; indeed, at present, there is no technique able to rank individuals into those with a low and those with a high seizure threshold. Indirect evidence comes from empirical observation that some individuals

may develop epileptic seizures as a consequence of a stimulus which is normally ineffective in the majority of persons (slight brain injury, mild emotional events, etc.). With regard to drug intake, for example, cases of seizures or status epilepticus triggered by low/therapeutic doses of antidepressants have been described.[13,55-60] In these vulnerable patients it is sometimes possible to identify a family history of seizures.

Conversely, it is common experience that some individuals do not exhibit any seizure even in the presence of conditions (such as brain calcifications, angioma cavernous, perinatal cerebropathy) which are known to be associated with a high risk of epileptic seizures.

2.2 Significance of Pre-existing Electroencephalogram (EEG) Activity

It is known that EEG activity is frequently found to be normal in patients with epilepsy. On the other hand, some individuals without any clinically evident pathological condition show various abnormalities in their EEG, the significance of which, in most cases, remains uncertain. This aspect has been investigated both by an epidemiological approach in large populations of individuals without epilepsy and by pharmacological studies in small groups.

In one of the most representative studies, based on 6497 unselected individuals without epilepsy, EEG 'epileptiform' discharges (spikes, sharp waves, and spike-and-slow-wave complexes) were observed in only approximately 2% of participants.[61] In these individuals, however, congenital and perinatal acquired brain damage, mental retardation, biochemical disorders or other organic pathologies were found and some of them were treated with antineoplastic agents or corticosteroids.[61] 20 of these patients (14.1%) subsequently developed epileptic seizures. Hence, the conclusions may be drawn that the incidence of epileptiform discharges is high only in patients with organic general and brain disorders, and that only susceptible patients, a percentage of approximately 15%, develop epileptic seizures.

The pharmacological approach led to similar results. The studies of Kiloh et al.[9] and Davidson[10] can be considered benchmarks in this respect. These authors found that imipramine and amitriptyline, after a single intravenous bolus, cause activation and aggravation of epileptiform discharges only in patients with epilepsy and especially in those already exhibiting EEG alterations.[9,10,39] Neither imipramine nor amitriptyline have been found to induce epileptiform discharges in patients without a history of epilepsy. Similar data have been produced with other antidepressants, such as trimipramine and maprotiline,[12,62,63] lithium and antipsychotics.[47,63] In particular, phenothiazines and butyrrophenones have been found to exacerbate pre-existing EEG abnormalities and to trigger epileptiform discharges.[47,64] In all these studies, however, EEG activation was rarely followed by epileptic seizures, unless additional facilitating factors were present. In a recent study, for example,[65] chlorpromazine has been used to activate EEG in patients with adult-onset partial epilepsy. The effect of the drug has been found to be similar to that of sleep deprivation in activating epileptiform discharges (figure 3). Administration of the drug, however, was not followed by seizures in any of the patients investigated.

Taken together, the above data indicate that psychotropic drugs may actually induce activation or aggravation of epileptiform discharges almost exclusively in patients with pre-existing EEG abnormalities and/or history of epilepsy, and that these EEG discharges have to be considered clinically relevant in heralding an epileptic seizure only in patients with additional seizurogenic conditions. Evaluation of these conditions is, therefore, essential before starting psychotropic medication.

2.3 Acquired Seizurogenic Conditions

A number of conditions have been described by various authors as being able to promote seizures. Table II gives a list of those most frequently reported in various investigations. As discussed in sections 1 and 2.2, their presence must be carefully checked in patients undergoing treatment with psy-

chotropic drugs and their role is extremely important in evaluating results published in the literature. In the study by Logothetis,[22] for example, the seizure rate during phenothiazine therapy was 2% in 202 patients with organic pathology, but only 0.9% in 657 patients without organic disease. In another investigation,[37] in which the incidence of seizures was retrospectively evaluated in 200 patients receiving imipramine and 200 receiving amitriptyline, the only four seizures observed occurred in the latter group, in which two patients already had a history of epilepsy. In an analysis[66] based on 41 patients with seizures, 28 patients were considered to have seizures secondary to treatment with chlorpromazine or trifluoperazine. By comparing these patients with the control group, the authors found, among other observations, that patients with seizures were more likely to have postnatal brain damage.[66] The literature is rich in such examples. Most of the conditions listed in figure 2 and table II are obvious general factors facilitating seizures, such as a history of epilepsy, brain damage, or malignant hypertension causing encephalopathy. It must be stressed, however, that none of these factors has been formally investigated and that their relative individual roles remain to be established.

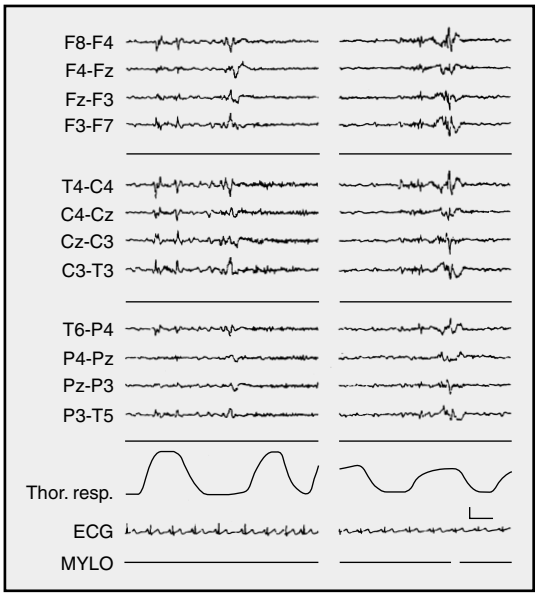

Fig. 3. Sleep electroencephalogram recordings of a 23-year-old untreated woman experiencing rare nocturnal partial seizures with frequent secondary generalisation. Both computed tomography and magnetic resonance imaging were normal. On the left side no abnormalities are evident during stage II of sleep after sleep deprivation (note K-complexes and vertex spikes). On the right side diffuse spike-wave discharges are observed during sleep stage II induced by chlorpromazine (with permission from Springer-Verlag: J Neurol 1994: Chlorpromazine versus sleep deprivation in activation of EEG in adult-onset partial epilepsy. Aguglia et al., Vol. 241: 605-610). **ECG** = electroencephalogram; **MYLO** = mylohyoid muscle; **Thor. resp.** = thoracic respiration.

3. Drug-Related Factors

3.1 Intrinsic Seizurogenic Potential of Individual Drugs

3.1.1 Experimental Data

Clinical studies have largely failed to rank psychotropic drugs on a scale with a progressive rate of seizurogenic potential. An attempt in this regard has been made in experimental studies. The relative potential of various antidepressants and antipsychotics for triggering seizures has been investigated in *in vitro* studies.[67,68] The authors have examined the effect of different compounds on spike activity produced in perfused guinea-pig hippocampal slices through addition in the perfusion medium of more potassium chloride and sodium benzylpenicillin (penicillin G). The spike activity produced by this method was then displayed on a paper chart. Slices were exposed to a single antidepressant or antipsychotic at progressively increasing doses to obtain concentrations close to the higher values of the commonly accepted therapeutic range, when available for that drug, or to those usually observed in clinical practice in patients treated with therapeutic doses. Figure 4 summarises data relating to some commonly used antidepressants. This interesting model led to important findings. Firstly, the various compounds differed from each other in the degree to which they increased spikes and the effect was strictly dose-related. Imipramine and haloperidol showed the highest activating effect.

Secondly, some antidepressants, such as amitriptyline, were able to inhibit spike activity at lower concentrations and some others, such as protriptyline and trimipramine, not only did not exhibit any activating effect, but were able to reduce spikes (figure 4). This very interesting action, which has also been confirmed in animals and humans, is analysed in detail in section 4.1.

3.1.2 Effects of Psychotropic Drugs on Spontaneous EEG Activity

Following earlier studies[9,10] investigating the effect of psychotropic drugs on the EEG activity illustrated above, further research has been developed in an attempt to characterise individual compounds and/or classes of drugs on the basis of their detailed effects on spontaneous EEG activity. The literature in this field is immense and cannot be reviewed here. Therefore, this section is limited to general psychotropic EEG findings commonly observed in clinical practice. Available evidence indicates that many drugs, even belonging to different classes, share similar EEG features, and differentiation is impossible. Hence, TCAs, monoamine oxidase inhibitors (MAOIs), lithium, phenothiazines and butyrrophenones induce slowing of background activity with increased amounts or voltage of theta activity and, to a lesser extent, delta activity. Simultaneously, frequency of the alpha rhythm and beta activity diminish.[64,69-72] Lithium may cause EEG changes even at therapeutic serum concentrations, most frequently diffuse, continuous slow activity and paroxysmal bursts of generalised slow waves.[73,74] Classically, anxiolytic and hypnotic agents, such as benzodiazepines, induce or enhance beta activity (>13Hz).[72] As discussed in section 2.2, all observed EEG activities induced by psychotropic drugs are usually unspecific and are rarely followed by a seizure unless additional facilitating factors intervene. Their appearance in a given patient, therefore, does not automatically imply discontinuation of psychotropic medication. If particular compounds are used, however (i.e. those exhibiting a high seizurogenic potential), a different therapeutic approach may be required. In a study based on 35

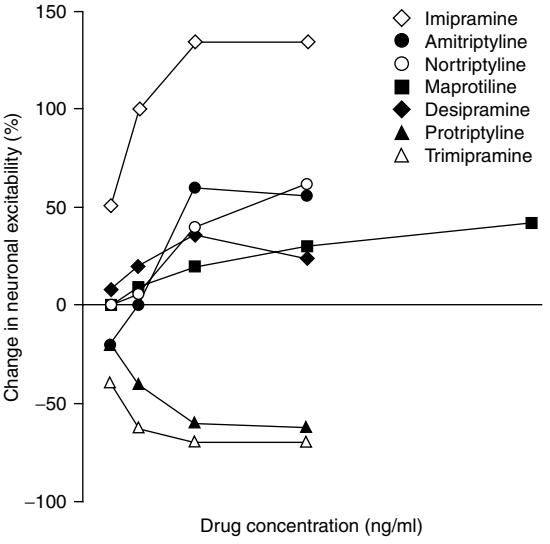

Fig. 4. Percentage change in neuronal excitability induced by various antidepressants using the guinea-pig hippocampal slice technique (reproduced from Luchins et al.,[67] with permission).

patients with schizophrenia, 26 of them showed various EEG alterations while receiving clozapine (slowing, dysrhythmia or paroxysmal discharges) and 7 patients had seizures.[75] Other studies are in line with these findings, indicating that clozapine frequently induces remarkable EEG changes even at low doses[76] and that these changes are usually correlated with high serum drug concentrations.[77] Another of the recently developed antipsychotics, olanzapine, has been shown to induce less pronounced EEG changes than clozapine,[78] but unspecific EEG abnormalities have been observed more frequently than with use of other antipsychotics.[79] Consequently, the authors recommend careful surveillance of patients with risk factors for seizures when they are undergoing treatment with olanzapine.[79]

3.1.3 Clinical Findings

As stated above, occurrence of epileptic seizures has been reported with almost all psychotropic drugs. With regard to antidepressants, although the literature on TCAs is abundant, epileptic seizures have been reported during treatment with

almost all antidepressants, including MAOIs, trazodone, the selective serotonin reuptake inhibitors (SSRIs; such as fluoxetine, citalopram, fluvoxamine, paroxetine and sertraline), lithium and the more recent compounds, such as venlafaxine.[2,20,48,80-88] Attempts to assign relative seizure risks to various antidepressants have been made by some authors.[2,3,18,26,45] However, because of the various limitations of the human studies illustrated above, any comparison should be made cautiously. The bulk of evidence suggests that clomipramine and, especially, maprotiline have a relatively high risk with a seizure incidence frequently reported as being ~10% at high doses; conversely, the MAOIs phenelzine and tranylcypromine, doxepin, trazodone and, possibly, SSRIs and venlafaxine exhibit the lowest seizure risk[2,3,18,26,48,51,89] (table III).

Similarly to antidepressants, with regard to antipsychotics, epileptic seizures have been described with almost all conventional and new compounds.[25,26,30,90,91] The literature can be summarised as follows: haloperidol, fluphenazine, pimozide and trifluoperazine have a low seizurogenic potential;[27,90,92,93] antipsychotics with potent sedative effects, typically chlorpromazine, more frequently cause EEG alterations and epileptic seizures, whereas less sedative compounds with more extrapyramidal effects, typically haloperidol, have a lower seizurogenic potential[47,94,95] (table III); apart from chlorpromazine, clozapine and, possibly, olanzapine have been found to frequently cause EEG alterations and to trigger epileptic seizures.[78,79] In particular, clozapine has been associated with a cumulative risk of seizures of 10%, based on data from 1418 patients treated for up to 3.8 years.[23] Conversely, no seizures were observed in 18 patients taking high doses of risperidone,[28] while quetiapine may have an intermediate risk, i.e. between clozapine and risperidone.[26]

Table III. Relative risk for seizures exhibited by some antidepressants and antipsychotics during therapeutic use[a]

High risk	Intermediate to low risk
Antidepressants	
Bupropion	MAOIs
Clomipramine	Mirtazapine
Maprotiline	Nefazodone
	Various TCAs[b]
	Various SSRIs[b]
	Venlafaxine
Antipsychotics[c]	
Chlorpromazine	Fluphenazine
Clozapine	Haloperidol
	Pimozide
	Risperidone
	Thioridazine
	Trifluoperazine

a According to various references (section 3.1.3). [The list of drugs is not exhaustive and some compounds are not listed here because of insufficient or conflicting data; see sections 1, 3.1.3 and 5 for the limits of establishing an accurate seizure risk for each drug].

b See throughout text for specific compounds.

c Drugs, such as quetiapine and olanzapine, might be less epileptogenic than clozapine, but more epileptogenic than risperidone (see section 3.1.3).

MAOIs = monoamine oxidase inhibitors; **SSRIs** = selective serotonin reuptake inhibitors; **TCAs** = tricyclic antidepressants.

3.2 Drug Dose, Plasma Drug Concentrations and Rate of Upward Dosage Titration

Drug dose is a crucial factor in triggering seizures during psychotropic medication. This aspect has been partly discussed in section 1 and is clearly evident from the data presented in table II. One of the most evident findings is that reported in one of the earliest surveys, where no seizures were observed in patients receiving dosages of promazine less than 900 mg/day, while 29% of patients exhibited at least one seizure at doses of more than 900 mg/day.[54] Subsequent studies partly confirmed that survey. Hence, in one study seizure incidence rose from 0.5% in patients treated with a dosage of chlorpromazine (or its equivalent) of less than 1000 mg/day to 9% in those taking 1000 mg/day or more.[22] Another study leading to similar results gave incidence values of 0.5% at 300 mg/day of chlorpromazine, and of 5% at 2000 mg/day.[96]

In reviewing 26 studies, including a total population of 2536 patients overdosed with antidepressants, Frommer et al.[97] found a seizure incidence of 8.4%, which is much higher than the values reported in table II. When looking at populations

of patients taking very high doses or overdoses, the seizure rates reported achieve values of up to 40%.[37,52,89,97]

A clearcut example of the fundamental role of the drug dose in provoking seizures is given by the antipsychotic clozapine. Seizure rate has been reported to be about 1% at daily doses of less than 300mg, about 2.5% at 300 to 599mg, and about 4.5% at doses above 599mg (figure 5).[23] Another example is that regarding bupropion. This drug displays antidepressant effects and it has recently been approved to help in smoking cessation. No seizures were observed in a sample of 1153 patients given bupropion at dosages of 450 mg/day or less, but 3 out of 353 patients (0.85%) exhibited epileptic seizures while receiving dosages of 500 to 700 mg/day.[16] Monitoring of serum concentrations of bupropion and clozapine, drugs that appear to have a low therapeutic index, might be especially useful to lessen the risk of seizures.

Few studies have included information on plasma concentrations of psychotropic drugs. These observations suggest that the risk of epileptic seizures is substantially higher as plasma drug concentrations increase above the commonly accepted therapeutic levels.[53,98-102] In some investigations,[55,100] for example, plasma concentrations of amitriptyline + nortriptyline of 250 to 450 μg/L were associated with asymptomatic EEG alterations, while values of TCAs markedly higher (around 700 μg/L) were associated with seizures. Occurrence of generalised seizures was observed in a patient with plasma haloperidol concentrations of 80 μg/L, which were much higher than levels considered devoid of drug toxicity (i.e. 30 μg/L).[102] A recent prospective study has compared clozapine serum concentrations with EEG changes in a cohort of 50 patients with schizophrenia.[77] Three of these patients developed seizures: one exhibiting serum clozapine concentrations of 320 μg/L and the remaining two, who had prior histories of seizures, showing lower concentrations, 200 to 300 μg/L. In this study, a more frequent and more severe slowing in EEG activity was found at serum clozapine concentrations between 350 and 450 μg/L compared with levels below 300 μg/L.[77]

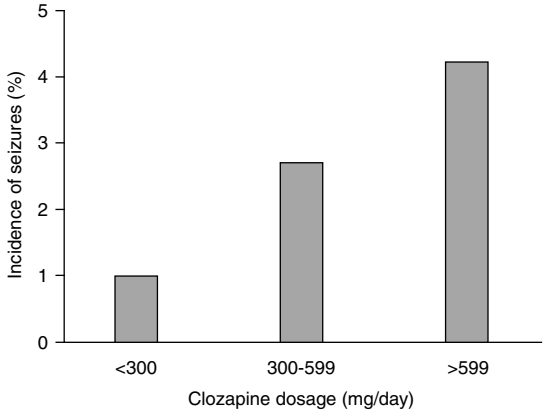

Fig. 5. Incidence of epileptic seizures associated with different dosages of clozapine (reproduced from Stimmel & Dopheide,[25] with permission).

It might also be speculated that unusually high plasma concentrations account for the cases described in the literature in which seizures or status epilepticus are associated with therapeutic or low doses of TCAs.[13,55-60] At least in some of these cases, reduced capacity for drug elimination or possible pharmacokinetic interactions with additional drugs might have played an important role. In a recently described case of status epilepticus during clomipramine treatment,[59] for example, the elevated plasma concentrations of clomipramine (342 μg/L; therapeutic range 70 to 270 μg/L), following a 'therapeutic' dosage of 75 mg/day, were probably caused by concomitant treatment with valproic acid, which is a well known inhibitor of hepatic drug metabolism.

Regarding possible additional risk factors, such as the rate of dose escalation, the amount of dose administration during dose titration and the duration of treatment, these have not been thoroughly investigated. However, a sudden increase in drug dose and/or a rapid dose escalation are usually indicated as risk factors.[18,25,26,31,66]

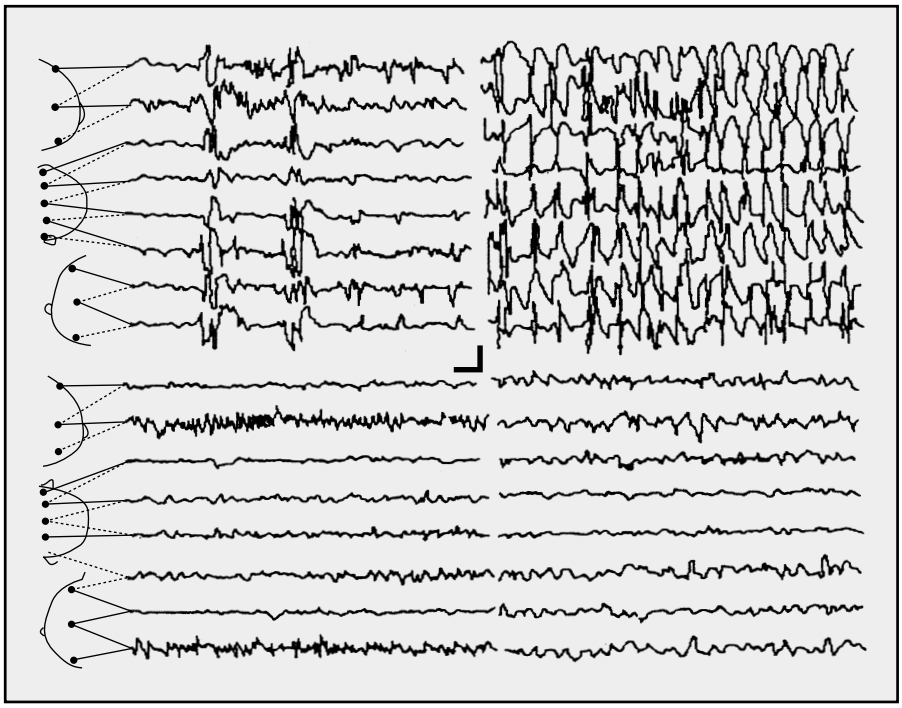

Fig. 6. Electroencephalogram recorded in awake child with Landau-Kleffner syndrome (left) and during sleep (right), before (above) and after (below) 10-day treatment with amphetamine sulphate 0.25 mg/kg/day. Calibrations 1 sec and 100μV (reproduced from Marescaux et al.,[135] with permission).

3.3 Drug Combinations

Most psychotropic and, especially, antiepileptic drugs 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.[46,103-106] For example, imipramine, nortriptyline and viloxazine may increase the plasma concentrations of phenytoin, carbamazepine and phenobarbital[46,103-106] and this may lead to drug toxicity including paradoxical activation of seizures.[107-109] Similarly, some SSRI compounds inhibit the cytochrome (CYP) 2D6 isoenzyme in the liver and may reduce the elimination of other concomitant drugs.[105] Probably, at least in part, this mechanism might have played a role in determining the toxic effects observed during comedication of fluoxetine with carbamazepine[110] and with phenytoin.[111]

On the other hand, phenytoin, carbamazepine, phenobarbital and primidone are potent inducers of the hepatic microsomal enzymes and, through this mechanism, stimulate the elimination of different psychotropic drugs including nortriptyline, clomipramine, protriptyline and others.[46,103-106] This effect may result in decreased plasma drug concentrations, possible reduction in efficacy and possible formation of toxic metabolites displaying convulsant action.[107] Drug interactions, therefore, may have detrimental effects on seizure control and represent one of the most important reasons for monotherapy being suggested to be more advantageous than polytherapy in treating patients with epilepsy.[112]

Since the number of drug interactions documented in the literature is very large, readers may refer to specific reviews.[103-107]

4. Antiepileptic Effects of Psychotropic Drugs and Paradoxical Convulsant Effects of Antiepileptic Drugs: Is There a Link?

4.1 Antiepileptic Effects of Psychotropic Drugs

Observations from various authors suggest that proper use of psychotropic medication may not only induce beneficial effects on the mental state of patients with epilepsy, but positively influence seizure frequency and severity. From a clinical point of view, this aspect, which apparently contrasts with all the information given in the previous sections, is a very important one. Psychosis, depression and other psychiatric disorders have been found to be more common in persons with epilepsy than in the general population[113,114] and, hence, availability of psychotropic agents displaying a simultaneous antiepileptic action would be a great therapeutic advantage.

In a population of 100 institutionalised patients with epilepsy and various behavioural disorders, use of thioridazine at therapeutic doses has been reported to induce both improvement of the psychiatric condition and reduction in seizure frequency in 41 patients.[115] Similarly, in a retrospective study, based on 59 patients with epilepsy treated with TCAs, antipsychotics and/or lithium, it was found that 56% of patients showed a marked improvement in their psychiatric disturbances and that this was paralleled by reduced seizure frequency.[116] These findings do not necessarily suggest that some psychotropic drugs have specific antiepileptic effects, but might indicate, for example, that they produce favourable effects on seizures as a consequence of an amelioration of the mental state. However, this may be a simplified view, since other observations are in favour of a specific anticonvulsant action of some psychotropic drugs.

Probably, the first report on a possible anticonvulsant effect of TCAs is that of Millichap in 1965.[117] Subsequent investigators have observed that low doses of imipramine reduced the frequency of absences and minor motor seizures in small groups of patients.[118-120] In particular, in a double-blind, crossover study, these authors reported a significant reduction in absence and myoclonic-astatic seizures in 5 of the 10 patients receiving imipramine, despite discontinuation of antiepileptic medication.[120] These findings are in line with other reports, suggesting a therapeutic effect of clomipramine against absences[121] and partial seizures[122] and of fluoxetine against partial seizures.[123] Since all these observations have been based on very few patients, any conclusion has to be taken cautiously.

Some data in animals reinforce the possibility that some psychotropic drugs may exert specific anticonvulsant action. In a series of elegant experiments in cats and mice, it has been demonstrated that imipramine exerts a clear biphasic effect on brain excitability with anticonvulsant effects occurring at lower doses and convulsant effects at higher doses.[124] The drug was most effective as an antiepileptic agent in those models of experimental epilepsy considered as models of major motor seizures, i.e. maximal electroshock seizures in mice, penicillin-induced epileptiform activity in cats and afterdischarge duration in cats.[124] In accordance with these results, it has been demonstrated that some antidepressants and antipsychotics exhibit anticonvulsant properties in various experimental models especially at low doses: imipramine and amitriptyline against maximal electroshock seizures in mice and afterdischarges in rabbits,[124-127] viloxazine against photosensitive epilepsy in baboons,[128] desipramine and doxepin against electroconvulsive fits in the genetically epilepsy-prone rat,[127,129,130] haloperidol against hippocampal kindled seizures in cats,[131] and clozapine against pentetrazol-induced convulsions in mice.[132] For most of these compounds, progressive increase in dosage resulted in an opposite effect, i.e. activation of EEG phenomena and/or occurrence of seizures.[133,134]

In a very interesting study,[135] a short period of treatment with amphetamine induced a remarkable and surprising improvement of the daytime and

night-time EEG activity in some patients with Landau-Kleffner syndrome (figure 6). This syndrome is characterised by the triad alteration of language, epilepsy and spike-wave discharges that increases during sleep. In the above-quoted study, EEG amelioration was also paralleled in a patient by a clear reduction of absences. These findings, however, were transitory.

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

4.2 Paradoxical Convulsant Effect of Antiepileptic Drugs

Some antiepileptic drugs are currently used as psychotropic drugs. Carbamazepine and valproic acid have a well established place among mood stabilisers and benzodiazepines are universally known to have potent antiepileptic and anxiolytic properties. Carbamazepine, in particular, has been most frequently involved in seizure aggravation. The drug has been described as having caused, in patients with generalised epilepsy and especially in children, exacerbation and even *de novo* induction of various types of seizures, including typical and atypical absences, atonic, tonic and myoclonic seizures, and absence status.[136-140]

In the case of valproic acid, although occurrence of myoclonic seizures may be caused by overdose,[141] its ability to exacerbate epileptic fits has been more frequently described in the context of severe hepatotoxicity[142] or toxic encephalopathy.[143]

Various benzodiazepines, including diazepam, nitrazepam, clonazepam and lorazepam, have been reported occasionally to precipitate tonic seizures amounting to tonic status.[144-148] Development of tonic seizures or tonic status has been also described in patients with Lennox-Gastaut syndrome after intravenous injection of a benzodiazepine for the treatment of absence status.[145-147] Recognising this event is very important to avoid further administration of the drug in an attempt to control seizures. It is to be stressed, however, that the phenomenon, given the number of patients receiving benzodiazepines, is a rare occurrence.

Analysis of the available data suggests that seizure aggravation may be the result of at least two causes: drug overdose[141,149] or inappropriate use of a given drug because of an erroneous diagnosis of seizure type/syndrome (e.g. carbamazepine in typical absences).[136-140] Different specific mechanisms may be involved, which are mediated by the γ-aminobutyric acid (GABA) system and other neurotransmitters. Discussion of these mechanisms is beyond the scope of this review and readers may refer to specific reviews.[150]

4.3 Do Psychotropic and Antiepileptic Drugs Share Some Common Mechanisms?

A very important question arising from the last two topics (antiepileptic effect of psychotropic drugs and seizure worsening caused by drugs primarily used as anticonvulsants) is whether the effects displayed by the two classes of drugs are totally or partly mediated by common mechanisms. The problem may also be expressed in terms of seizure precipitation by psychotropic drugs and psychotropic favourable effects of antiepileptic drugs. A deeper insight into this matter may provide great support in developing safer compounds and/or more advantageous drugs exerting both psychotropic and antiepileptic effects selectively and more efficiently. The specific literature is very scanty, and therefore this issue is largely a matter of speculation at present. Some authors[49] have suggested that antidepressants may trigger seizures because of their local anaesthetic or their antihistaminic/antimuscarinic action rather than because of their known property of blocking noradrenaline or serotonin reuptake. Indeed, the latter mechanism might explain, apart from the antidepressant effect,[150] their capacity to inhibit seizures. Increasing serotonergic transmission is associated with anticonvulsant action in animal models of epilepsy and in humans.[151-156] In particular, it has been recently demonstrated that carbamazepine increases the release of serotonin[157] and that depletion of serotonin greatly decreases the anticonvulsant

effect of the drug.[158] Apart from serotonergic pathways, additional mechanisms may be mediated by the GABA system. GABA has a well established role in the antiepileptic effect of some anticonvulsants and may also have an important function in the pathogenesis of mood disorders.[159] A possible example in which a role of GABA may be hypothesised to explain concomitant implementation of both effects is electroshock. This technique, commonly used to treat refractory depression, has been found to increase seizure threshold and has been proposed as antiepileptic treatment in patients with refractory epilepsy.[160-162]

Although involvement of the serotonin and GABA systems may, at least in part, account for possible coexistence of antidepressant and anticonvulsant effects, to date there is no convincing experimental evidence in favour of a given mechanism coupling both actions and, as stated above, this issue remains largely a matter of speculation.

5. Concluding Remarks and Future Directions

Analysis of the available literature indicates that psychotropic drugs may lower seizure threshold and provoke epileptic seizures. This adverse event probably occurs as a manifestation of two different conditions. The first is probably an unspecific symptom of drug intoxication, as is frequently seen in patients undergoing aggressive treatment with high drug dosages. Epileptic seizures, however, may also be triggered by therapeutic doses of compounds with a relatively high seizurogenic potential, such as maprotiline and clozapine, or even when predisposing factors coexist. Since anticipation of the phenomenon is virtually not feasible, it is advisable to adopt simple empirical rules to minimise the risk of seizures. A number of these recommendations in patients with psychiatric disorders without concomitant epilepsy and in patients with both epilepsy and psychiatric disorders is given in table IV. When psychotropic drugs are used properly, it must be emphasised that seizures have to be regarded as a rare adverse event, the incidence of which approaches that observed for seizure occurrence in the general population, that is, less than 0.1%.[15] Accordingly, in prospective studies, no significant changes in seizure frequency have been observed in patients with epilepsy undergoing treatment with some antidepressants, including amitriptyline, nomifensine or fluvoxamine.[93,163]

There are no homogeneous strategies to manage seizures once they occur. Hence, reduction of drug dose or shift to an alternative compound may primarily be considered;[164] however, addition of an antiepileptic drug has been also suggested.[165]

Use of psychotropic drugs in patients with epilepsy may be more problematic either because of possible complex pharmacokinetic and/or pharmacodynamic interactions between antiepileptic and psychotropic drugs or because of the abnormal seizure threshold of the patient. The question of which psychotropic drugs at therapeutic doses can be used safely in patients with epilepsy, although it was identified some decades ago, still merits great

Table IV. Practical recommendations to minimise the risk of epileptic seizures during treatment with psychotropic drugs

Patients with epilepsy and psychiatric disorders	Patients with psychiatric disorders but without epilepsy
Consider using antiepileptic drugs with psychotropic properties (e.g. carbamazepine, valproic acid, lamotrigine)	Check carefully for predisposing factors
Do not use drugs with a documented high seizurogenic potential	Give attention to acute, transitory clinical manifestations (differentiation between an epileptic seizure and various psychiatric states can be sometimes difficult)
Start with very low doses	In the case of manifestations of doubtful interpretation, an EEG record may clarify the situation
Proceed slowly with small dose increments	Consider that the risk of an epileptic seizure is increased with higher drug dose
Keep the lowest effective dosage	In the case of high drug doses being required for the severity of the psychiatric illness, adopt the precautions suggested for patients with epilepsy (left side of table)
Avoid complex multidrug therapies	
Whenever possible, monitor plasma drug concentrations	
Give attention to sudden electroencephalogram (EEG) changes	
If EEG and/or seizures worsen, consider the option of changing the psychotropic drug and/ or reinforcing/re-optimising antiepileptic therapy	

attention. As stated above, psychotropic medication in this population of patients may also exert beneficial effects. Apart from a possible positive influence on epilepsy induced by amelioration of the mental state, a specific antiepileptic mechanism of some psychotropic drugs may be hypothesised. This is an interesting concept and might be considered a field for future research. As stated above, carbamazepine and valproic acid have gained a well established place as mood stabilisers. Furthermore, among recently developed antiepileptic drugs, lamotrigine has proved to be efficacious in the prophylaxis of rapid-cycling bipolar disorder.[166] These drugs, therefore, are particularly useful in treating patients with epilepsy and psychiatric disturbances. Availability of additional drugs exhibiting both antiepileptic and, more specifically, antidepressant or antipsychotic effects is desirable and would represent a great therapeutic advantage in clinical practice.

With regard to currently available psychotropic drugs, the lack of direct comparisons among compounds and important differences in methodology of investigations performed make any conclusion only tentative and to be accepted cautiously. Table III shows a number of antidepressants and antipsychotics with their relative degree of risk for seizures during therapeutic use. However, it must be stressed that a considerable part of the information remains at a superficial level, and consequently a large part is left to the physician's experience in facing the problem of psychotropic-triggered seizures.

Further studies are required to correctly evaluate the prevalence of this phenomenon with a specific compound, to investigate the mechanisms by which drugs modulate neuronal excitability and attenuate psychic disorders, and to characterise additional prognostic factors that may be used for early identification of patients at risk.

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