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COMMENTARY

Antidepressants and Seizures: Clinical Anecdotes Overshadow Neuroscience

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ABSTRACT. Pharmacological treatment of depression in persons with epilepsy has been an area of controversy because some drugs commonly are perceived specifically to induce or exacerbate seizures in patients with seizure disorders. This prevailing misconception is unjustified by scientific studies, yet it continues to prevent afflicted persons from receiving appropriate therapy. The scientific literature shows that tricyclic antidepressant drugs cause seizures in overdose in both animals and humans. In lower doses, these drugs have anticonvulsant activity in humans and animals. Thus, the antidepressant drugs are like several antiepileptic drugs that can both prevent and cause seizures. The anticonvulsant activity of antidepressant drugs has been studied extensively in animals and almost certainly stems from their capacity to block norepinephrine and/or serotonin reuptake. The pharmacodynamic action responsible for their convulsant effects has not been well studied but may be due to their local anesthetic, antihistaminic, or antimuscarinic activity. The newer, more selective monoamine uptake blockers have very low convulsant liability, and it is suggested that their anticonvulsant activity, which is well documented in animals, be investigated further in humans. If their effects in humans are analogous to those in animals, these drugs can be used safely in epileptic patients with depression, and it is possible that their anticonvulsant activity can be exploited for use in the treatment of epilepsy. BIOCHEM PHARMACOL 52;9:1323–1329, 1996. *Copyright © 1996 Elsevier Science Inc.*

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Chronic illnesses are associated with a high incidence of severe depression. In the treatment of epilepsy, it is often necessary to treat depression. The treatment of depression in persons with epilepsy has been an area of debate and controversy, since some treatments commonly have been perceived to induce or exacerbate seizures. This prevailing misconception, like many truisms in medical therapy, is unjustified by scientific studies. Even worse, it continues to prevent afflicted persons from receiving proper therapy. This commentary summarizes current scientific data surrounding the use of antidepressant drugs in patients with seizure disorders.

CONVULSIONS INDUCED BY ANTIDEPRESSANT DRUGS

There is a considerable body of evidence that overdose with antidepressant drugs, particularly those with the tricyclic structure, can produce convulsions. These convulsions may be induced in virtually every mammalian species that has been investigated. This pharmacodynamic action of this class of drugs is well recognized by clinicians and neuroscientists. Since an important pharmacologic mechanism of these drugs is to block the neuronal reuptake of norepinephrine and serotonin, many clinicians and neuroscientists maintain the belief that this mechanism is responsible for inducing convulsions. However, there is an almost overwhelming body of animal data and a number of human studies showing that norepinephrine and serotonin function as anticonvulsant neurotransmitters. Nonetheless, the frequency and fervor with which this statement is repeated in the clinical arena have made it into an *ipse dixit* fallacy: "*Everyone knows* that the tricyclic antidepressants cause convulsions because they block norepinephrine and/or serotonin reuptake. This is a case where the animal data do not predict the human response." As in most biology, the animal data *do* predict the human response. Animal studies show that antidepressants have both anticonvulsant and convulsant properties, and the anticonvulsant properties are most likely mediated by blockade of serotonin and/or norepinephrine reuptake.

NOREPINEPHRINE, SEROTONIN, AND SEIZURES

Norepinephrine attenuates seizures in virtually every animal species in which it has been investigated, including

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mice, rats, cats, dogs, rhesus monkeys, baboons, and humans [1–4]. An important exception to this generalization is the tottering mouse model in which excessive noradrenergic innervation is associated with increased seizure sensitivity [5, 6]. Serotonin, like norepinephrine, plays an anticonvulsant role in most mammalian seizure models [7–11]. An in-depth review of the literature supporting a role for norepinephrine and serotonin in reducing human seizure predisposition is beyond the scope of this commentary. For a review, the reader is referred to an earlier work by Snead [12].

CONVULSANT AND ANTICONVULSANT PROPERTIES OF ANTIDEPRESSANT DRUGS

That antidepressant drugs can produce convulsions in humans is well established. Less well known is that these drugs also can produce convulsions in many other species and animal models including: epileptic rats [13], epileptic mice, epileptic baboons [14], non-epileptic rats [13, 15], cats [16], and rhesus monkeys [17]. Very few studies have addressed the pharmacodynamic properties that cause these drugs to produce convulsant effects. One such study was carried out in our laboratories. If blockade of serotonin or norepinephrine reuptake were responsible for the convulsant properties of these drugs, then depletion of these monoamines in brain should prevent the convulsions produced by high doses of tricyclic antidepressant or at least increase the dose of antidepressant required to produce convulsions. We found that depletion of brain monoamines with reserpine did not change the incidence of convulsions caused by large doses of desipramine in genetically epilepsy-prone rats or non-epileptic Sprague–Dawley rats. These results are shown in Table 1.

Since depletion of monoamines did not change the convulsant properties of desipramine, it is very unlikely that desipramine produced convulsions by blocking norepinephrine or serotonin reuptake. Thus, the data indicate that blockade of norepinephrine and/or serotonin reuptake is not responsible for the convulsant properties of this drug. Other evidence strongly suggests that increasing extracellular norepinephrine and/or serotonin produces an anticonvulsant effect [1–4, 7–12].

Although most, if not all, antidepressant drugs have been reported to cause seizures, the risk of seizures appears to be very low during usual therapy. When drug monitoring has been instituted to avoid high drug levels, the risk of seizures has been estimated at only 0.4% [18]. Not all antidepressants have equal convulsant liability. The tricyclic antidepressants produce more overall toxicity and more seizures than do the selective monoamine oxidase-A inhibitors and the selective serotonin reuptake inhibitors [19–22]. Among the atypical antidepressants, bupropion has more convulsant liability than does trazodone which produces a low incidence of seizures in overdose [21, 22]. The selective serotonin reuptake inhibitors fluoxetine, sertraline, and fluvoxamine carry a much lower seizure risk than do the tricyclic antidepressants or bupropion [19–23]. In one study, forty-four reported fluoxetine overdoses were studied retrospectively. In none of these patients was fluoxetine overdose associated with seizures [23].

TABLE 1. Effect of monoamine depletion on desipramine-induced convulsions

Drugs	Fraction convulsing	
	GEPR-3	Non-epileptic control
Reserpine, 5 mg/kg, + desipramine, 66 mg/kg	23/30	21/30
Vehicle + desipramine, 66 mg/kg	24/30	20/29

In the most recent edition of Goodman and Gilman's *The Pharmacological Basis of Therapeutics*, Baldessarini [24] prepared a table listing side-effects for antidepressant drugs. In this table (pp. 433–435), he lists the seizure liability for a large number of antidepressants. Among those compounds with increased risk were: bupropion (4+), maprotiline (3+), amitriptyline (2+), doxepin (2+), imipramine (2+), nortriptyline (+), and desipramine (+). At the other end of the spectrum were: trazodone (0), sertraline (0), paroxetine (0), fluvoxamine (0), and fluoxetine (0/+). All of these compounds block either norepinephrine and/or serotonin reuptake, yet some have significant seizure risk while others have a relatively small seizure risk. Thus, it does not seem reasonable to assume that the compounds with the significant seizure risk produce seizures *because* they block norepinephrine and/or serotonin reuptake.

Although the scientific literature effectively shows the existence of the anticonvulsant properties of antidepressants, these effects are less well known and have not been exploited for antiepileptic drug development. Nevertheless, antidepressant drugs have anticonvulsant properties that may be observed across a number of species [14, 23–34]. In humans, anticonvulsant properties of tricyclic antidepressants have been demonstrated in retrospective and prospective studies including case reports, open label studies, and double-blind crossover studies [35–38].

An early report of an antiepileptic effect of tricyclic antidepressants was published by Millichap [35]. Also, Fromm *et al.* [36] reported that low doses of imipramine suppress convulsive seizures. A more detailed study of imipramine subsequently appeared [37]. In this study of 20 refractory patients with petit mal or minor motor seizures, 15 exhibited at least a 50% decrease in seizure frequency, with 11 having a 90–100% reduction. Subsequently, Fromm *et al.* [38] reported a double-blind crossover study with imipramine in patients with absence and myoclonic-astatic seizures. A significant reduction in seizure frequency occurred in 5 of the 10 patients despite discontinuation of other antiepileptic medication. Finally, Ojemann *et al.* [39] reported a retrospective study of the antidepressant doxepin on seizure frequency in persons with both epilepsy and de-

pression. In this study, 15 of 19 patients had improved seizure control while on doxepin.

Recently, anticonvulsant properties for fluoxetine, a selective serotonin reuptake blocker, have been reported [40]. In this unblinded, open-label, add-on trial in 17 patients with partial seizures with and without secondary generalization, 6 patients showed complete disappearance of their daily seizures. In the remaining patients, seizures decreased by 30%. The mean follow-up duration was 14 months. This positive report was offset by another study in a similar group of patients in which fluoxetine was found to have no demonstrable anticonvulsant effect [41].

Drug dose appears to be the most prominent factor in determining whether antidepressant drugs produce anticonvulsant or convulsant effects. The acute convulsant ED_{50} for antidepressants appears to be approximately 2- to 9-fold higher than the anticonvulsant ED_{50} in genetically epilepsy-prone rats (GEPRs) [13, 15], genetically epileptic baboons [14], and in non-epileptic cats and mice [31, 42]. In humans, dose also plays the same prominent role in determining whether antidepressant drugs produce convulsant or anticonvulsant effects [37, 43].

An additional question that must be addressed is why tricyclic antidepressants sometimes appear to produce convulsions even when they are given in therapeutic doses [21]. A potential explanation can be found in a report by Preskorn and Fast [18]. These authors examined plasma levels of tricyclic antidepressants (doxepin, desipramine, imipramine, or amitriptyline) in patients who experienced convulsions while ingesting usual "therapeutic doses." Usual therapeutic doses of these compounds produce plasma levels in the therapeutic range of approximately 30–300 ng/mL depending on the drug [44]. The plasma levels in the patients experiencing seizures ranged from 438 to 1200 ng/mL and far exceeded the therapeutic plasma level in each case. According to Preskorn and Fast [18], there are no reports in the literature of tricyclic-induced seizures at *therapeutic plasma concentrations*. These investigators suggest that patients who exhibit convulsions in response to "therapeutic doses" of antidepressants are slow metabolizers of these drugs.

Studies in our laboratories support the concept that blockade of serotonin and/or norepinephrine reuptake accounts for the anticonvulsant properties of antidepressant drugs. Drug-induced depletion of norepinephrine abolishes the anticonvulsant effect produced by imipramine in genetically epilepsy-prone rats [45]. Similarly, depletion of serotonin greatly reduces the anticonvulsant effect of fluoxetine [46]. Enhancing serotonin release by combining 5-hydroxytryptophan and fluoxetine synergistically increases extracellular brain serotonin and the anticonvulsant effect of these two drugs [47, 48]. Finally, we and others have found that some established and experimental antiepileptic drugs (carbamazepine [49], valproate [50, 51], antiepilepsirine [49], loreclezole [52]) increase extracellular serotonin as part of their anticonvulsant mechanism of action. Thus, we have concluded, based on the literature and our own studies, that the anticonvulsant properties of antidepressant drugs are due to the effects these drugs have on norepinephrine and/or serotonin in brain.

CASE REPORTS OF ANTIDEPRESSANT-INDUCED CONVULSIONS

The literature is replete with case reports describing seizures or convulsions that occur in patients who are taking antidepressants. The conventional wisdom is that patients who suffer from pre-existing seizure disorders are more likely to experience convulsions from antidepressant drugs than are patients without an underlying seizure disorder. This may or may not be the case since there is insufficient rigorous prospective human scientific data on which to draw a valid conclusion. Undoubtedly, many of these studies accurately concluded that antidepressants did, in fact, cause convulsions. However, the patients may have taken an overdose or may be slow metabolizers and attained antidepressant blood levels high enough to produce convulsions. This scenario would induce convulsions in patients regardless of whether they have an underlying seizure disorder. Whether individuals with an underlying seizure disorder experience greater risk for antidepressant-induced seizures remains, in our view, an open question. When these persons experience an increase in seizure frequency, it is rarely assumed that antiepileptic drugs caused the seizure. However, if a person with epilepsy has an exacerbation of seizures while being medicated with an antidepressant drug, it is often presumed that the drug was the causative agent. Antidepressant drugs do have the capacity to induce seizures, yet so do antiepileptic drugs [53]. Indeed, antidepressants and antiepileptic drugs are similar in that they can both cause and prevent seizures. We do not wish to leave the impression that antiepileptic drugs are as likely to induce seizures as are antidepressant drugs. They are not. We do wish to emphasize that patients with a seizure disorder are more likely to have seizures than are normal individuals. This fact is rarely considered in case reports "documenting" increased sensitivity to "antidepressant-induced convulsions" in epileptic patients.

As noted above, there is a paucity of evidence to show that patients with seizure disorders are more likely to experience antidepressant-induced convulsions than are normal individuals. In animal studies in our laboratories, overdoses of three different tricyclic antidepressant drugs were no more likely to cause convulsions in epileptic rats than in non-epileptic rats [13]. In our view, more study of this issue is warranted, because many patients with seizure disorders and depression have antidepressant medications withheld because of fears that treatment of the depression may cause the patients to experience convulsions.

ANTIDEPRESSANTS AND POTENTIAL CONVULSANT MECHANISMS

Tricyclic antidepressants found their way into clinical use after medicinal chemists synthesized, in the 1940s, a series

of more than 40 iminodibenzyl derivatives for possible use as antihistamines, sedatives, analgesics, and antiparkinsonian drugs [24]. One of these compounds was the tricyclic antidepressant imipramine. In 1950, a phenothiazine, chlorpromazine, was synthesized in France as part of a program designed to produce antihistamines and sedatives. The chemical structures of carbamazepine, chlorpromazine, and imipramine are shown in Fig. 1. Note that an important difference in these structures is that the sulfur in the phenothiazine is replaced with a two-carbon bridge which creates a seven-member ring in imipramine and carbamazepine, an antiepileptic drug developed later. The structural similarity between imipramine and carbamazepine initially caused us to examine the effect of carbamazepine on norepinephrine and serotonin release using *in vivo* microdialysis [49]. As noted previously, we found that as part of its anticonvulsant mechanism of action carbamazepine increases extracellular serotonin. Since phenothiazines and tricyclic antidepressants both resulted from drug development programs designed to produce similar products, it should not be surprising that they have some similar pharmacodynamic actions. An early European trade name for chlorpromazine, Largactil, acknowledges that this drug has a large number of pharmacodynamic actions. Indeed, among their pharmacodynamic effects, both chlorpromazine and imipramine cause prominent sedation, considerable antimuscarinic effects, α-adrenergic blockade, local anesthesia, and antihistaminic effects, and *both produce convulsions in overdose*. Indeed, it is characteristic that all phenothiazines and tricyclic antidepressants can produce convulsions when there is an overdose or their blood levels become sufficiently high [24, 54].

Phenothiazines and tricyclic antidepressants each produce a major pharmacodynamic effect that is not prominent in the other. Phenothiazines block dopamine receptors, and tricyclic antidepressants block norepinephrine and/or serotonin reuptake. These pharmacodynamic actions are thought to account for their respective therapeutic uses as antischizophrenics and antidepressants [24, 54]. Most who have studied the pharmacology of these compounds usually ascribe the convulsant properties of these compounds to pharmacodynamic actions they have in common rather than actions they do not share. It should be noted that drug-induced convulsions frequently are present after overdoses of antimuscarinic drugs [55], antihistamines [56], and local anesthetics [57]. As noted previously, these pharmacodynamic actions are shared by many phenothiazines and tricyclic antidepressants.

According to a recent evaluation of poisonings reported to the San Francisco Bay Area Regional Poison Control Center, the leading causes of seizures reported to the center were the cyclic antidepressants (55 cases, 29%); cocaine, a local anesthetic, and other stimulants (55 cases, 29%); and diphenhydramine and other antihistamines (14 cases, 7%) [58]. Thus, two classes of drugs that share properties (local anesthetic and antihistaminic) inherent in the structure of tricyclic antidepressants are among the leading causes of seizures caused by all types of drug overdoses.

In two recent studies of toxicities from drug overdose, the convulsant liability of tricyclic antidepressants [59] and neuroleptics [60] was evaluated. Among 388 patients admitted for tricyclic antidepressant overdose, 6.2% experienced seizures [59] while the rate of seizures among 299 patients overdosed on neuroleptics was between 1 and 2% [60]. These rates are from patients who were presumed to have taken an overdose of only one drug. When all of the possible variables (magnitude of overdose, age, gender, seizure predisposition, overall health, etc.) are considered, the *rates* of drug-induced seizures for overdoses of tricyclic antidepressants and for neuroleptics are not markedly different.

Most clinicians would probably agree that tricyclic antidepressant-induced convulsions occur much more frequently than those induced by phenothiazines. Indeed, tricyclic antidepressant overdose is reported to be the most common cause of death from prescription drugs [61], and convulsions have long been known to be a complication of tricyclic antidepressant overdose [62]. However, the reason that tricyclic antidepressant-induced seizures occur more frequently than do neuroleptic-induced seizures may be as much related to the diseases for which these drugs are used as to the drugs themselves. Although both phenothiazines and tricyclic antidepressant drugs have more than one therapeutic use, they are used principally for different psychiatric disorders. High doses of phenothiazines are used primarily for schizophrenia, whereas high doses of antide-

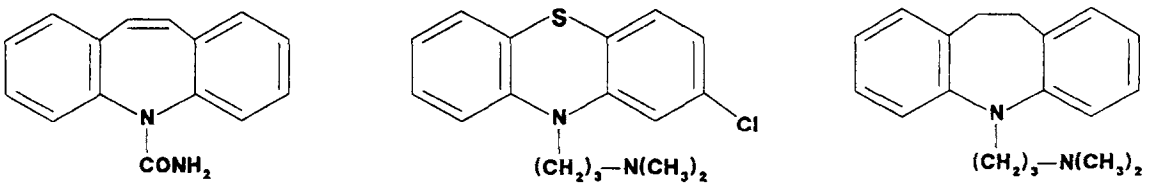

FIG. 1. Chemical structures of carbamazepine, chlorpromazine, and imipramine.

pressants are used mainly for severe depression. More convulsions are seen with tricyclic antidepressants, at least in part, because depression is more common than schizophrenia. In the United States, the lifetime prevalence of schizophrenia is 0.6 to 1.9% of the population [63], while the lifetime prevalence of depression has been reported to be as high as 18% with more conservative estimates of 3.2 to 6.4% [64]. Since depression is more common than schizophrenia, more convulsions are seen with antidepressant therapy. Additionally, persons with severe depression attempt suicide, often by overdosing with their antidepressant medication. Finally, depression occurs frequently in patients with epilepsy, and many of these individuals will have seizures regardless of their drug therapy [65].

Over the last several years, the belief that drugs which block monoamine reuptake cause seizures has been reinforced by mass media reports of prominent individuals dying from cocaine overdose, and from a variety of reports that patients taking therapeutic doses of tricyclic antidepressants have experienced convulsions. Although both cocaine and tricyclic antidepressants block monoamine reuptake, cocaine is also a potent and very effective local anesthetic. Local anesthetics are well known to cause convulsions in overdose [57].

Taken together, the total body of information strongly suggests that the pharmacodynamic action by which antidepressant drugs cause seizures is unrelated to their ability to block norepinephrine or serotonin reuptake. Rather, it seems more likely that these drugs produce convulsions by virtue of their local anesthetic or their antihistaminic/antimuscarinic properties.

In summary, antidepressant drugs have both convulsant and anticonvulsant properties. The anticonvulsant properties predominate at lower doses, while the convulsant properties become prominent at higher doses or higher blood levels. The tricyclic antidepressant drugs produce more overall neurotoxicities and a higher incidence of seizures than do the selective serotonin reuptake blockers. The weight of scientific evidence strongly suggests that increasing extracellular norepinephrine and/or serotonin by blockade of the reuptake of these monoamines is the pharmacodynamic action responsible for the anticonvulsant effects of antidepressants. The convulsant properties of tricyclic antidepressants probably result either from their local anesthetic, antihistaminic, or antimuscarinic properties. Studies should be undertaken to identify the pharmacodynamic properties that enable these compounds to produce convulsions so that these properties can be eliminated from drugs developed in the future. Studies also should define the antiepileptic potential of the newer antidepressants that may prove useful for the treatment of epilepsy.

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