

THE ROLE OF THIRD-GENERATION ANTICONVULSANTS IN THE TREATMENT OF BIPOLAR DISORDER

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The history of the psychopharmacology is, to a great extent, the history of drugs with anticonvulsive action. Just by mentioning barbiturates, benzodiazepines, or carbamazepine and valproate, one may understand the reach and the impact of this class of compounds in the treatment of the psychiatric disorders throughout history. The reasons are diverse: the consideration of epilepsy as a mental disorder during centuries (what, in fact, supposed a progress on its consideration as states of demonic possession or witchcraft), the sedative action of many of them (when Psychiatry just aspired to tranquilize the patients), and the more recent availability of good epilepsy animal models. All of them have contributed to promote the investigation and the use of this type of drugs in several indications beyond neurology. In the last decades, the discovery of their mood stabilizing properties has enhanced their use as alternatives to lithium in the treatment of bipolar disorder, but as we will see many of them have not demonstrated a comparable effectiveness to lithium, and in many cases not even superior to placebo. In addition to the mood stabilizing properties of some of them, favorable effects have been described on impulsivity, aggressive behavior, anxiety, eating disorders, and addictions. For this reason their utility is greater in bipolar patients with comorbid conditions, rather than in pure manic-depressive patients. The psychiatric comorbid conditions in which the mentioned properties can be from special interest are personality disorders, eating disorders, addictions, and also atypical forms of bipolar disorder.

Table 1 shows the historical evolution based on the commercialization of new anticonvulsants, that not always agrees with the chronology of synthesis of the compound. For example, oxcarbazepine has been commercialized in several countries since a few years, although it was synthesized in the Seventies.

Lamotrigine was the third antiepileptic of new generation in being commercialized, after vigabatrin and felbamate. These two drugs have not been studied as mood-stabilizers because after their commercialization as antiepileptics important idiosyncratic side-effects were discovered, such as visual field problems or aplastic anemia, that have limited their use to very special cases

of epilepsy (for example, Lennox-Gastaut syndrome). Lamotrigine seems to act through the inhibition of the presynaptic liberation of glutamate, although it also blocks sodium channels and serotonergic receptors (5HT₃) (Ketter et al. 1997). Among all third-generation anticonvulsants, it is so far no doubt the one that has obtained the best results in controlled trials for bipolar disorder. Lamotrigine is, unlike second-generation drugs, which prevent better mania than depression, especially effective in patients with predominance of depressive episodes. One disadvantage is the risk of serious rash, which may rarely happen (3 by thousands), unlike benign rash, which is quite common (10% of the cases), and can be reduced by titrating the doses slowly (Vieta 2003). Its potential effectiveness in rapid cyclers has been suggested, as an add-on to the usual treatment regimen (Calabrese et al. 1996, Fatemi et al. 1997), but in a controlled clinical trial with placebo the data were only positive in bipolar II patients (Calabrese et al. 2000).

The most interesting characteristic of lamotrigine is its antidepressant mood-stabilizer profile. Indeed, the results of a double-blind clinical trial against placebo confirmed its effectiveness at a dose between 50 and 200 mg/day in bipolar depression (Calabrese et al. 1999), although the improvement in the Hamilton depression scale, that was the primary variable of efficacy, was not significant. Another study suggested that lamotrigine would be particularly indicated in depressed bipolar II patients (Vieta et al. 2003a). However, lamotrigine does not seem to have strong antimanic properties, since two placebo-controlled double blind trials have been negative in acute mania (Bowden and Karren 2002). The risk of switch from depression to mania, nevertheless, is not superior to the one of placebo. As mentioned, the real strength of lamotrigine is in the long-term treatment. Lamotrigine has excellent studies in prophylaxis of relapses in bipolar disorder. Two double-blind, randomized trials compared the effectiveness of lamotrigine versus lithium and placebo throughout 18 months. Altogether, both trials indicated that lithium was superior to lamotrigine and placebo in the prevention of manic phases, and that lamotrigine was superior to lithium and placebo in the prevention of depressive phases (Bowden

et al. 2003, Calabrese et al. 2003a). These results confirm the characteristically antidepressant profile of lamotrigine as a mood-stabilizer, unlike drugs available until now, and suggests the possibility of combining it with lithium to obtain more symmetrical results in the prevention of relapses (Calabrese et al. 2003b). Further analyses of pooled data from these two studies suggest that lamotrigine has also some efficacy in the prevention of mania (Goodwin et al. 2004). The incidence of weight gain is low, and its tolerability profile is, generally, rather favorable, in spite of the feared and infrequent Syndrome of Stevens-Johnson. Benign rash, as an isolated symptom, is generally maculo-papular and it appears in near a 10% of the cases. The usual doses for affective disorders range between 150 and the 225 mg/day (Fatemi et al. 1997), although can be raised up to 500 mg/day (Dichter and Brodie 1996), but to reduce to the incidence and the inherent risks of rash, a slow titration of the dose when initiating the treatment becomes crucial (Vieta 2003). Treatment should be started without surpassing the 25 mg per week of increase, and stopping the drug to the first indication of serious skin reaction. The combination of lithium and lamotrigine seems safe and could be useful in refractory bipolar depressions (Freeman and Stoll 1998), and the combination with valproate or carbamazepine is also possible, although it has more risks of interactions (Calabrese et al. 2003b), thus requiring different titration speeds.

Gabapentin was synthesized as an analog of the gamma-aminobutyric acid (GABA), which is the main inhibiting neurotransmitter of the central nervous system. It was tried to obtain a clean, almost physiological compound, with a gabergic action and profile that would provide antiepileptic, anxiolytic and analgesic properties. It was one of the first third-generation anticonvulsants to be studied in bipolar disorder, and like almost them all, it was firstly evaluated in the treatment of mania. Although it has a good tolerability and interactions profile, the doses that presumably could be effective for acute episodes are uncertain and might turn out to be too high to be acceptable, given its short half-life (Dubovsky and Buzan 1997). Although open studies were mainly positive (McElroy et al. 1997, Stanton et al. 1997, Cabras et al. 1999), two controlled trials were negative (Frye et al. 2000, Pande et al. 2000) and raised remarkable doubts about its effectiveness. In the first of them (Frye et al. 2000), lamotrigine was demonstrated superior to gabapentin. In the second, surprisingly enough, placebo surpassed gabapentin in manic patients treated with lithium (Pande et al. 2000). However, a randomized double blind trial against placebo in social phobia was positive (Pande et al. 1999). In fact, open studies already could not demonstrate, like in the clinical trials, any sign of antimanic effectiveness, but a mild antidepressant action due to, mainly, improvement of anxious symptoms (Vieta et al. 2000, Wang et al. 2002, Carta et al. 2003). Actually, Perugi et al. (2002) have suggested that comorbid panic disorder and alcohol abuse would be predictors of response to gabapentin in bipolar patients. Therefore, gabapentin could be an interesting medicine as an adjunct of other mood-stabilizers in cases with great component of anxiety, which are quite frequent (Vieta 1999a). It is particularly ad-

equated at the present moment, at which many authors plead for combination treatment to delay the natural progress of the disease towards the shortening of the periods of remission (Post et al. 1998). However, more methodologically solid data are necessary that support its possible utility as a mood-stabilizer, and unfortunately the soundest studies have been carried in mania, where it clearly has no role. There is still a chance that some of these drugs may not work very well during acute episodes, but be useful for prophylaxis.

The history of the topiramate is very paradigmatic of how the investigation with potentially anticonvulsive drugs is evolving. Topiramate was initially synthesized as an antidiabetic drug. In fact, it is a sugar, a derivative of the molecule of fructose. This explains many of the peculiarities of this compound. After verifying that its potential effectiveness in diabetes was very limited, the molecule was evaluated in several animal models for different diseases, showing anticonvulsant properties in rats. Preclinical research demonstrated that the presumed antidiabetic was a powerful antiepileptic drug. Topiramate has a complex mechanism of action, which combines the selective blockade of glutamate receptors, with a calcium-antagonist action, the inhibition of the GABA and the inhibition of carbonic anhydrase (Marcotte 1998). Clinically, it is supposed to combine common therapeutic mechanisms of carbamazepine and valproate (Marcotte 1998), yielding a strong anticonvulsant action (which might supposedly correlate with the antimanic effect). An outstanding characteristic of topiramate is that it is associated to significant reduction of body weight (Perugi et al. 2002), unlike most of the treatments available until now for bipolar disorder. Numerous open studies suggested that it could be an effective add-on therapy for bipolar disorder (Marcotte 1998, Gordon and Price 1999, Vieta et al. 2003b, Chengappa et al. 1999, McElroy et al. 2000), and that it might work as antimanic even in monotherapy (Calabrese et al. 2001). Others, describing quite a modest effectiveness (Vieta et al. 2001) suggested that it could rather have prophylactic than acute efficacy (Vieta et al. 2002), and be particularly helpful to control the weight gain of the patients who receive adjunctive atypical antipsychotics (Vieta et al. 2003c, Vieta et al. 2004). The truth is that to date, nevertheless, no randomized placebo-controlled trial has been able to demonstrate its advocated efficacy in bipolar illness (Chengappa et al. 2001). For this reason, its use is being focused on patients with overweight or comorbid conditions, such as bulimia (Hoopes et al. 2003), binge eating (McElroy et al. 2003), as well as in alcoholism (Johnson et al. 2003), in which already it has demonstrated that it may be useful.

Tiagabine was synthesized looking for an action of enhancement of the inhibiting activity of the GABA, and works by inhibition of its reuptake. It is commercialized for the treatment of some forms of resistant epilepsy. There are little references beyond the theoretical scope with respect to its use on psychiatric disorders, except for preliminary results of a German trial in 8 manic patients, who did not improve (Grunze et al. 1999), and some other moderately positive clinical studies in refractory patients (Shaffer and Schaffer 1999). Recently, a study by the Stanley Bipolar Network, indi-

cated that tiagabine would have little or null mood-stabilizing properties, with certain risk of induction of seizures (Suppes et al. 2002). It seems very unlikely, therefore, that tiagabine ends being a treatment used in bipolar disorder. It is probable that the enhancement of the GABA plays a marginal role in the treatment of mania, and for this reason antiepileptic drugs such as phenobarbital, ethosuximide, baclofen, vigabatrin, gabapentin, pregabalin and tiagabine seem less effective in that indication (Post and Speer 2002).

Oxcarbazepine was developed in the Seventies, in a typical pharmacosynthesis strategy, as an improved alternative for carbamazepine. In fact, it is a 10-keto analog of the carbamazepine. Although its commercialization is relatively recent, it is a quite old patent that was already tried years ago in manic-depressive patients in a few randomized open studies, and showed effectiveness near 50% (Emrich et al. 1985, Cabrera et al. 1986, Kouzavkova et al. 1996). Its main interest stands in its possible analogy with carbamazepine with respect to the therapeutic profile, improving the tolerability and interactions (Spina and Perugi 2004). The only side-effect of oxcarbazepine that seems to be more frequent than with carbamazepine is hyponatremia, which rarely implies clinically relevant complications. Most studies on bipolar patients used doses between 600 and 1200 mg/day. Other antiepileptics, such as carbamazepine, phenytoin, phenobarbital and valproate may reduce oxcarbazepine serum levels between 20 and a 40% (Dietrich et al. 2001). For this reason, adjustments of dose may be necessary in combined treatments. Contraceptives with greater dose of estrogens are also advised during oxcarbazepine therapy, as it may slightly reduce their effectiveness. In addition to the initial studies from the 80's, limited but recent experience with the use of oxcarbazepine in bipolar patients exists. Series of cases with good response have been communicated (Dietrich et al. 2001, Ghaemi et al. 2002, Benedetti et al. 2004) and an open study with 12 mildly manic patients reported good results with oxcarbazepine in some patients, who worsened when interrupting the use of the drug and returned to improve again when taking it for second time (Hummel et al. 2002). This experience has been replicated with another design, in which the effectiveness of oxcarbazepine in bipolar II patients was evaluated during an hypomanic episode (Comes et al. 2003). At the present time new controlled trials are ongoing in order to confirm the results of the initial studies, which suggested effectiveness but had several methodologic limitations. In any case, the American Association of Psychiatry already advises the use of oxcarbazepine like a reasonable option in the treatment of bipolar patients who do not respond to the established treatments (APA 2002), but it will be necessary to wait to the ongoing trials to confirm its possibilities in maintenance treatment as mood-stabilizer.

Levetiracetam is a third generation anticonvulsant with a mechanism of action that is not well known so far. Levetiracetam treatment seems to be associated to depressed mood in epileptic patients, what makes it a potential antimanic drug. There are hardly few data published to date of its use in psychiatric disorders, except a case of good response to 2,500 mg/day in a manic

patient (Goldberg and Burdick 2002). Studies are being made in the United States, Germany and Spain to explore its possibilities as mood-stabilizer. Recently, its possible effectiveness in the prevention of drug-induced hypomania in the elderly bipolar II has been communicated (Soria and Remedi 2002), and so its possible utility in acute mania combined with haloperidol (Grunze et al. 2003).

Pregabalin seems to have a mechanism of action similar to gabapentin, acting on the sodium channels and facilitating GABA inhibiting action. Although clinical trials have been carried in bipolar patients, the results have not been communicated to date, and the investigation has focused more on anxiety disorders (social phobia, panic disorder, generalized anxiety disorder) and neuropathic pain, where it seems to have more possibilities.

Zonisamide is an antiepileptic developed in Japan that is already available in the United States, but has not been commercialized in Europe yet. It counts already on one specific study in bipolar patients (Kanba et al. 1994). This study suggested that it could be a useful drug for the treatment of mania, but no further trials have been published to verify this information. There are doubts with respect to the linearity of its pharmacokinetics (Vieta 1999b) and, therefore, of the optimal doses in bipolar disorder. It is associated, like topiramate, to loss of weight.

Retigabine is an anticonvulsant with a probable GABA-agonistic action and an interesting action on the potassium channels, which has been used effectively in combination with other anticonvulsants in partial seizures. Its use as a mood-stabilizer has not been evaluated yet.

Licarbazepine is the main active metabolite of oxcarbazepine. Hence, its mechanism of action is very similar, and it consists on the blockade of voltage-sensitive sodium channels, increased conductance of potassium, and modulation of calcium channels. Controlled trials are ongoing in order to test its safety and efficacy in bipolar illness.

The great increase of the use of antiepileptics that has been a constant in the history of Psychiatry, came with the demonstration of the antimanic effectiveness of valproate, in its bivalent form (divalproex), and its commercialization in the United States as antimanic in the middle of the nineties. Although carbamazepine was already being used in Europe as a substitute of lithium or in combination in treatment-resistant cases, the commercial success of divalproex was the ultimate reason that stimulated the evaluation of third-generation anticonvulsants in the treatment of bipolar disorder. Further to the promise of less side-effects and interactions, minor toxicity and teratogeny, and no need of blood monitoring, already verified in epilepsy, the new antiepileptics were seen as candidates to replace lithium and second-generation anticonvulsants in the treatment of a pathology that constituted an emergent market, such as bipolar disorder, and the back door to the huge market of other clinically-related mental disorders.

Table 1. *The novel antiepileptics as new mood-stabilizers*

Drug	Efficacy Doses (mg/day)			Doses (mg/day)	Side Effects
	Mania	Depression	Prophylaxis		
Gabapentin	-	-/+	?	900-3200	Somnolence, fatigue, ataxia, instability, dyspepsia
Lamotrigine	-	++	++	50-400	Rash, migraine, ataxia, diplopia, tremor, dyspepsia, instability
Levetiracetam	-/+	?	?	1000-3000	Depression, somnolence, anxiety
Licarbazepine	?	?	?	750-2500	Dizziness, diplopia, instability, fatigue, hyponatremia
Oxcarbazepine	+	?	+	600-1800	Instability, diplopia, ataxia, migraines, weakness, rash, Hyponatremia
Pregabalin	-	?	?	150-600	Cognitive problems, Somnolence, instability
Retigabine	?	?	?	400-1200	Cognitive problems, asthenia, migraine, somnolence, nausea, tremor,
Tiagabine	-	?	?	4-20	Confusion, instability, dyspepsia, anorexia, seizures
Topiramate	-	-/+	-/+	100-500	Cognitive problems Paresthesia, loss of weight, instability, ataxia, migraine, myopia, kidney stones
Zonisamide	-/+	?	?	100-600	Somnolence, migraines, instability, ataxia, kidney stones.

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