Anticonvulsant drugs in bipolar disorder

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Although much progress has been made in successfully treating bipolar disorder, there is increasing awareness of the limitations of traditional treatment regimens such as lithium and neuroleptics. The large family of anticonvulsant drugs, however, appears to be capable of providing new treatment options, not only as medication of second choice in patients refractory to treatment, but often as a treatment standard with high efficacy and low incidence of side effects. Besides established mood stabilizers such as carbamazepine and valproate, new antiepileptic drugs are entering the field with promising initial results in the treatment of bipolar patients. Furthermore, bringing to light the mechanisms of action of anticonvulsants and the similarities between anticonvulsants effective in bipolar disorder may also deepen our understanding of the pathophysiological basis of the disorder.

Keywords: *anticonvulsant; bipolar disorder; mania; depression; prophylaxis; carbamazepine; valproate*

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Recent epidemiological studies on the prevalence of bipolar disorder (BD), as defined by the ***Diagnostic and Statistical Manual of Mental Disorders,*** IVth edition (DSM IV),[1] have revealed a lifetime prevalence of 0.3% to 1.5% across countries.[2] However, there is increasing awareness that this may be only the tip of the iceberg.[3] Two large ongoing French studies on the epidemiology of mania and depression (EPIMAN and EPIDEP, respectively),[4] seek to characterize possible subgroups of the bipolar spectrum. One of the preliminary findings in the EPIMAN study is the relatively high incidence of dysphoric mania (38%). On the other hand, the EPIDEP study showed that careful screening of patients revealed in 20% to 30% of the patients, previously diagnosed as unipolar depression, a short hypomanic episode, thus classifying them as bipolar II disorder (BD II) (ie, BD with hypomanic and depressive episodes) in the International Classification of Diseases, Tenth Revision (ICD 10),[5] but not necessarily in DSM IV, where a cutoff point of four hypomanic days is defined. Inclusion of these forms of BD is likely to increase the prevalence to 3% to 6 %, which has also been estimated from the studies of Angst.[6]

A meta-analysis of studies published so far reveals that lithium is only effective in approximately 60% of acutely manic patients, and probably even less in prophylaxis.[7,8] Lithium appears especially helpful in euphoric mania, but with atypical forms such as dysphoric mania or mania within a rapid cycling course, its efficacy rapidly declines. However, as the epidemiological study of Bourgeois et al pointed out,[4] these forms of mania, despite being called atypical, are quite frequent.

In contrast, the antiepileptic drugs carbamazepine (CBZ) and valproate (VPA) appear more able to cover a broader spectrum of BD. Their acute antimanic as well as their prophylactic efficacy appear to be relatively uniform across subtypes of the disease, with an estimated efficacy of 50% to 60%. New antiepileptic drugs such as lamotrigine (LTG) may add another valuable aspect as an effec-

tive treatment for bipolar depression, where most other mood stabilizers exhibit only small benefit.[9]
In order to enrich our possibilities in the treatment of BD, and to choose the drug appropriate for the specific symptomatology and course of disease, we need to know more about the underlying pathophysiology of the different forms of disease within the bipolar spectrum and the decisive mechanisms of action of mood stabilizers. This may also supply a rationale for the selection of upcoming mood stabilizers for their possible value in treating BD.

Selected abbreviations and acronyms

BD	*bipolar disorder*
BD II	*bipolar disorder–II (with hypomanic and depressive episodes)*
CBZ	*carbamazepine*
CIBS	*cocaine-induced behavorial sensitization*
ECT	*electroconvulsive therapy*
EPIDEP	*EPIdemiology of DEPression*
EPIMAN	*EPIdemiology of MANia*
GABA	*γ-aminobutyric acid*
GAT-1	*γ-aminobutyric plasma membrane transporter*
L-5-HTP	*L-5-hydroxytryptophan*
LEG	*late effector gene*
LTG	*lamotrigine*
NGF	*nerve growth factor*
NMDA	*N-methyl-D-aspartate*
RCBD	*rapid-cycling bipolar disorder*
TRH	*thyrotropin-releasing hormone*
VPA	*valproate*

Accordingly, Stoll and Severus[10] analyzed mood-stabilizing drugs such as lithium and anticonvulsants for common modes of action. Their literature search revealed that the most effective compounds inhibit postsynaptic signal transduction—mainly by decreasing intracellular calcium mobilization—and kindling processes, thus dampening excessive intra- and intercellular signaling. Besides these common actions that may also contribute to additive efficacy of the combination of lithium with different antiepileptic drugs, anticonvulsants also exert multiple actions on different receptors of biogenic amines, such as dopamine, serotonin, glutamate, and γ-aminobutyric acid (GABA). CBZ and VPA are especially interesting drugs in this respect. This article gives an overview of the cellular basis of action of anticonvulsants, as far as they may contribute to the amelioration of acute illness and prophylactic efficacy in BD, and reviews their clinical spectrum and usefulness in BD, in monotherapy as well as in combination with other drugs, as combining mood stabilizers may enhance efficacy, but can also possibly multiply side effects.

Mechanism of action of anticonvulsants with respect to bipolar disorder

Until the discovery of neuroleptics and lithium in the treatment of BD, electroconvulsive therapy (ECT) was the only available—and still is the most effective—treatment of mania. The antimanic response is estimated to be approximately 80%[11] Although the decisive cellular mechanisms for response remain speculative, it appears that with every application of ECT the seizure threshold increases. Thus, ECT has, paradoxically, an anticonvulsant effect. Interestingly, manic patients show an increase in seizure threshold with fading manic symptomatology.[12] These observations may supply a clinical rationale for using anticonvulsants in the acute treatment of mania.
When considering the cellular mode of action of anticonvulsants, we have to distinguish between three different levels: synaptic transmission, intracellular signaling, and, finally, gene activation. Following this hierarchy, we will first consider the impact of anticonvulsants on the metabolism and the synaptic action of biogenic amines.

GABA

Both established mood stabilizers, CBZ and VPA, exhibit agonistic effects on the GABAergic system. CBZ is a positive modulator of the GABA A receptor that increases the GABA A receptor–mediated chloride current.[13]
VPA increases GABA release in different areas of the brain.[14] This action of VPA was one of the supporting arguments leading to a GABA hypothesis of BD.[15-17] However, we are now facing a situation where we have to note that the most specific GABAergic anticonvulsants appear not to be as efficacious in BD as drugs with a wider range of action such as CBZ and VPA. A double-blind randomized trial of gabapentin[18] could not support antimanic efficacy previously observed in open trials[19,20] and a first open trial for the γ-aminobutyric acid plasma membrane transporter–1 (GAT 1) inhibitor tiagabine also showed no benefit in manic patients.[21] Another highly specific GABAergic compound, vigabatrine, is even suspected of inducing affective disorders and psychosis in epileptic patients.[22]

Excitatory amino acids

Inhibition of *N*-methyl-D-aspartate (NMDA) receptor–mediated currents have been reported for CBZ.[23] In addition, a decrease in aspartate release was observed for VPA.[24] As far as the new antiepileptic drugs are concerned, much thought has been given to the inhibition of glutamate and aspartate release by LTG.[25,26] However, this appears to be more an effect mediated by the blockade of sodium channels rather than a direct effect on synthesis and release of excitatory amino acids. Furthermore, it is still unclear how much this may contribute to antiepileptic potencies of these drugs, and, even more so, to efficacy in BD. Nevertheless, antiglutamatergic properties have been at least discussed for LTG as possibly decisive for antidepressant efficacy in bipolar patients.[27]

Dopamine

Catecholamines have been implicated in the pathophysiology of affective disorders for more than three decades,[28] either alone or in the context of a noradrenergic/cholinergic imbalance theory.[29] Whereas anticonvulsants have only little effect on norepinephrine turnover, their modulatory effect on dopaminergic transmission is more marked.

In epileptology, the effect of dopamine appears complex and dependent on receptor specifity and brain area: D_2 antagonists, eg, neuroleptics, may lower the seizure threshold, whereas D_1 agonists, eg, antiparkinsonian drugs, are also thought to increase seizure probability.[30] However, epileptic discharges in the low magnesium model are inhibited by D_1 agonists in vitro.[31] In many brain areas, dopamine turnover is increased by VPA,[32] an effect not seen with CBZ.[33] A dopamine hypothesis of mania has been proposed by several authors,[34-36] and, as a matter of fact, mainly dopaminergic-acting neuroleptics such as haloperidol are still one of the first choices in treating acute mania. Furthermore, recent genetic findings imply a role of the dopamine D_4 receptor gene[37] and the dopamine transporter gene[38,39] in BD.

Although evidence is abundant, the specific role of dopamine in BD still remains nebulous, due to the lack of clinical experience with receptor-specific compounds, both in epileptology and psychiatry, and the strong secondary interactions of dopamine with other monoaminergic transmitters.

Serotonin

Although the receptor pharmacology of serotonin is probably even more complex than that of dopamine, there is great enthusiasm for attributing a decisive role to serotonin in BD. Serotonin 1A ($5\text{-}HT_{1A}$) receptor agonists decrease epileptic discharges in the low magnesium model in vitro.[40] Serotonergic hypofunction has been implied as a major underlying disturbance in mania.[41] Supporting evidence comes from the finding of increased platelet serotonin content in mania and hypomania, compared to unipolar depressed and control subjects.[42] Furthermore, lithium appears capable of increasing central serotonergic transmission as shown both in the fenfluramine stimulation test in remitted bipolar patients,[43] and by measuring the loudness dependency of the N1/P2 component of auditory evoked potentials in patients with affective disorders.[44,45] In the rat, it also exerts direct effects on $5\text{-}HT_{1A}$ binding sites in the hippocampus.[46] Regarding antiepileptic drugs, an increase in extracellular serotonin has been observed with VPA[47] and CBZ treatment in animal models,[48] and in vitro with LTG.[49,50] However, at least for VPA, this may not be decisive for the antiepileptic action, as VPA still suppresses seizures in serotonin-depleted mice.[51] In bipolar patients, however, Maes et al[41] showed by means of the L-5-hydroxytryptophan (L-5-HTP) test an ameliorating effect of VPA treatment on central serotonergic transmission in manic patients. Unfortunately, due to the small number of subjects, it was not possible to obtain a significant correlation between clinical treatment response and changes in serotonergic transmission.

Effects of anticonvulsants on intracellular messaging systems

Activation of receptors of these biogenic amines initializes a cascade of intracellular signaling that ultimately leads to the expression of early genes. Anticonvulsants may, however, interfere with this cascade on different levels of the signaling pathways, either intracellularly or by blocking transmembraneous ionic fluxes. In particular, a disturbed intracellular calcium homeostasis may be a final common pathway in BD.[52,53]

At the presynaptic terminal, mobilization of calcium stores, both intracellular and by influx of extracellular calcium mainly through voltage-gated calcium channels, regulates neurotransmitter release by presynaptic facilitation and by controlling the fusion and exocytosis of neurotransmitter vesicles. On the postsynaptic side, calcium mobilization is essential for adenylyl cyclase and protein kinase C activation, and thus for many enzymatic processes, and, ultimately, early gene activation. Postsynaptic early gene activation, in turn, modulates the expression of enzymes, receptors, and

other proteins involved in neuronal transmission, thus also affecting the presynaptic terminal *(Figure 1, next page)*.
Increased intracellular calcium concentrations, under baseline conditions or after mobilization following specific stimulation paradigms, have been described in platelets and lymphocytes of bipolar patients, in both manic and depressive episodes.[54] Slightly elevated intracellular calcium release increases the metabolism of the cell to a maximum, probably resembling hyperexcitability in mania as a clinical correlate. However, high levels of intracellular calcium can dampen the activity of the cell in at least two major ways, by inhibition of Na/K adenosine triphosphatase (ATPase)[55] and of adenylyl cyclase,[52] thus slowing down the metabolic rate again. An analogue to depression has been suggested for this state. It should be noted that some authors also suggest a special sensitivity of Na/K ATPase in bipolar patients to calmodulin and calcium,[56] which would enhance these effects. Finally, excessive intracellular calcium causes cell death by activating calcium-dependent proteases and phospholipase A. Thus, calcium is an essential and, in excess, potentially cytotoxic component in all major signal transduction pathways: the cyclic adenosine monophosphate (cAMP) system, the inositol/triphosphate-diacylglycerol (IP_3-DAG) system, and the arachidonic acid system *(Figure 2, next page)*.[57]
In conclusion, this hypothesis combines special potential factors of vulnerability in bipolar patients, such as altered Na/K ATPase and adenylyl cyclase activity (probably on a genetic basis), with the multiplying effects of increased intracellular calcium mobilization or calcium influx into the cell.
Potentially beneficial effects of anticonvulsants through interference with intracellular calcium signaling are reported at various cellular levels.
A decreased Na/K ATPase activity has been described as a state marker in acutely ill bipolar patients, as it is not seen in healthy relatives.[58] Besides lithium, CBZ is also capable of stimulating Na/K ATPase, measured as rubidium 86 uptake into synaptosomes[59] causing a reduction in intracellular calcium.
Like lithium, CBZ also reduces the activity of protein kinase A and C by reducing cAMP-dependent protein phosphorylation. This also, in turn, reduces the gene expression of proteins responsible for neurotransmission.[60]
However, anticonvulsants may also affect voltage-dependent calcium channels directly. CBZ exerts strong calcium channel antagonism in vitro, synergistic with verapamil, thus making an action on L-type calcium channels likely.[61]
Similar findings are also true for VPA, which seems to exert calcium-antagonistic effects through blockade of another voltage-dependent calcium channel, the T channel.[62] The two new antiepileptic drugs gabapentin and LTG also exert calcium-antagonistic effects.[63-67] It has to be said, however, that in another study both CBZ and VPA, in therapeutic concentrations, appeared not to affect calcium currents in neocortical neurons in vitro.[68] Thus, a special aberration of intracellular calcium regulation, as assumed for bipolar patients, may be a prerequisite for the calcium-antagonistic action of these antiepileptic drugs in man.
In addition, other actions on ionic currents that may be especially important for suppression of seizures by CBZ, VPA, and LTG include inhibition of voltage-dependent sodium channels,[69,70] and an increase in an early transient potassium outward current.[71-73]
Table I (page 29) summarizes the modes of action on the synaptic and cytoplasmic levels of some anticonvulsants commonly used as mood stabilizers.

Sensitization and kindling—behavioral models explaining the recurrence of bipolar disorder?

Although many aspects of unipolar depression find their equivalent in behavioral animal studies, eg, learned helplessness paradigms or olfactory bulbectomized rats, it still appears difficult to explain characteristics of BD, such as swings of mood and increased vulnerability in the course of the disease, in terms of an integrative model. Although still speculative in some aspects, sensitization and kindling as described by Post et al[74] may be helpful in understanding the course of BD, starting from a molecular level and evolving towards behavioral changes.
Kraepelin[75] had already noticed in 1921 that a marked psychosocial stressor usually preceded the first affective episode, whereas subsequent episodes showed minor or even absent notable life events. At the same time, the frequency of episodes tends to increase, in some patients to the point of autonomous rapid cycling, with decreasing efficacy of mood-stabilizing drugs.
Post and Contel[76] developed the model of cocaine-induced behavioral sensitization (CIBS). Cocaine administration causes hyperlocomotion in rats and hypomanic-like symptoms in man. Repeated cocaine administration, however, may cause a shift of symptomatology toward signs of dysphoric mania (which has a high incidence in BD, as shown by the EPIMAN study) or even paranoid symptoms. Lesioning experiments in the amygdala show that CIBS involves different neuromodulatory changes depending on the dura-

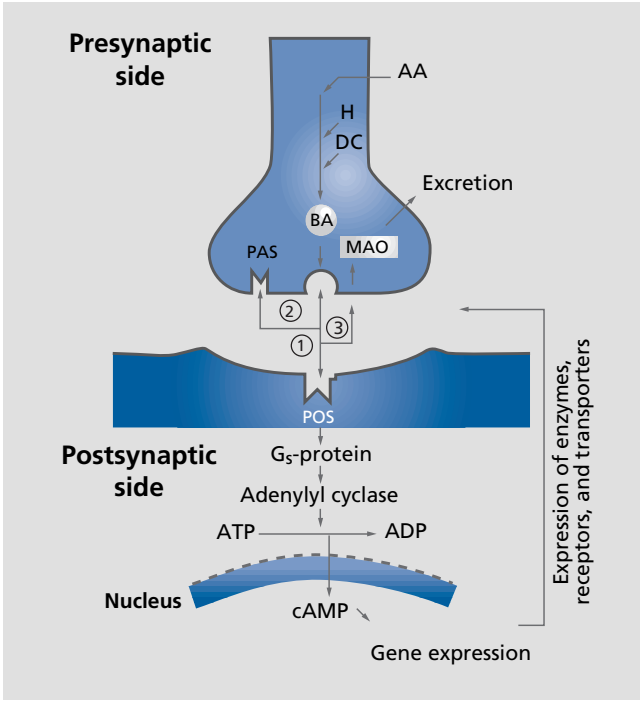

Figure 1. Schematic representation of the synaptic action of biogenic amines (norepinephrine, dopamine, and serotonin). Amino acids, tyrosine, and tryptophan are metabolized by a hydroxylase and a decarboxylase to their respective biogenic amines, and stored in vesicles. After release into the synaptic cleft, these molecules can follow three different paths: ① Activation of the postsynaptic receptor side. Mediated by a G-protein, this will activate adenylyl cyclase, breaking down ATP to ADP and cAMP, which, in turn, migrates into the nucleus and activates early gene expression; ② Activation of a presynaptic autoreceptor, leading to reduction of further release of the neurotransmitter; ③ Presynaptic reuptake of the transmitter, which may either be restored in vesicles or broken down into inactive metabolic end products by the monoamine oxidase before excretion. AA, amino acid; BA, biogenic amines; DC, decarboxylase; H, hydroxilase; MAO, monoamine oxidase; PAS, presynaptic autoreceptor; POS, postsynaptic receptor.

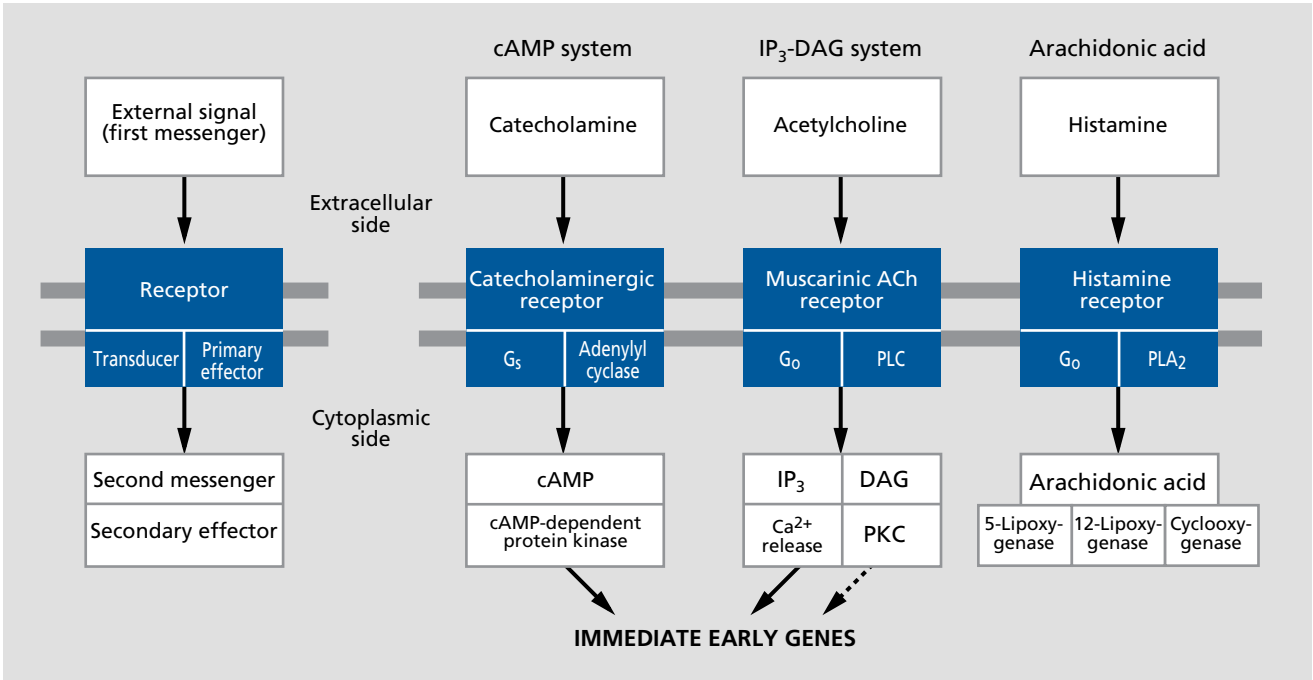

Figure 2. Graphic representation of the three major intracellular pathways, the cAMP system, the IP_3-DAG system, and the arachidonic acid system. G_0 and G_s, G-protein receptors; IP_3-DAG, inositol 1,4,5-triphosphate-diacylglycerol; PKC protein kinase C; PLA, phospholipase A; PLC, phospholipase C.
Modified from ref 57: Schwartz JH, Kandel ER. Synaptic transmission mediated by second messengers. In: Kandel ER, Schwartz JH, Jessell TM, eds. *Principles of Neural Science.* 3rd ed. Norwalk, Conn: Appleton & Lange; 1991:174. Copyright © 1991, Appleton & Lange. With permission.

tion and frequency of cocaine administration. Thus, not only the symptomatology can shift, but also the neuronal pathways involved, becoming independent of a direct action on the amygdala. Furthermore, cocaine is also capable of influencing neuromodulators in a similar fashion to stress, ie, by causing an increase in CRF, ACTH, cortisol, cytokines, catecholamines, and indolamines.

Relating these findings to intracellular transcriptional processes, another important analogy to stress sensitization can be noted. Both conditions, CIBS and repeated stress, lead at the end of the intracellular signal-transducing cascade to the expression of immediate early genes (c-*fos* and *zif*-268) in the amygdala and related limbic structures as well as late effector genes (LEG).[77] The composition of early genes and their occupation of the activator protein–1 (AP-1) receptor is partially specific for different stressors, eg, electroconvulsive seizures or cocaine, as well as for mode of application, ie, acute, repetitive or chronic.[78,79] This may provide a molecular background for speculation as to why psychosocial stressors may be more likely to cause symptoms of depression, whereas others, like acute pain, do not. Whereas activation of early immediate genes primarily induces expression of genes, such as neurotransmitter transporter genes, and finally modulates the acute symptomatology, induction of LEGs such as neurotropins and nerve growth factor (NGF) will modulate synaptic connectivity and nerve end sprouting, thereby giving rise to neuroanatomical changes.

Taken together, CIBS is a useful model to study acute events and long-term changes in symptomatology caused by episodes of affective disorders. However, to explain the aspect of sequential unfolding of episodes with increasing autonomy from the stressor, the amygdala-kindled rat appears to be a more suitable model. Kindling reflects a cumulative and progressive unfolding of physiological and behavioral changes in response to repeated stimulation over time that eventuates in seizures, initially triggered then occurring spontaneously.[80] Although epileptic seizures may have some mechanisms in common with affective disorders, eg, increased transmembranous calcium fluxes,[81] we are aware that they clearly are two different conditions. However, the rough anatomical substrate is similar, as the amygdaloid complex plays a key role in both diseases. Repeated electrical stimulation of the basolateral amygdala decreases the threshold for epileptic seizures, often leading to spontaneous epileptic activity. The correlate on the synaptic level is an increase in both NMDA- and non-NMDA-receptor–mediated glutamatergic transmission with a parallel decrease in inhibitory GABAergic transmission.[82] At the level of expression of early genes and neuropeptides, an increase in c-*fos* and thyrotropin-releasing hormone (TRH) mRNA was observed.[83] With full manifestation of seizures, these changes at the synaptic level and of substrate expression also involve the contralateral, nonstimulated amygdala complex. It is assumed that, like electrical kindling, recurrent affective episodes cause analogous long-term changes in neuronal networks, such as lowering the threshold for any consecutive episode. This hypothesis is backed up by a clinical study by Goldberg and Harrow.[84] Although having a comparable total number of episodes before, patients who had a pattern of close periodicity of episodes showed an increased relapse risk during follow-up, interpreted as an indicator of a previous kindling process.

Different drugs useful in BD exert antikindling potencies, such as lithium, nimodipine, and different anticonvulsants, eg, CBZ, VPA, and LTG. However, they can all induce tolerance, leading to insufficient suppression of seizures in the kindling model.[85] At the clinical level, this may correspond to tolerance or drug resistance observed with long-term treatment and/or discontinuation of lithium, CBZ, and VPA, as seen in some bipolar patients.[86,87]

Substance	Main modes of action
Carbamazepine	• Inhibition of voltage-gated sodium, potassium and calcium (L) channels • GABAergic, adenosinergic, serotonergic, and glutamate antagonistic properties
Valproate	• Increase in potassium outward current • Inhibition of voltage-gated sodium and calcium (T) channels • GABAergic and serotonergic properties
Lamotrigine	• Increase in potassium outward current • Inhibition of voltage-gated sodium and calcium channels • Inhibition of glutamate release and serotonin reuptake
Gabapentin	• Inhibition of sodium and calcium channels (possibly) • Indirect GABAergic properties (possibly)

Table I. Anticonvulsants used as mood stabilizers and their proposed mode of action.

(Table II)

Study	Design	Diagnosis	Duration	Agents	Efficacy
Ballenger & Post[92]	Double-blind	Manic, SA	11-56 days	Carbamazepine (n=10)	7/10 marked improvement
1978	ABA-design			Placebo (crossover)	
Okuma et al,[94]	Double-blind	Manic (ICD-9)	6 weeks	Carbamazepine (n=32)	21/30 (70%) improved on CBZ
1979				Chlorpromazine (n=28)	15/25 (60%) improved on CPZ
					Fewer side effects on CBZ
					Slightly faster onset with CPZ
Grossi et al,[95]	Double-blind	Manic (DSM-III)	21 days	Carbamazepine (n=18)	10/15 improved on CBZ
1984				Chlorpromazine (n=19)	10/17 improved on CPZ
					Fewer side effects on CBZ
					Slightly faster onset with CPZ
Klein et al,[96]	Double-blind	"Excited psychosis"	5 weeks	Haloperidol +	13/23 (57%) improved on
1984		RDC: mania,		carbamazepine (n=23)	CBZ+HAL
		excited SA/S		Haloperidol + placebo	11/20 (55%) improved on
				(n=20)	HAL+PLC
Müller & Stoll,[97]	Randomized	Mania	14 days	Oxcarbazepine (n=10)	OXCBZ ≈ HLD
1984				Haloperidol (n=10)	BRMS scores decreased in both
					groups
					Faster onset with OXCBZ
Emrich et al,[98]	Double-blind	Manic (ICD-9)	variable	Oxcarbazepine (n=7)	OXCBZ ≈ VPA
1985	ABA-design			Valproate (n=5)	OXCBZ > PLC
				Placebo (crossover)	VPA > PLC
Gonçalves & Stoll,[99]	Double-blind	Manic, SA	3 weeks	Carbamazepine (n=6)	CBZ > PLC
1985				Placebo (n=6)	
Lenzi et al,[100]	Double-blind	Excited	3 weeks	Carbamazepine +	CBZ + CPZ ≈ LI + CPZ
1986		psychosis		chlorpromazine (n=15)	Significant improvement on CGI
				Lithium +	(BPRS) in both groups
				chlorpromazine (n=15)	CBZ group required less CPZ
					CBZ group: less paranoia, EPS
Stoll et al,[101]	Randomized	Manic (ICD-9), SA	3 weeks	Carbamazepine (n=29)	12/14 (86%) improved on CBZ
1986				Haloperidol (n=29)	12/18 (67%) improved on HAL
					CBZ ≥ HAL
Desai et al,[102]	Double-blind	Manic	4 weeks	Carbamazepine +	CBZ + LI > PLC + LI
1987				lithium (n=5)	
				Placebo + lithium (n=5)	
Lerer et al,[103]	Double-blind	Manic (DSM-III)	4 weeks	Lithium (n=19)	LI ≥ CBZ
1987				Carbamazepine (n=15)	

(Table II, continued)

Study	Design	Diagnosis	Duration	Agents	Efficacy
Lusznat et al,[104]	Double-blind	Manic/hypomanic	6 weeks	Lithium (n=27)	LI ≈ CBZ (efficacy)
(1988)				Carbamazepine (n=27)	LI ≥ CBZ (comedication,
					depression scores)
Okuma et al,[105]	Double-blind	Manic	6 weeks	Carbamazepine (n=103)	50% improved
1988				Placebo (n=98)	on CBZ
					30% improved
					on PLC
Brown et al,[106]	Double-blind	Mania (DSM-III)	4 weeks	Carbamazepine (n=8)	6/8 (75%) marked
1989				Haloperidol (n=9)	improvement on CBZ
					2/9 (33%) marked
					improvement on HAL
Möller et al,[107]	Double-blind	Manic/SA	3 weeks	Haloperidol +	HLD + CBZ ≈ HAL + PLC (efficacy)
1989		(RDC, ICD-9)		carbamazepine (n=11)	HLD + CBZ ≥ HAL + PLC
				Haloperidol +	(comedication)
				placebo (n=9)	
Emrich,[108]	Double-blind	Manic	15 days	Oxcarbazepine (n=19)	OXCBZ ≈ HLD (efficacy)
1990				Haloperidol (n=19)	OXCBZ ≥ HLD (side effects)
Emrich,[108]	Double-blind	Manic	15 days	Oxcarbazepine (n=28)	OXCBZ ≈ LI (efficacy)
1990				Lithium (n=24)	LI ≥ OXCBZ (side effects)
Okuma et al,[109]	Double-blind	Manic (ICD-9)	4 weeks	Carbamazepine (n=51)	31/51 (62%) improved on CBZ
1990				Lithium (n=54)	30/54 (59%) improved on LI
					LI ≈ CBZ
Small et al,[110]	Double-blind	Manic (DSM-III-R)	8 weeks	Carbamazepine (n=24)	8/24 improved on CBZ
1991				Lithium (n=24)	8/24 improved on LI
					CBZ ≈ LI

TABLE II. Controlled studies of carbamazepine and oxcarbazepine in acute mania.
ABA, off-on-off design; BPRS, Brief Psychiatric Rating Scale; BRMS, Bech-Raefelson Mania Scale; CBZ, carbamazepine; CGI, Global Clinical Impression scale; CPZ, chlorpromazine; DSM-III, Diagnostic and Statistical Manual of Mental Disorders–III; DSM-III-R, Revised; EPS, extrapyramidal symptoms; HAL, haloperidol; ICD-9, International Classification of Diseases–9; LI, lithium; PLC, placebo; OXCBZ, oxcarbazepine; RDC, Research Diagnostic Criteria; S, schizophrenic; SA, schizoaffective; VAL, valproate; >, significantly better; ≥, slightly better; ≈, no difference.
Modified from ref 93.

The clinical issue: spectrum of efficacy of anticonvulsants in bipolar disorder

Carbamazepine and oxcarbazepine

In the 60s and early 70s, antiaggressive and emotionally stabilizing features had been observed with phenytoin and CBZ, both in epileptic patients and otherwise emotionally disturbed populations.[88-90] These reports, together with observed antikindling potencies in the animal model, initiated independent trials of the effects of CBZ in bipolar patients both in Japan and the US.[91,92]

Since then, 19 controlled studies *(Table II)* have been conducted on the antimanic efficacy of CBZ and its derivative,

oxcarbazepine. Comparison was made with lithium (6 studies), neuroleptics (6 studies), and placebo (2 as a parallel arm study, 2 in an A-B-A substituting design of the active drug). In addition, three trials tested CBZ versus placebo as an add-on to active treatment. A meta-analysis of these studies by Post et al[93] gave an overall improvement rate of 61% (123/203) for CBZ-treated patients, and 86% for oxcarbazepine.[93] However, only six trials did not allow coadministration of neuroleptics and/or lithium. In those methodologically unconfounded studies, CBZ was still effective in 50% of manic patients (defined as an at least 50% reduction of manic symptoms).[111] Those studies gave the general impression that, in contrast to lithium, CBZ may successfully cover a wider field of different subtypes of bipolar disorder, such as schizomanic states, mixed mania, or rapid cycling patients.[7]

In all studies, CBZ showed superiority compared with placebo. Assigning lithium as the gold standard, CBZ showed in five out of six studies efficacy at least equal to that of lithium in classic mania. Compared to neuroleptics (six studies), equal efficacy was observed for CBZ in four studies, and in two studies, CBZ appeared more efficient. When using CBZ in mania, the aim is to reach sufficient plasma levels quickly and ensure reliable intake of the medication. This can be done by using a suspension formulation of CBZ. Initially, 20 mL (400 mg) can be used, followed by 10 mL 3 to 4 times daily.[112] This regimen quickly achieves serum concentrations considered sufficient for antiepileptic treatment (4-12 µg/mL). Interestingly, although CBZ has been used in BD for a long time, no attempt has yet been made to establish reliable serum concentrations for antimanic efficacy.

As far as side effects are concerned, initial sedation and ataxia are often seen with CBZ, especially when used as an antimanic loading therapy. These effects are mainly due to the metabolite 10,1-CBZ-epoxide. These side effects appear much less often with oxcarbazepine, due to the different route of metabolism. Autoinduction and heteroinduction of metabolism also lead to decreased serum levels during continuation treatment and to changes in serum levels of concomitantly used drugs whose metabolism also uses the 3A4 isoform of cytochrome P450. This needs to be kept in mind, especially when combining CBZ with VPA, haloperidol, and some antidepressants, or with concomitant use of hormonal contraceptives.[113,114]

Carbamazepine in depression

Data on the antidepressant efficacy of CBZ are clearly much less robust than those relating to its use in mania. Additionally, they are confounded by the methodological problem that these studies mostly included both unipolar and bipolar depressed patients. A meta-analysis of all open studies suggests an antidepressant effect in 55% of patients (both uni- and bipolar), and in 44% in all controlled studies.[93] However, due to the small samples of patients, especially in the controlled trials, and the mixing with unipolar depressed patients, it has been impossible to prove the antidepressant effects of CBZ so far. If these exist at all, they appear to be less pronounced than the antimanic properties.

Carbamazepine in prophylaxis

The benefits of CBZ in BD with regard to possible prophylactic efficacy—in addition to its antimanic action—had been considered as far back as 1973 in a controlled study by Okuma et al.[91] In the following years, five double-blind randomized trials against lithium were carried out,[111] but only one against placebo,[115] which reported a 60% response rate compared to 22% for placebo after 1 year. Those earlier studies against lithium suggest a comparable prophylactic efficacy. However, all these studies suffer from the methodological shortcoming of short observation periods. A recent study by Greil et al[116] in 144 patients had a more appropriate observation period of 2.5 years. Forty-seven percent of CBZ-completers experienced a relapse compared to 28% of lithium-completers, a significant outcome in favor of lithium. Extending this analysis to a basis of 171 patients divided into classic BD (BD I without mood-incongruent delusions and without comorbidity) and nonclassic BD (BD II, mood-incongruent delusions, comorbidity), lithium was clearly superior in the classic BD patients; CBZ, however, appeared favorable in the nonclassic group.[117] Another recent controlled study showed a higher efficacy for lithium, especially in controlling manic relapses.[118] However, all of these studies have been conducted over relatively small observation periods in selected patient populations and may not reflect naturalistic clinical conditions. An extensive prospective 5-year follow-up of patients in a lithium clinic was recently published.[119] It revealed that, in the end, only 23% of patients derived real benefit, meaning that no relapse and no discontinuation due to side effects occurred during prophylactic lithium treatment. Similarly, a retrospective study by Frankenburg et al[120] in patients receiving CBZ for 3 to 4 years revealed that only 18% remained stable on CBZ alone. Besides problems of compliance, it has been

suggested that tolerance and discontinuation-induced refractoriness may add to the decreasing efficacy in long-term prophylaxis, both for lithium and CBZ.[86]

Research on prophylactic efficacy may be conducted more easily in patients with rapid cycling bipolar disorder (RCBD), as even with shorter observation periods the natural course of the disease would predict a fair chance of relapses and recurrences. Twenty open and three controlled studies support the prophylactic efficacy of CBZ in RCBD.[121] Only one open study, which, however, included more patients (n=215) than all the other studies together, refuted the utility of CBZ in the prophylaxis of RCBD.[122] However, it should be kept in mind that RCBD may represent an entity biologically different from BD, with a low frequency of recurrence.

In summary, even though prophylaxis with CBZ has a more favorable outcome than the natural course of the disorder, more research into the prophylactic efficacy of mood stabilizers remains top of the agenda.

Valproate

Valproate in mania

The treatment of acute manic episodes remains, to this day, the major indication of VPA in bipolar patients. The first reports on mood-stabilizing properties came from a French group using the VPA derivative dipropylacetamide.[123] Soon afterwards, the first open trials on VPA in mania were conducted, both in Europe[15] and the US[124] *(Table III)*, where

Study	Design	Diagnosis	Duration	Agents	Efficacy
Emrich et al,[15]	Double-blind	Manic		Valproate (n=5)	4/5 marked improvement
1980	ABA-design			Placebo	
Brennan et al,[124]	Double-blind	Manic		Valproate (n=8)	6/8 (75%) marked
1984	ABA-design			Placebo	improvement on VPA
Pope et al,[126]	Double-blind	Manic (DSM-III)	1-3 weeks	Valproate (n=17)	53% improved on VPA
1991				Placebo (n=19)	11% improved on LDC
					VPA > PLC
Freeman et al,[125]	Double-blind	Manic (DSM-III-R)	3 weeks	Lithium (n=13)	LI: 12/13; VPA: 9/14
1992				Valproate (n=14)	LI ≈ VPA
Bowden et al,[127]	Double-blind	Manic (RDC)	21 days	Lithium (n=35)	LI: 49% response rate
1994				Valproate (n=68)	VPA: 48% response rate
				Placebo (n=73)	PLC: 25% response rate
					LI > PLC; VPA > PLC
					LI ≈ VPA
McElroy et al,[130]	Randomized	Manic with	7 days	Valproate (n=21)	VPA ≈ HAL
1996		psychotic symptoms		Haloperidol (n=15)	
Müller-Oerlinghausen	Double-blind	Manic (ICD-10)	21 days	Valproate (n=69) or	VPA + HAL: 67% response rate
and Retzow,[128]				Placebo (n=67) as	PLC + HAL: 50% response rate
1997				add-on to haloperidol	Significantly less HAL needed
					in the VPA group

TABLE III. Controlled studies of valproate in acute mania. ABA, off-on-off design; DSM–III, Diagnostic and Statistical Manual of Mental Disorders–III; DSM-III-R, Revised; HAL, haloperidol; ICD-10, International Classification of Diseases, Tenth Revision. LI, lithium; PLC, placebo; RDC, Research Diagnostic Criteria; VPA, valproate; >, significantly better; ≥, slightly better; ≈, no difference.
Modified from ref 127.

mostly divalproex was used, an equimolar mixture of sodium VPA and valproic acid that may cause fewer gastrointestinal side effects. Antimanic efficacy has been reported in open studies with a combined total of more than 1000 patients, and has been definitely confirmed by several controlled double-blind studies.[125,126]

The largest study that finally obtained Food and Drug Administration (FDA) approval for VPA in mania was conducted by Bowden et al.[127] These authors tested the antimanic potency of VPA in 179 patients against lithium and placebo. Forty-eight percent of the VPA and 49% of the lithium patients (compared to 25% for placebo) showed an at least 50% symptom reduction after 21 days of treatment. Both VPA and lithium were significantly superior to placebo (P=0.004 for VPA). Similar favorable results were reported by the European study group[128] where VPA was compared in a double-blind fashion with placebo as an adjunct to neuroleptic treatment *(Table III)*.

Summarizing the experiences of those trials, it appears that VPA is effective in a broader spectrum of mania than lithium. In the study of Bowden et al,[127] it was noted that VPA was equally effective in mania in RCBD patients. Compared to lithium, VPA also seems superior in mixed states with coexistence of a neurological disease, a history of head trauma, substance abuse, or anxiety disorders.[129] To date, there is only one controlled study for anticonvulsants concentrating on psychotic features in mania,[130] in which VPA showed equal efficacy to haloperidol.

A great advantage of VPA in the treatment of mania is its wide therapeutic window, allowing a loading therapy strategy. With a dosage of 20 mg/kg/day, therapeutic plasma levels can be reached already on the first day. It appears that 50 µg/mL is the threshold serum concentration for antimanic efficacy.[131] Recent observations have shown that intravenous VPA loading may even shorten the delay of antimanic response.[132] Dose-related adverse effects of VPA include sedation, nausea, diarrhea, asthenia, and thrombocytopenia, but these are usually mild and controllable by dosage adjustment.[127]Taken together, VPA appears to be an effective and well-controllable treatment of acute mania. Today, it is considered in many treatment guidelines, besides lithium, as first-choice treatment for acute mania, especially in atypical cases.[133-135]

Valproate in depression

As with CBZ, the body of evidence in favor of the antidepressant efficacy of VPA is rather small compared to mania. A meta-analysis of open trials suggests an antidepressant efficacy of VPA in 25% of patients (35/138).[93] As a matter of fact, this figure is not much different from the placebo response rate usually observed. However, summarizing trials in RCBD patients, 45% showed an acute antidepressant response in open studies.[136]

Valproate in prophylaxis

Open studies using VPA either alone or as an add-on to lithium have suggested a possible prophylactic efficacy. A meta-analysis of 11 open studies showed a response rate of 64% among 496 patients.[137] In RCBD, data from Calabrese et al[138] from 101 patients suggest good prophylactic efficacy of VPA during the observation period of 17 months. Patients who initially presented with a mixed episode had the greatest benefit: 94% stayed relapse-free, compared to 72% with pure mania and 33% of the depressed patients. In view of the unconvincing data in support of the prophylactic efficacy of lithium and the controversial data for CBZ, VPA, despite the lack of controlled trials, remains the current first-line treatment in the prophylaxis of RCBD.

Only recently, initial double-blind controlled findings have been released on the prophylactic efficacy of VPA compared to lithium and placebo in BD in general.[139] In this study including 372 patients, VPA showed advantages in secondary, but not primary, outcome measures compared to both lithium and placebo. However, several questions remain open. The main drawback is again the short study duration of 1 year, which makes it difficult to assess the long-term benefit of VPA.We therefore will have to wait a few more years before getting a better picture of the prophylactic efficacy of VPA.

The new generation of anticonvulsants

Lamotrigine

Compared to the older antiepileptic drugs, much more enthusiasm has arisen from the latest generation of anticonvulsants, lamotrigine (LTG), gabapentin, and, more recently, topiramate and tiagabine.

LTG in particular has become a major focus of attention as it shares many cellular mechanisms of action with the established mood stabilizers CBZ and VPA. Whereas the use of LTG in acute mania is limited by the need for slow titration, initial single case reports[140] and open studies[141,142]

have suggested good prophylactic efficacy. Most important, these open trials pointed towards efficacy in difficult-to-treat conditions such as bipolar depression and rapid cycling. A small double-blind trial at the National Institute of Mental Health (NIMH)[18] confirmed the antidepressant effect of LTG, with 48% of patients responding after 6 weeks compared to 20% in the placebo group. The most favorable response was seen in BD I depressed patients (about two thirds of patients), whereas less than one third of unipolar depressed patients improved. Recently, this antidepressant efficacy was verified in a large multicenter study in 192 patients who showed statistically significant improvement of bipolar depression with 200 mg LTG, compared to placebo.[9]
Controlled, double-blind multicenter studies on the prophylactic efficacy of LTG, especially in RCBD, are still ongoing. Like other anticonvulsants, LTG may also have beneficial effects in the prophylaxis of schizoaffective disorder.[143]

Gabapentin

Like LTG, the introduction of gabapentin stirred up much enthusiasm. This derivative of GABA appeared to be very well tolerated, and open studies supported beneficial effects in mania,[19,20,144] bipolar depression,[145] and prophylaxis.[146] Double-blind clinical trials for all three indications are still ongoing. However, at least in bipolar depression, gabapentin seemed not to be superior to placebo in a small controlled trial.[18]

Topiramate and tiagabine

Very recently, preliminary findings from open trials on the potential benefits of topiramate in BD have become available. First synthesized in 1990, topiramate belongs to a new class of antiepileptics, the sulfamate-substituted monosaccharides. Topiramate shows cellular mechanisms of action similar to those of established antiepileptic drugs, namely blockade of voltage-dependent sodium influx, as well as GABAergic and antiglutamatergic effects.[147] Observations from McElroy et al[148] and Calabrese et al[149] suggest at least moderate antimanic efficacy, and from the observations of Marcotte and Gullick,[150] also possible efficacy in prophylaxis of RCBD. However, conclusions are still premature as long as the results of ongoing controlled trials are not in. Fewer data are available on the GABA transporter inhibitor tiagabine. In an open trial in 10 manic patients, no antimanic response was observed despite high dosing.[21]

Upcoming candidates

Among anticonvulsants that have been released very recently or are currently in the last stages of clinical testing, losigamone and retigabine appear to have potential as future candidates for use in BD, based on their basic mechanisms of action. Retigabine in particular shows strong antikindling effects.[151] Felbamate is unlikely to be routinely used in bipolar patients due to its possible severe side effects, especially acute hepatic necrosis.[152]

Older anticonvulsants with potential benefits in bipolar disorder

Clonazepam

In neurology, the 7-nitrobenzodiazepin derivative clonazepam is used in treating myoclonic and epileptic absence. In BD, clonazepam was tested for antimanic efficacy in three double-blind trials[153-155] as monotherapy against lithium, placebo, or lorazepam. Clonazepam appeared superior to placebo and as efficient as lithium, but less efficient than lorazepam. This suggests that the main effect of clonazepam, and probably of benzodiazepines in general, may be an initial calming of the patient, which also results in a reduction in scores in mania rating scales. A longer-lasting effect on core manic symptoms cannot be concluded from those studies, as they were only of short duration (maximum 14 days) and carried out in a small number of patients. Beneficial effects of clonazepam in the short-term control of agitation in manic patients were also found in an open study of Bottai et al[156] where the manic symptomatology was rated in a time-blind fashion and retrospectively correlated with plasma levels. The initial plasma levels that led to sufficient control of agitation were in the range of 18.9 to 34.0 µg/L. Chouinard et al[157] also conducted a double-blind trial with clonazepam IM compared to haloperidol IM as initial treatment of agitated manic patients and reported equal efficacy with fewer, especially extrapyramidal, side effects.
Only two controlled studies have been conducted on the prophylaxis of recurrence of BD, with disappointing results. Sachs et al[158] compared clonazepam with haloperidol as an add-on to lithium prophylaxis. No significant difference was observed between the small groups (n=6 randomized to each treatment) after 12 weeks, however, 3 out of 6 patients on clonazepam still needed additional haloperidol. The other trial, by Aronson et al,[159] was prematurely discontinued after the first 5 patients enrolled relapsed after 2 to 15 weeks.

In summary, clonazepam may be an effective treatment, like other benzodiazepines, for rapid control of manic agitation; however, its medium- and long-term efficacy, especially against core manic symptoms, cannot be concluded from the trials so far.

Phenytoin

The efficacy of phenytoin in patients with affective disorders has not yet been investigated systematically. Earlier anecdotal reports showed an effect on mood and hostility in populations with aggressive behavior[88,89] and neurotically depressed patients.[160] Not all of these results could be replicated in further case reports, so that these findings remain controversial. In contrast, one case report suggests that phenytoin induces organic mania.[161]
In a currently ongoing open trial, we are attempting to characterize potential benefits in manic patients receiving high oral loading doses of phenytoin (600-1000 mg/d for 3 days, then tapering down according to plasma level). Preliminary results in the first 5 patients included suggest good tolerability and an initial beneficial effect on manic agitation; however, the effect appears transient and leaves other core manic symptoms unchanged.

Barbiturate anticonvulsants

Besides phenytoin, barbiturates are another group of anticonvulsants that has not received much attention in the treatment of BD. The only open trial on effects of primidone and mephobarbital comes from Hayes,[162] who described a sustained positive effect on the course of illness with primidone in one third of patients (9/27) having previously failed on standard treatment regimens. Clearly, this group of substances is still an unexplored field in bipolar disorder, but should be followed up as an alternative in refractory patients.

Acetazolamide

The carbonic anhydrase inhibitor acetazolamide is used as an add-on medication in some treatment-refractory epilepsies. Hayes[163] reported on 16 bipolar patients who failed to remain stable on standard mood stabilizers. Addition of acetazolamide, however, resulted in improved prophylactic efficacy in 7 out of 16 patients (44%). Unfortunately, the usefulness of carbonic anhydrase inhibitors in BD has not been followed up since then.

Combining mood stabilizers

In clinical practice, anticonvulsants are often used in combination treatment with lithium and/or neuroleptics in patients that have been refractory to the first-line treatment. In these cases, increased efficacy may be obtained, but attention should be paid to possible side effects occurring in combination treatment. These issues have recently been extensively reviewed by Freeman and Stoll.[164] Data suggesting that combined treatment with lithium increases the efficacy both of VPA and CBZ appear to be relatively firm; for the new generation of anticonvulsants, gabapentin and lamotrigine, only preliminary observations are available. The addition of LTG to lithium may be an efficacious approach, especially in the treatment of bipolar depression.[141] Whereas combination of lithium with VPA, gabapentin, and LTG appears relatively safe, there have been reports of increased neurotoxicity with concomitant lithium-CBZ treatment. Such a combination should especially be avoided in patients with preexisting central nervous system disease.[165] However, this judgment may include a bias as the number of patients receiving CBZ together with lithium exceeds by far any other lithium/anticonvulsant combination therapy; thus, reports of side effects become much more likely.
Combinations within anticonvulsants, although in many cases effective, should be administered only with rigorous control of plasma levels, as CBZ, VPA, and LTG interfere with each other's metabolism. Through cytochrome P450 3A, CBZ induces both autometabolism as well as metabolism of VPA. CBZ also increases the metabolism of LTG, whereas VPA slows it down.[147] ❑

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Mecanismo de acción e indicaciones de los anticonvulsivos en el tratamiento de los trastornos bipolares

A pesar de los grandes progresos que se han realizado en el tratamiento exitoso de los trastornos bipolares, se tiene una mayor conciencia de los límites de los protocolos terapéuticos tradicionales tales como el litio y los neurolépticos. Sin embargo, la gran familia de fármacos anticonvulsivos parece ser capaz de agregar opciones terapéuticas, no solo como medicación de segunda elección en pacientes refractarios al tratamiento, sino como tratamiento estándard con una alta eficacia y una baja incidencia de efectos secundarios. Además de los reguladores del humor tales como la carbamazepina y el valproato, aparecen nuevos fármacos antiepilépticos en la práctica clínica con prometedores resultados iniciales en el tratamiento de los pacientes bipolares. Más aún, el esclarecer los mecanismos de acción de los anticonvulsivos y las semejanzas entre los diferentes fármacos eficaces en los trastornos bipolares, puede también ayudarnos en la comprensión de las bases fisiopatológicas de dicho trastorno.

Mécanismes d'action et indications des anticonvulsivants dans le traitement de la maladie bipolaire

Bien que beaucoup de progrès aient été faits dans le traitement de la maladie bipolaire, les thérapeutiques traditionnelles telles que le lithium et les neuroleptiques montrent progressivement leurs limites. Un choix thérapeutique supplémentaire s'ouvre avec la grande famille des anticonvulsivants, non seulement comme traitement de recours pour les patients réfractaires aux thérapeutiques classiques, mais aussi comme traitement standard d'une grande efficacité entraînant peu d'effets secondaires. En plus des stabilisateurs de l'humeur avérés tels la carbamazépine ou le valproate, de nouvelles molécules antiépileptiques font leur entrée dans le traitement de la maladie bipolaire avec des résultats initiaux prometteurs. En outre, la mise en lumière des mécanismes d'action des anticonvulsivants et les similitudes présentées par ceux qui sont efficaces dans la maladie bipolaire devrait permettre d'approfondir notre compréhension de la physiopathologie de la maladie.

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