The effectiveness of anticonvulsants in psychiatric disorders

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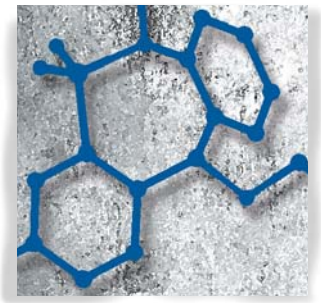

Anticonvulsant drugs are widely used in psychiatric indications. These include mainly alcohol and benzodiazepine withdrawal syndromes, panic and anxiety disorders, dementia, schizophrenia, affective disorders, bipolar affective disorders in particular, and, to some extent, personality disorders. A further area in which neurology and psychiatry overlap is pain conditions, in which some anticonvulsants, and also typical psychiatric medications such as antidepressants, are helpful. From the beginning of their psychiatric use, anticonvulsants have also been used to ameliorate specific symptoms of psychiatric disorders independently of their causality and underlying illness, eg, aggression, and, more recently, cognitive impairment, as seen in affective disorders and schizophrenia. With new anticonvulsants currently under development, it is likely that their use in psychiatry will further increase, and that psychiatrists need to learn about their differential efficacy and safety profiles to the same extent as do neurologists.

 Dialogues Clin Neurosci. 2008;10:77-89.

Keywords: *anticonvulsant; addiction; agitation; anxiety; bipolar disorder; depression; pain; personality disorder; schizophrenia*

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It is virtually impossible to draw a clear dividing line between neurology and psychiatry, as many neurological disorders, including epilepsy, also have a strong component of behavioral impairment. On the other hand, disorders such as dementia that are primarily cognitive and behavioral involve massive neuroanatomical and neurofunctional changes. Research into this psychiatry/neurology interface—neuropsychiatry—attracts participants from many disciplines, as disorders thus described may help understanding of how neuroanatomical or neurochemical underpinnings can be expressed in (aberrant) behavior. Medications used in these neuropsychiatric disorders usually focus on symptoms. As in the case of anticonvulsants, they may not act purely on a neurological phenomenon, such as preventing or terminating a full seizure, but, due to the close link between epilepsy and emotional and behavioral brain functions, also on areas such as mood regulation, or fear and anxiety. Whereas negative effects on mood and anxiety states have been described quite frequently with the first generation of antiepileptic drugs, especially bromium and later barbiturates, it was in the 1960s that the first observations describing positive and mood-stabilizing effects of anticonvulsant drugs (ACs) were published. In 1967 Turner published an observational study entitled "The usefulness of diphenylhydantoin in treatment of non-epileptic emotional disorder,"[1] separating for the first time the mood effects of antiepileptic drugs from their antiepileptic efficacy. At the same time, or soon afterwards, the first reports on the mood-stabilizing efficacy of carbamazepine[2] and valpromide[3] were

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published, and nowadays the portfolio of ACs with proven or potential usefulness in treating mood-disordered patients in particular is quite respectable. More recently, newly developed ACs have also been tested more rigorously in anxiety states, to the point where some of the newer ACs are now more frequently used in treating anxiety than epilepsy. Finally, as ACs act against a state of neuronal hyperexcitability, it was obvious that they should be tested in other conditions thought to be caused by aberrant excitability, such as substance abuse and withdrawal and pain conditions, the latter also including a strong negative affective component. This article aims to provide a condensed overview of the proposed mechanisms of action and effectiveness of older and newer ACs by looking at various psychiatric disorders or syndromes. *Table I* supplies an overview of the candidate ACs for psychiatric indications, and the level of evidence for their use.

Although safety and tolerability are aspects of utmost importance, they will not be dealt with in this article for the sake of comprehensiveness. However, it is strongly recommended that readers educate themselves about the individual safety issues of ACs before applying them in routine practice. Recent reviews (eg, refs 4-7) are a comprehensive source of information for further reading.

Mechanisms of action beyond antiepileptic properties

A common link between the different indications where ACs are used may be an underlying state of hyperexcitability which may manifest itself as sleep disturbances, mood swings, anger, or impulsiveness. There are several hypotheses about a common underlying pathophysiology, but excessive sodium and calcium fluxes may play a role both in epilepsy and the abovementioned psychiatric conditions. Several anticonvulsants, including carbamazepine, valproate, lamotrogine, and phenytoin, have a regulating effect on these ion fluxes,[8] and this may explain part of their efficacy in some psychiatric disorders such as withdrawal states, pain, or, as a state of behavioral hyperactivity, acute mania.[9,10] Antidepressant effects may also be explainable, at least in part, through modulation of serotonin (valproate and lamotrigine[11-13]), dopamine (valproate[11]), noradrenalin (lamotrigine[14]) and hypothalamic-pituitary activity (lamotrigine[15]). For the

	Indication												
	Anxiety disorders				Affective disorders					Schizophrenia	BPD	Neuropathic pain	Other pain conditions
Anticonvulsant	GAD	PD	SP	PTSD	MDD (a)	MDD (p)	BPm	BPd	BPp			PHN, DPN	Migraine, trigeminal neuralgia
Carbamazepine	0	-	0	+	+	+	+++	+	++	++	++	+	+++
Valproate	0	++	0	+	+	0	+++	+	++	++	+	+	+++
Lamotrigine	0	0	0	++	++	0	++	-	+++	+++	+	-	+
Phenytoin	0	0	0	+	+	0	++	-	++	0	0	++	+ (fosphenytoin)
Oxcarbazepine	0	0	0	+	+	+	++	+	+	+	+	++	++
Gabapentin	0	++	++	+	0	0	-	+	++	0	0	+++	+
Pregabalin	+++	0	++	0	0	0	0	0	0	0	0	+++	+++
Vigabatrin	0	0	0	0	0	0	0	0	0	0	0	0	0
Topiramate	0	0	0	++	++	0	-	+	0	++	+++	-	+++
Tiagabine	-	0	0	0	0	0	-	0	0	0	0	0	0
Levetiracetam	0	0	0	0	0	0	+	+	0	0	0	0	0
Zonisamide	0	0	0	0	0	0	+	+	0	0	0	0	0

Table I. Evidence from monotherapy and add-on studies for the efficacy of anticonvulsants in psychiatric and neuropsychiatric disorders. Evidence: +++, evidence from at least two randomized, placebo-controlled studies; ++, evidence from one placebo-controlled study or at least two randomized comparator studies or a systematic metaanalysis; +, evidence from only one comparator study, open studies; 0, not tested (or no published results); -, negative evidence. GAD, generalized anxiety disorder; PD, panic disorder; SP, social phobia; PTSD, post-traumatic stress disorder; MDD, (a)= major depressive disorder (= unipolar depression), acute treatment; MDD, (p)= major depressive disorder (= unipolar depression), prophylactic treatment; BPm, bipolar disorder, manic; BPd = Bipolar disorder, depressed; BPp =Bipolar disorder, prophylaxis; BPD, borderline personality disorder; PHN, postherpetic neuralgia

treatment of anxiety states, the γ-aminobutyric acid (GABA)ergic action of some anticonvulsants, eg, pregabalin and gabapentin, may be more decisive.[16] However, these acute receptor-transmitted effects are largely insufficient to explain, eg, long-term stabilization of mood such as that provided by lithium. During the last decade, it has been demonstrated that not only lithium, but also valproate and, in part, carbamazepine, regulate numerous factors enhancing cellular plasticity and resilience, including inositol biosynthesis (MIP synthase), cyclic adenosine monophosphate (c-AMP) response element binding protein, brain-derived neurotrophic factor (BDNF), the extracellular signal-regulated kinase pathway, the arachidonic acid pathway, the cytoprotective protein bcl-2 and mitogen-activated protein kinases.[17-24] All these intracellular actions may contribute to preventing a kindling process which otherwise leads to a constant decline of the threshold for relapses. The amygdala kindling model, originally developed to explain progression of epileptic seizures,[25] may also be applicable to affective episodes, panic attacks and anxiety states, or alcohol and drug relapses.[26]

Substance abuse

Alcohol

Although their mechanism of action is not completely understood, the efficacy of anticonvulsants in the alcohol withdrawal syndrome is thought to be related to their ability to inhibit kindling and facilitate GABA inhibitory neurotransmission. A recent Cochrane meta-analysis of 48 studies involving 3610 subjects compared different ACs with placebo for alcohol withdrawal, Therapeutic success tended to be more common among the anticonvulsant-treated patients (relative risk (RR) 1.32; 95% confidence interval (CI) 0.92 to 1.91), and ACs tended to show a protective benefit against seizures (RR 0.57; 95% CI 0.27 to 1.19), but no effect reached formal statistical significance.[27] Nevertheless, there is limited positive evidence for some ACs. Carbamazepine[28] and oxcarbazepine[29] alone or, especially in Germany, in combination with tiapride,[30] are frequently used for alcohol withdrawal because they reduce the risk of convulsions and, especially in the case of carbamazepine, cause an initial sedation when titrated rapidly. For oxcarbazepine, open data also suggest anticraving effects in sober alcoholics.[31] There are also some reports on the use of valproate for alcohol withdrawal. Myrick et al[32] reported comparable effects of lorazepam and valproate in reducing alcohol withdrawal symptoms in an open trial. In a double-blind randomized study, Tress et al[33] compared valproate with clomethiazol, observing no difference in somatic symptoms and the absence of severe delirious states with both medication. The so-far largest controlled study using valproate for alcohol withdrawal syndromes was conducted by Hillbom et al[34] comparing valproate with carbamazepine and placebo. The reduction of withdrawal seizures was more pronounced with valproate (2.2% vs 4.7% with carbamazepine and 6.1% with placebo). However, there was also a higher, but not significant, rate of delirium (valproate 4.4%). compared with 2.2% for placebo and none with carbamazepine. The authors also report a better general tolerability of valproate compared with carbamazepine. In conclusion, there is some evidence for effectiveness not only of carbamazepine, but also of valproate in uncomplicated alcohol withdrawal, but it is obvious that better controlled studies are needed. So far, of all the anticonvulsants only carbamazepine reached such a level of confidence that it has been recommended in guidelines as suitable for the pharmacological management of alcohol withdrawal.[35] Newer antiepileptic drugs that had been tested in open-case series in the indication of alcohol withdrawal have produced conflicting results, eg, gabapentin, vigabatrin and topiramate[36-38]; however, randomized studies are missing or negative.[39]

Valproate and lamotrigine have also been tested in controlled studies in bipolar patients with comorbid alcohol abuse for their effects on drinking habits. For valproate, a significant reduction in heavy drinking days was found in a controlled study,[40] and also lamotrigine reduced alcohol intake and craving in an open study.[41] There are also some case series on carbamazepine and lamotrigine lowering alcohol consumption in comorbid schizophrenia and alcohol dependence.[42,43]

Cocaine dependence

As there is a high comorbidity, especially between bipolar disorder and cocaine dependence, some mood-stabilizing anticonvulsants have been tested in terms of their utility in limiting drug abuse. Both valproate[44] and lamotrigine[45] demonstrated mood-stabilizing effects in open-label trials, and some positive effects on drug abuse, such as diminished consumption (valproate) and less craving

(lamotrigine). In a small placebo-controlled pilot trial, topiramate also proved effective in attaining at least 3 weeks of continuous abstinence.[46] However, more controlled evidence still needs to be collected.

Sedatives and tranquilizer abuse

A potential role for GABA uptake inhibitors such as tiagabine for benzodiazepine withdrawal has been suggested,[47] but never been rigorously tested. Of the older anticonvulsants, valproate has been tested in open case series,[48] and has been compared against trazodone and placebo for benzodiazepine withdrawal. Rickels et al[49] reported that more patients were free of benzodiazepines after 5 weeks when treated with valproate or trazodone compared with placebo. However, they did not find a significant reduction of somatic symptoms during benzodiazepine tapering. According to a Cochrane meta-analysis of available trials, carbamazepine shows a rather modest benefit in reducing withdrawal severity, but it does significantly improve drug-free outcome.[50] However, a note of caution should be used when using carbamazepine (and oxcarbazepine) in withdrawal states. Patients' predisposition to hyponatremia and consecutive seizures despite anticonvulsant treatment may be increased.[51] Other newer substances, eg, gabapentin and topiramate, show promise from case studies; however, randomized studies are still lacking.[28,52]

Smoking cessation

A very recent field with potential usefulness of some new anticonvulsants is smoking cessation. Due to 2-(aminomethyl)phenylacetic acid AMPA/kainate antagonism, topiramate has been assumed to be a potential candidate medication. A small open study by Khazaal et al[53] supports this assumption; however, in briefly abstinent smokers topiramate may also enhance withdrawal and rewarding effects when relapsing, thus calling into question its usefulness.[54]

Anxiety disorders and post-traumatic stress disorder (PTSD)

A broad area for the use of antiepileptic drugs in psychiatry is anxiety disorders, especially generalized anxiety (GAD), social phobia and panic attacks, as well as post-traumatic stress disorder (PTSD). This area has been most recently comprehensively reviewed by Mula et al.[16] Repetitive activation and kindling of brain structures involved in fear responses, such as the amygdala and the hippocampus, may result in an inadequate, excitatory output, similar to that observed in epilepsy. Thus, ACs could be of potential value by limiting this excessive activation. Open studies provide some limited evidence for the usefulness of carbamazepine in PTSD,[55-57] whereas for other anxiety syndromes the evidence is vague or negative (eg, for panic disorder[58]). For valproate, one controlled study and several open studies reported efficacy in panic disorder alone or when accompanied by mood symptoms.[59] Lum[60] compared valproate with placebo for 6 weeks. He observed a significant reduction in the intensity and the duration of panic attacks. However, this study is clearly limited by the small number of patients (n=12). Also of interest is an open study by Keck.[61] In patients with a history of panic attacks, panic attacks were induced by lactate infusions. After treatment with valproate for 1 month, almost half of the patients were free of spontaneous panic attacks, and 10 out of 12 patients tested no longer developed panic attacks provoked by lactate infusions. For other anxiety syndromes and PTSD, evidence is again restricted to open-label trials (eg, ref 62) and case series.

Moderate evidence stemming from a small, but controlled study exists for the use of lamotrigine in PTSD[63]; however, no proper-sized randomized studies have been conducted so far. Another double-blind, placebo-controlled trial assessed efficacy and safety of topiramate monotherapy in civilian posttraumatic stress disorder and found evidence supporting topiramate's efficacy.[64] The GABA transporter inhibitor tiagabine and GABA transaminase blocker vigabatrine, which theoretically should be useful in anxiety states,[65] were either not tested in controlled studies (vigabatrine) or could not fulfil the promises of open studies in a randomized placebo-controlled study of GAD (tiagabine[66]).

This situation is different for two other antidepressants, gabapentin and pregabalin. For gabapentin, two double-blind placebo-controlled studies showed positive results in panic disorder and social phobia.[67,68] Even more compelling is the evidence for pregabalin. Five positive double-blind, placebo-controlled studies in GAD[69-73] and one positive controlled study in social phobia[74] make this compound indeed a well-proven anxiolytic medication. For GAD, an optimal dosage of 200 to 450 mg /day had been determined.[75]

Agitation in dementia

Following up on earlier observations that antiepileptic drugs reduce aggressiveness in behaviorally disturbed epileptic patients, several antiepileptic drugs were also tested in demented patients with destructive behavior. After several case reports showed efficacy on aggressiveness with valproate, a recent review article by Lindenmayer[76] analyzed these case reports of violent and aggressive demented patients and found an overall response rate of 77.1%, defined as an at least 50% improvement on the applied scale for aggressiveness. However, a combined analysis of four small controlled studies could not support valproate's efficacy.[77] Case reports also suggested beneficial effects of lamotrigine,[78] gabapentin,[79] and levetiracetam[80] in agitated and aggressive demented patients, but, as with other indications there is still an obvious need for more controlled studies.

Pain

Many neurologists might object to a section on pain as a psychiatric condition. However, most types of pain cannot be conceptualized as a pure neurological dysfunction, but also involve strong subjective and emotional aspects. The exact mechanisms of how ACs work in pain conditions are far from being understood; however, it is intuitive that they may be able to dampen many of the proposed causes of chronic pain, such as peripheral sensitization, central sensitization, wind-up, hyperexcitability, neuronal disinhibition, ectopic impulse formation, and finally, the subjective impression and emotional handling of pain. For example, abnormal activation of the NMDA receptor is believed to be an integral part of kindling in epilepsy as well as wind-up in neuropathic pain; consequently, pharmacologic agents that suppress this excitation may explain their utility in both conditions.[81] In addition, as already detailed in the section on neurobiology, several ACs also have intrinsic, antidepressant–like effects on serotonin and noradrenalin, eg, the long known activating effect of carbamazepine on locus coeruleus neurons,[82] the postsynaptic serotonin $(5\text{-HT})_{1A}$ receptor activity of lamotrigine in the forced swimming test,[83] the presynaptic enhancement of serotonin transmission by valproate via a subsensitization of 5-HT_{1A} autoreceptors,[84] and theories about the close linkage between depression and epilepsy have been evolved.[85] Given the efficacy of several antidepressants in pain conditions, these effects may be helpful for the subjective side of pain.

Not all ACs appear to be as effective as antidepressants (tricyclics and noradrenalin and serotonin reuptake inhibitors) in treating pain syndromes,[86] but at least gabapentin and pregablin can be recommended, among other medications, as first-line treatment for neuropathic pain[87,88] and related conditions. Both medications are also licensed for the treatment of neuropathic pain, based on a large portfolio of controlled studies.

Relief from pain has been greater with gabapentin than with placebo in controlled studies of postherpetic neuralgia (PHN), painful diabetic polyneuropathy (DPN), phantom limb pain, diverse peripheral neuropathic pain conditions, Guillain-Barré syndrome, neuropathic cancer pain, and acute and chronic spinal cord injury pain.[89-98] The effective dosage in these studies was usually between 1800 and 3600 mg/day. In addition, several of these studies described positive effects on mood and sleep quality.

Pregabalin has demonstrated efficacy in seven controlled studies in PHN, DPN, or either of these conditions[99-105] A randomized controlled trial in patients with spinal cord injury neuropathic pain also demonstrated greater pain relief with pregabalin than with placebo.[106] Maximum benefits typically occurred after 2 weeks of treatment at target dosages of 300 to 600 mg/day.

In contrast to their established efficacy in trigeminal neuralgia,[107,108] carbamazepine and oxcarbazepine have yielded inconsistent results in controlled studies of other types of neuropathic pain.[86] These studies have generally had limited methodological quality.

Three positive trials of valproate in DPN or PHN were reported from a single center, but a controlled study conducted in patients with painful polyneuropathies by a different research group was negative.[109] In migraine prophylaxis, however, several studies, including a Cochrane meta-analysis, clearly support the efficacy of valproate.[110]

In a number of relatively small randomized studies, lamotrigine showed evidence of efficacy in several types of neuropathic pain or in subgroups of patients with these conditions. However, intention-to-treat analyses were negative in three large recent randomized controlled studies, two of which were in painful DPN[111] and one in neuropathic pain of different origin.[112]

In patients with painful DPN, topiramate showed efficacy in one RCT but not in three others, and its efficacy was equivocal in a trial of chronic lumbar radicular pain.[87] In migraine, at least five controlled studies now support the efficacy of topiramate.[113-117]

Pharmacological aspects

Schizophrenia

Although not licensed in this indication, antiepileptic drugs, especially carbamazepine and valproate, are also widely used in schizophrenic patients who do not improve sufficiently on neuroleptic medications. This may be the case in up to 20% of all schizophrenic patients.[118] GABAergic drugs, such as valproate or carbamazepine, may decrease the dopaminergic drive by acting on the mesoprefrontal dopamine tract. Consecutively, Simhandl et al[119] reported a significant effect in chronic schizophrenia for adjunctive carbamazepine treatment in an 8-week double-blind, placebo-controlled study. However, the use of carbamazepine may also diminish serum levels of some antipsychotics, eg, risperidone or haloperidol, and thus lead to worsening of psychosis.[120] A recent Cochrane meta-analysis also came to the conclusion that carbamazepine cannot be recommended for routine clinical use for the treatment of augmentation of antipsychotic treatment of schizophrenia.[121]

The widespread use of valproate—especially in the US—in schizophrenic patients is backed up by at least 6 open positive studies including difficult-to-treat late-life schizophrenia,[122] and two double-blind add-on studies.[123,124] A meta-analysis including all randomized studies, however, again gave no unambiguous evidence in favor of valproate.[125]

The antiglutamatergic actions of lamotrigine and topiramate may be of particular interest because of hypothesized glutamatergic mechanisms in schizophrenia. They may be capable of reducing excessive glutamatergic hyperactivity due to selective NMDA receptor blockade of interneurons.[126] A well-controlled experimental study observed protective effects of lamotrigine against ketamine-induced psychosis[127] followed by three blinded, placebo-controlled studies in which lamotrigine was shown to be effective (in combination with clozapine or other atypical antipsychotics) in treatment-refractory schizophrenic patients.[128-130] However, again, a meta-analysis including all randomized studies was not able to support lamotrigine's effectiveness, mostly due to the poor quality of reporting of every single trial.[131] For topiramate, a small (n=26) but placebo-controlled add-on study of ongoing atypical antipsychotics was suggestive of effects on general psychopathology, but was unable to show a significant improvement in positive or negative symptoms.[132]

Affective disorders

Unipolar depression

Although large randomized, placebo-controlled monotherapy trials failed,[133] lamotrigine may be of interest for the treatment of refractory unipolar depression. Retrospective chart reviews (eg, ref 134) open[135] and randomized open-label,[136] and controlled augmentation studies[137,138] are supportive of an antidepressant effect of lamotrigine add-on in treatment-resistant major depressive disorder (MDD).

In a double-blind, placebo-controlled study, topiramate appeared to be an effective agent in the reduction of depressive symptoms and anger in moderately depressed women,[139] but these results have not yet been replicated.

Of the older anticonvulsants, carbamazepine has shown limited evidence in open studies for an acute antidepressant[140-143] and prophylactic effect.[144] Valproate may be effective in major depression as demonstrated by an open trial,[145] especially when agitation is a prominent symptom,[146] but conclusive controlled studies are missing. Phenytoin showed some efficacy in a comparator study against fluoxetine,[147] but not in an augmentation study in SSRI nonresponders.[148]

Bipolar disorder

The classical psychiatric indication for antiepileptic drugs is clearly bipolar disorder. Licensed in this indication or at least used with good evidence are valproate, carbamazepine, and lamotrigine, but phenytoin, oxcarbazepine, levetiracetam, topiramate, zonisamide, and gabapentin may also be beneficial in some, yet insufficiently characterized patients. Carbamazepine has proven antimanic[149] and prophylactic efficacy,[150] and has been traditionally used in patients who were not sufficiently responding to lithium. Comparing the prophylactic efficacy of carbamazepine against lithium, the two most recent studies suggest superiority of lithium treatment.[151,152] However, carbamazepine appeared in the MAP study to be the better alternative for atypical manifestations of bipolar disorder, such as rapid cycling course, frequent recurrence of dysphoric or psychotic mania, or other comorbid psychiatric or neurological conditions.[153] In patients not sufficiently responsive to lithium, addition of carbamazepine can greatly enhance prophylactic efficacy as shown in a large controlled study.[154] Valproate has nowadays established itself as a first-line

treatment of acute mania. Superiority over placebo has been shown in double-blind controlled monotherapy and add-on studies.[155-158] Compared with lithium, valproate was especially effective in conditions less responsive to lithium such as mixed states and a rapid cycling course.[159] For bipolar depression, one small placebo-controlled study has been published, showing significant effects.[160] The so-far only large-scale randomized maintenance study comparing valproate against placebo and lithium could not prove efficacy either for valproate or lithium for the primary outcome criterion (time to any mood episode). Further analysis revealed that this was mainly due to a selection bias, as patients having a benign course of the illness were overrepresented in the study. Looking for secondary outcome parameters, however, clinically useful information was detected, eg, valproate was significantly better than placebo in preventing new depressive episodes. In addition, patients who were previously responsive to valproate when treated for an acute episode also performed better when randomized to valproate maintenance treatment compared with when randomized to lithium or placebo. However, reanalyzing this study together with other, smaller studies, a meta-analysis was able to support the prophylactic efficacy of valproate.[150]

It is of note that phenytoin-exerted antimanic and prophylactic properties, but no antidepressant action, has also been found in randomized, placebo-controlled studies.[161-163] This has been interpreted as potential proof for an involvement of sodium channel dysregulation in manic states. However, other mechanisms, such as an as anti-glucocorticoid mechanism, are also possible.[164]

Of the new generation of antiepileptic drugs, lamotrigine in particular is a useful addition to the treatment portfolio. For acute bipolar depression, only one study showed a positive result in a secondary outcome parameter,[165] whereas three further studies failed to separate it from placebo. In direct comparison with other treatment modalities, lamotrigine was equal to citalopram,[166] but less effective than the olanzapine/fluoxetine combination[167] or tranylcypromine.[168] The place of lamotrigine in bipolar disorder is obviously in prophylactic treatment. Two double-blind, randomized maintenance trials over 18 months proved the efficacy of lamotrigine when compared with placebo and lithium.[169,170] Both lamotrigine and lithium were superior to placebo. Looking for differential rates of relapse, lamotrigine was more effective in preventing new depressive episodes, whereas lithium was better in preventing manic episodes.[171] This finding is also reflected in a double-blind study where lamotrogine was effective against acute bipolar depression.[165]

For oxcarbazepine, a double-blind study against haloperidol in acute mania showed comparable efficacy.[172] In a more recent study applying an on-off-on design, however, oxcarbazepine appeared inefficacious in severely manic patients, but only in mildly to moderately manic patients.[173] This is in line with a recent randomized, single-blind trial showing similar efficacy of oxcarbazepine and valproate in hypomania.[174] In addition, a randomized, controlled study in adolescent mania failed to separate oxcarbazepine from placebo;[175] thus, the case for oxcarbazepine in acute mania is rather weak. As far as bipolar depression and prophylactic treatment are concerned, evidence from methodologically rigorous trials is also lacking.

The story of gabapentin in bipolar disorder is largely similar: after promising open studies, two add-on studies in acute mania failed.[176,177] For bipolar depression, open augmentation studies suggest some efficacy in the absence of controlled data.[178,179] As far as long-term treatment is concerned, a recent controlled maintenance study suggests that maintenance treatment with gabapentin can be beneficial,[180] but larger replication studies are needed.

For levetiracetam, positive open studies in acute mania[181,182] have been reported, but controlled evidence is missing. More recently, a 31% remission rate was reported in patients with bipolar disorder who were in the depressed phase at baseline and who received levetiracetam as add-on therapy for 8 weeks in an open-label trial.[183] Other modern antiepileptic drugs, such as tiagabine and retigabine, appear not to be promising in bipolar disorder.[184-189]

Topiramate first appeared to be a promising treatment option in pilot studies; however, five double-blind, randomized studies could not prove efficacy in acute mania.[190,191] Nevertheless, due to their weight-reducing effect, topiramate as well as zonisamide, which showed distinct antimanic and antidepressant properties in open trials,[192-196] may still be options as an add-on treatment in patients who massively gain weight with established mood stabilizers.

Personality disorders

Personality disorders accompanied by mood instability may be a potential target for ACs. In a double-blind, placebo-controlled crossover trial, carbamazepine significantly decreased the severity of behavioral problems in 11 women with borderline personality disorder.[197] Open stud-

ies also suggest efficacy of valproate, lamotrigine, and oxcarbazepine in borderline personality disorder,[198-201] but controlled studies are missing. Of the newer ACs, the efficacy of topiramate has been tested by one group of investigators in controlled studies, showing efficacy, especially on symptoms related to anger,[202-204] but replication of these positive results from other investigators is still lacking.

Conclusion

Anticonvulsants as a group are today an established part of the treatment portfolio in many psychiatric conditions, especially in bipolar disorder, anxiety, and pain disorders. In some instances, their use in psychiatric indications may even exceed their use in epilepsy. However, their individual strengths in these different indications, and the strength of recommendations, may vary considerably. The story will continue, as new anticonvulsants such as lacosamide, rufinamide, talampanel, eslicarbazepine, 10-hydroxy carbazepine, valrocemide, isovaleramide, brivaracetam, and seletracetam are potential future candidates for psychiatric indications, and some of them are already in the process of being tested in clinical trials. ❑

La efectividad de los anticonvulsivantes en los trastornos psiquiátricos

Los medicamentos anticonvulsivantes son ampliamente utilizados en indicaciones psiquiátricas. Estas incluyen principalmente los síndromes de privación por alcohol y benzodiazepinas, trastornos de ansiedad y de pánico, demencia, esquizofrenia, trastornos afectivos, especialmente el trastorno afectivo bipolar, y en alguna medida en los trastornos de personalidad. Un área adicional en la que la neurología y la psiquiatría se sobreponen es en las condiciones de dolor, en las cuales son útiles algunos anticonvulsivantes y también medicamentos psiquiátricos típicos como los antidepresivos. Desde el inicio de su empleo en psiquiatría los anticonvulsivantes se han usado también para reducir síntomas específicos de trastornos psiquiátricos, independientemente de su causalidad y de la enfermedad subyacente; por ejemplo, para la agresión y más recientemente, para el deterioro cognitivo, y como se observa en los trastornos afectivos y en la esquizofrenia. Es probable que en psiquiatría aumente el empleo de los nuevos anticonvulsivantes que están en desarrollo y que los psiquiatras necesiten aprender acerca de su eficacia diferencial y perfiles de seguridad al igual que los neurólogos.

Efficacité des anticonvulsivants dans les troubles psychiatriques

Les anticonvulsivants sont largement utilisés en psychiatrie. Le traitement des syndromes de sevrage d'alcool et de benzodiazépines, des attaques de panique et des troubles anxieux, les démences, la schizophrénie, les troubles affectifs, en particulier les troubles bipolaires, et, d'une certaine façon, les troubles de la personnalité, font tous partie des indications psychiatriques. La douleur est un autre domaine dans lequel la neurologie et la psychiatrie se chevauchent : certains anticonvulsivants, et aussi des médicaments typiquement psychiatriques, comme les antidépresseurs, sont utiles dans certains cas. Les anticonvulsivants ont aussi, depuis le début de leur utilisation en psychiatrie, été employés pour améliorer les symptômes spécifiques des troubles psychiatriques indépendamment de leur étiologie et de la maladie sous-jacente. Ces indications peuvent inclure par exemple, l'agressivité, et, plus récemment le déficit cognitif, comme les troubles affectifs et la schizophrénie. Il est probable que leur utilisation en psychiatrie va augmenter avec les nouveaux anticonvulsivants actuellement en développement, et que les psychiatres vont devoir apprendre à connaître leurs différents profils d'efficacité et de tolérance comme le font les neurologues.

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