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Review

Non-epilepsy uses of antiepileptic drugs

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Abstract:
Antiepileptic drugs (AEDs) affect various neurotransmitters (i.e. GABA, glutamate), receptors (i.e. GABAergic, glutamatergic), and ion channels (i.e. for sodium or calcium) which is responsible for their anticonvulsant activity. However, this broad spectrum of action may be also utilized in other pathological conditions. For example, both conventional and newer AEDs may be used in patients suffering from neuropathic pain, migraine, essential tremor, spasticity, restless legs syndrome and a number of psychiatric disorders (f.e. bipolar disease or schizophrenia). Also, isolated data point to their potential use in Parkinson's or Alzheimer's disease. There is experimental background indicating a potent neuroprotective efficacy of AEDs in numerous models of brain ischemia. However, the clinical data are very limited and this problem requires careful assessment.

Key words:
antiepileptic drugs, bipolar disorder, migraine, neuropathic pain, neuroprotection

Abbreviations: AEDs – antiepileptic drugs, BED – binge eating disorder, CABG – coronary artery by-pass graft, CNS – central nervous system, EBM – evidence-based medicine, GABA – γ-aminobutyric acid, HIV – human immunodeficiency virus, PDN – painful diabetic neuropathy, PHN – post-herpetic neuralgia, RLS – restless legs syndrome, U.S. FDA – United States Food and Drug Administration.

Introduction

The goal of this article is to present available experimental and clinical evidence of the use of antiepileptic drugs (AEDs) in diseases other than epilepsy. We focus on randomized, controlled trials, but also take into account open-label studies and case reports. Also, some experimental data have been reviewed.

AEDs can be divided into conventional and newer ones. The first group includes among others: benzodiazepines, carbamazepine, phenobarbital, phenytoin, valproate, and the second one comprises: felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, vigabatrin, zonisamide.

Although there are some main mechanisms of action of AEDs, most of these drugs act *via* more than one mechanism [19, 93]. AEDs may be divided into

three principal groups. The first one includes carbamazepine, oxcarbazepine, gabapentin, lamotrigine, phenobarbital, phenytoin, topiramate, and valproate, which reduce high-frequency repetitive firing in neurons by blockade of voltage-dependent sodium and calcium channels. AEDs belonging to the second group enhance GABA-mediated events (*via* interaction with specific binding sites on the $GABA_A$ receptor complex, inhibition of GABA metabolism or reduction of its neuronal uptake): benzodiazepines, gabapentin, phenobarbital, tiagabine, topiramate, vigabatrin, valproate. The third group includes ethosuximide and zonisamide, which act through blocking T-type calcium channels. Also, an additional category of AEDs may be distinguished, comprising felbamate, phenobarbital and topiramate which directly reduce excitation mediated by excitatory amino acids [19]. However, all mechanisms of action of newer AEDs are still not fully clear. It is noteworthy that the tolerability of novel AEDs is much better than that of conventional ones, which induce relatively more frequently adverse effects, like for instance cognitive impairment, hepatotoxicity, or rash [19, 93].

Neuropathic pain syndromes

Neuropathic pain is defined by the International Association for the Study of Pain as a symptom caused by dysfunction in the central (CNS) or peripheral nervous system. The development of neuropathic pain is connected with a series of changes in the nervous system, including hyperalgesia, sensitization, and wind-up phenomena [60]. The examples of pain syndromes include: post-herpetic neuralgia (PHN), painful diabetic neuropathy (PDN), central poststroke pain syndrome, trigeminal neuralgia and human immunodeficiency virus (HIV)-associated neuralgia. Clinically, patients may feel a dull, throbbing, burning or shooting attack of lancinating pain.

Historically, phenytoin was the first among AEDs, whose analgesic effect in neuropathy was documented more than fifty years ago [5]. Consequently, AEDs have been commonly used in the management of neuropathies since 1960s.

There are similar pathophysiological and biochemical reactions in neuropathic pain syndromes and in epilepsy. Therefore, AEDs can prove their efficacy in the management of this condition. They are a group of drugs displaying a common clinical effect (i.e. analgesic) in neuropathy. Most of them can reduce neuronal hyperexcitability by inhibiting ion channels, although simultaneously they may act on different parts of the nociceptive pathway. Therefore, if one AED is ineffective, it is rational to try another one [60].

Carbamazepine is the most extensively investigated AED used in the management of trigeminal neuralgia. This compound was approved by the United States Food and Drug Administration (US FDA) and is considered to be the treatment of choice for this condition. Daily doses ranging from 100–2400 mg caused pain relief or lower pain ratio in about 70% of patients compared with 25% of those receiving placebo [61].

In PDN only two small-sized, double blind, placebo-controlled studies were performed [55, 92], which showed only marginal superior analgesic effect of carbamazepine.

Carbamazepine cannot be also recommended as a first-line treatment in PHN, because of the lack of evidences for its efficacy from randomized trials. Large studies based on principles of evidence-based medicine (EBM) are needed to determine the role of carbamazepine in the management of diabetic and post-herpetic neuropathies.

Oxcarbazepine is a keto-derivative of carbamazepine that shares its antiepileptic and analgesic effects, while exhibiting a significantly better tolerability profile. This AED has been reported to be effective in patients with painful radiculopathy refractory to gabapentin [97]. However, this trial was not randomized and small-sized (18 patients). In patients with trigeminal neuralgia, oxcarbazepine (medium daily dose of 750 mg) has the same efficacy as carbamazepine, which has been proven in three multicenter trials [7, 8].

Current reports suggest that this is an effective agent in PDN and in patients refractory to the other AEDs. However, in patients with PDN this recommendation is based on open-label prospective, small-sized studies [15]. At present, five large, randomized, placebo-controlled studies in patients with PDN and lumbar radiculopathy are under way.

Phenytoin was the first drug used in the treatment of trigeminal neuralgia but there has been no randomized placebo-controlled trial in this disorder. Two randomized trials in diabetic neuropathy were performed. It was reported to be superior to placebo in one of these studies [16], but was found to be ineffective in

the other [77]. Nowadays, phenytoin is not widely used for other than epilepsy reasons, because of its particular adverse effect profile.

Valproate. There are some case reports showing effectiveness of valproate in the treatment of trigeminal neuralgia [68], post-herpetic neuropathy [71] and other neuropathies. In these studies, valproate relieved pain in some patients, but many of them were simultaneously treated with carbamazepine, phenytoin or clonazepam. Therefore, these results are not fully reliable.

The only double-blind, placebo-controlled trial in patients with spinal cord injuries failed to find out any beneficial effect of this AED [21]. There were no significant differences in analgesic effects between active-drug group and placebo-group.

At present, outcomes of further clinical trials are awaited.

Gabapentin. This agent was evaluated in five large (over 100 patients), randomized, double-blind clinical trials: two studies involved patients with PDN, the next two trials were carried out in patients with PHN and the last one with mixed neuropathy. In the US trial in patients with PDN, 165 of them were randomized into two groups (active drug and placebo) [2]. Gabapentin was titrated from 900 to 3600 mg/day (determined by each patient's maximum tolerated dose). Statistically significant decrease in mean pain score was observed in the gabapentin-treated group (from 40.6% to 21.6%).

Two trials in patients suffering from PHN comprised, respectively, 229 persons in the US study [74] and 334 ones in the British study [73]. Daily doses ranged from 900 to 3600 mg in the US study and 1800 or 2400 mg in the latter (based on a maximum tolerated dose for each patient). Significant reductions in pain score were achieved in both trials.

The Mixed Neuropathic Pain Syndromes Study [85] was performed in the United Kingdom and comprised 305 patients. Gabapentin was titrated from 900 to 2400 mg/day. Statistically significant improvement in pain scores was observed in patients receiving gabapentin as compared to placebo.

Gabapentin appears to have relatively good safety profile. This AED is probably the best agent of new generation AEDs, used for the treatment of neuropathic pain, studied so far [57].

Lamotrigine. There are some evidences showing that this agent can be effective in neuropathies, even refractory to other treatment methods (pharmacological and surgical).

It was significantly better than placebo in the management of trigeminal neuralgia [101].

A similar effectiveness was achieved by lamotrigine in PDN, when a daily dose was over 200 mg [49].

The significant reduction of pain was also achieved in two other studies: in patients with HIV-associated neuropathy [87] and poststroke pain [96]. Lamotrigine is usually initiated at 50 mg/day and increased by 50 mg weekly up to 300–400 mg.

Nevertheless, still large well-designed trials are needed to better define a role of this agent as an analgesic drug.

Topiramate. Clinical experience with this compound is limited. It was found to be effective in only one small (27 persons), placebo-controlled trial in patients with diabetic neuropathy [24]. However, the outcomes of other three trials of topiramate in PDN have not shown any better analgesic effects over placebo [90].

Also, there were no beneficial effects of this drug in patients with trigeminal neuralgia in the multicenter, double-blind study [32]. Therefore, the question whether topiramate has any place in other neuropathic pain syndromes still remains open.

Pregabalin. The only randomized trial comparing three different doses of pregabalin (75, 300 and 600 mg/daily) to placebo was performed in 337 patients with diabetic polyneuropathy [40]. The significant decreases in pain severity and associated sleep disorders were observed for those, who took 300 mg or more daily [40].

If other clinical trials show similar results, pregabalin will be another rational option in the management of neuropathic pain syndromes.

There have been so far insufficient data in the literature to evaluate the role of the other AEDs (phenobarbital, felbamate, vigabatrin, zonisamide, tiagabine) in the treatment of neuropathic pain.

Finally, one can conclude that some AEDs represent very important treatment option in neuropathic pain conditions. At present, the best evidences have been presented for efficacy of gabapentin in neuropathic pain syndromes and relatively well-tolerated adverse effect profile *vs*. other AEDs. It should be used as one of the first-line drugs (with tricyclic antidepressants) in PDN and PHN [2, 74]. Carbamazepine is also recommended as a treatment of choice for trigeminal neuralgia [61], but not for PDN [55, 92].

For some patients, treatment plan must be individualized. If one AED is ineffective, it should be changed to another member of the same class. If the pain is not controlled by a single medication, a combination therapy may be more successful. Unfortunately, the existing data on combination drug therapy for neuropathic pain are insufficient.

Migraine and tension-type headache

Migraine is an idiopathic, clinical disorder with typical symptoms: unilateral pulsating pain, which usually lasts 45 to 72 h, nausea, phono- or photophobia. The frequency of this disorder in adults ranges from 13% to 40% in women and from 3% to 33% in men [88].

Tension-type headache, in contrast to migraine, is usually diffuse, bilateral, pressing and rarely associated with nausea [62].

Some patients with migraine or tension-type headache require a prophylactic therapy because of frequent recurrences. There are several groups of drugs, which can be used in migraine prevention: triptans, β-adrenergic antagonists, calcium channel blockers, antidepressants and AEDs. Using AEDs in this disorder can be justified by their action on metabolism of GABA and presumed neurogenic vascular effect [5].

Valproate. This is the only AED approved by the US FDA for migraine prophylaxis. The effectiveness of valproate as a prophylactic agent was confirmed in two double-blind, placebo-controlled studies. The first one lasted 16 weeks and comprised 107 patients in two groups [53]. The significant reduction of days with migraine headaches was reported in active drug group compared with placebo-group. In the second study, valproate was administered in three doses 500, 1000 and 1500 mg/day in 171 patients [45]. The results proved that this AED provided an efficient prophylactic treatment and was generally well tolerated.

Gabapentin. The only double-blind, placebo-controlled, randomized trial of gabapentin in migraine prevention was performed in 143 patients (45 in placebo-group and 98 in gabapentin-group). Daily doses of active drug during fixed-dose phase ranged from 1800 to 2400 mg/day. About 46% of patients receiving active drug had over a 50% reduction of frequency of headaches (daily dose 2400 mg), compared with 16% in placebo-group [52].

Topiramate. Several open-label studies and two double-blind, randomized trials of topiramate in migraine prophylaxis have been published so far. The populations in both randomized trials were rather small – 30 and 40 patients, respectively [25, 69]. A maximum daily dose was 200 mg. The frequency of migraine attacks was significantly lower in topiramate-group than in placebo-group. But further investigations in larger populations are required to confirm these findings.

The randomized trials of valproate, gabapentin and topiramate proved their effectiveness in migraine prophylaxis. There are no randomized, placebo-controlled trials confirming efficacy of other AEDs in prophylactic therapy of headache disorders.

Essential tremor

Essential tremor is probably of CNS origin. It is postural and kinetic tremor, caused by contraction of agonist and antagonist muscles. It can affect all somatic muscles but most frequently arms are involved [20]. Some of AEDs block sustained repetitive firing in neurons [19] and this might be a reason for their efficacy in this neurological condition.

Primidone and propranolol are first-line drugs in management of this disorder. In patients refractory to this therapy, other treatment options can be helpful: benzodiazepines, gabapentin, topiramate, botulinum toxin.

Several studies have shown that primidone significantly better reduces tremor than placebo and phenobarbital and is equally effective as propranolol [29, 34, 76]. Daily doses in the trial with primidone ranged from 250 to 1000 mg and its effectiveness was not dose-dependent [46].

Gabapentin. It was compared with propranolol and placebo by Gironell et al. [33].

Gabapentin was titrated at doses of 1200 mg/day and propranolol at 120 mg. Gabapentin had the same efficacy as propranolol and was evidently superior to placebo. But in another study, there were no statistical differences between this AED and placebo [64]. These trials, however, possess low statistical power because of small number of patients involved, 16 and 18, respectively.

Topiramate was found in small (24 patients), placebo-controlled study to cause an improvement in patients with essential tremor [18].

Therefore, large double-blind, multi-center trials are awaited to define the place of topiramate and gabapentin in management of this condition.

Spasticity

Spasticity is a clinical symptom connected with different CNS disorders.

Progabide. This is the most investigated of AEDs in this condition. It has shown its efficacy in some studies, but a real problem with this drug is its hepatotoxicity [75]. Therefore, progabide has been withdrawn from markets of several countries.

Vigabatrin was also effective in small-sized trial, in which it was given at doses from 2000 to 3000 mg/day [35].

Gabapentin is another alternative drug, which was effective in significant reduction of pain and spasticity in two small trials including patients with multiple sclerosis [58] and spinal cord injury [36].

The existing data are promising, especially for gabapentin and vigabatrin, but large studies are necessary before these AEDs can be recommended for clinical use in spasticity.

Restless legs syndrome

Restless legs syndrome (RLS) is a common condition in people over 65 years old. Typical symptoms include paresthesia, dysesthesia of the legs and desire to move limbs, especially in the evening. It can cause related problems like insomnia and depression. This syndrome can be a primary disorder or a secondary one, associated with for example iron-deficiency, uremia or polyneuropathies [78].

The most commonly used drugs are: ergotamine dopamine receptor agonists (pergolide), non-ergotamine dopamine receptor agonists (pramipexole, ropinirole) and levodopa [78].

Some patients (especially with painful symptoms) may respond to AEDs such as carbamazepine, gabapentin and valproate.

Carbamazepine demonstrated its efficacy in relieving paresthesia in two placebo-controlled studies [38, 81]. The drug was given in the evening at doses between 100 and 400 mg/day.

Gabapentin. Current evidence of using this AED in RLS is limited to one non-blind study and only one placebo-controlled study. This trial was performed in patients with a secondary form of RLS, caused by renal insufficiency [91]. It was titrated from 100 to 400 mg in the evening and proved its superiority over placebo.

AEDs remain the second-line option in the treatment of RLS, especially recommended if the dopaminergic drugs are ineffective. Further trials in patients with this disorder are awaited.

AEDs in psychiatry

Bipolar disease

Carbamazepine was the first AED used in bipolar disorder. There are around twenty double-blind studies examining the efficacy of carbamazepine and its keto-derivative, oxcarbazepine. In pooled analysis, approximately 70% of over 400 patients with mania demonstrated significant positive response [13]. These findings were confirmed by data from five randomized trials, where carbamazepine was compared to lithium and chlorpromazine [43]. The results were similar in all three groups. In another randomized trial in mania, Emrich [26] revealed a comparable response of oxcarbazepine to haloperidol and lithium.

Valproate is another AED commonly used in mental illnesses. The US FDA approved it for the treatment of manic-phase of bipolar disorder. Two randomized, multi-center, double-blind clinical trials of valproate *vs*. lithium *vs*. placebo have been performed by Bowden et al. in 1994 and 2000 [10, 11]. Overall outcomes (measured on Mania Rating Scale) were significantly better for group of patients treated with valproate than in lithium-group or placebo-group.

Gabapentin. Two placebo-controlled studies of gabapentin in bipolar disorder have been published. The first one evaluated gabapentin (daily doses between 600 and 3600 mg) as an add-on therapy in pa-

tients with symptomatic mania or mixed episodes treated simultaneously with lithium, valproate or both. Gabapentin had no superiority over placebo [65]. In the second study, gabapentin also failed to achieve a significant difference to placebo [30]. Anyway, Yatham [100] represents a point of view that no final conclusions can be drawn at present and gabapentin should complete more double-blind trials.

Lamotrigine was an effective treatment for bipolar depression and relatively safe, because it did not increase the risk of inducing mania. This was proved by Calabrese et al. [12] in 199 patients. The same group [14, 59] then supported these results in other two open-label trials. The preliminary results from the recent study, which comprised over 900 patients, also confirmed the efficacy of lamotrigine [8]. This agent appears to be promising especially in some syndromes and subtypes (rapid cycling, dysphoric mania, commorbid substance abuse) refractory to traditional treatment (lithium). The available data suggest that combined treatment of lamotrigine and lithium can be beneficial for patients with bipolar disorder.

Currently, there are no sufficient data to support the use of topiramate in bipolar disorder. This AED does not seem to possess efficacy in the management of acute mania although its therapeutic potential in bipolar depression has not been evaluated in double-blind trials [100]. Phenytoin and also some other newer AEDs (levetiracetam, oxcarbazepine, and zonisamide) require more double-blind trials before they can be introduced to the management of bipolar disorder [100].

Schizophrenia and schizoaffective psychoses

The first-line drugs used in the management of schizophrenia are neuroleptics. However, this kind of treatment is not effective in all cases. Some patients have benefits from new treatment strategies (combination of neuroleptics and AEDs).

Carbamazepine. Most of 25 uncontrolled and 16 controlled studies of carbamazepine in schizophrenia showed a decrease in aggressive behavior, anxiety and depression, but lack of therapeutic effect on such psychosis symptoms like hallucinations and delusions [86]. It was usually administered as an adjunctive agent to neuroleptic drugs. Carbamazepine was observed to reduce the plasma level of haloperidol (by induction P 450 3A4 hepatic enzyme) [39]. Therefore, the use of carbamazepine (in combination therapy with neuroleptics) should only be recommended in a special group of schizophrenic patients with hyperactivity, violent outbursts and affective symptoms. Some patients refractory to traditional therapy (neuroleptics), who respond to carbamazepine may have unrecognized epilepsy.

Valproate is commonly applied in combined therapy of schizophrenia, especially in aggressive patients. However, there are no significant evidences for efficacy of valproate based on large placebo-controlled trials.

There are also only anecdotal observations and case reports, which suggest the benefits of treatment with lamotrigine as an adjunctive agent in schizophrenic patients [22, 28].

At present, there is only partial consensus on the use of AEDs in schizophrenia resistant to the first-line therapy. AEDs should be combined with neuroleptics in patients with violent behavior, hyperactivity and EEG abnormalities.

Novel AEDs deserve further studies in schizophrenia.

Other psychiatric or neurodegenerative disorders

Statistically significant alleviation of **social phobia** symptoms has been observed (on all major scales) in gabapentin-treated group in a randomized study conducted by Pandee et al. [66]. In this study, 84 patients were treated for 14 weeks with gabapentin (daily doses of 900 to 3600 mg) or placebo. Because of small size of this group further trials are needed to confirm these results.

In another trial, gabapentin was used in patients with **panic disorder** [67]. There was no difference in scores (measured on Panic and Agoraphobia Scale) between active drug group and placebo-group.

Binge eating disorder (BED) is the most common eating disorder. People who suffer from this disease are usually obese and have a great risk of such diseases as diabetes mellitus, hypertension, atherosclerosis and coronary artery disease. Similar abnormalities in EEG were identified in patients with BED and epilepsy. Therefore, AEDs were evaluated in these patients.

Phenytoin, valproate and carbamazepine failed to be effective in this disorder, because of their appetite-increasing effect [47].

The most promising agent is topiramate. It was tried in two open and one placebo-controlled randomized trial. In the latter study, topiramate was found to be significantly better than placebo and the effect was dose-dependent [54, 79]. Patients (64%) stopped eat-

ing in topiramate-group compared to 30% in placebo-group. An overall of 58 patients took part in this study which lasted 14 weeks. Significance of these data may be limited because of small group size (only one randomized study in 58 patients), short-term observations, being a single-center trial.

The research in the binge eating disorder is still in early stages. Current data indicate that antidepressants, appetite suppresants and AEDs are effective agents in this disorder. Further large, rigorously-designed trials are awaited to prove these promising results.

Pregabalin has some efficacy in generalized anxiety disorder but so far, this AED has not been evaluated in bipolar disease [100].

Gabapentin has been also tried in one double-blind, placebo-controlled, crossover trial in **Parkinson's disease.** This AED reduces rigidity, bradykinesia and tremor. As the trial was small-sized (only 19 patients), therefore, further trials are necessary to clarify its efficacy in Parkinson's disease [63].

Lamotrigine gave promising outcomes in patients with **Alzheimer's disease** [89], cocaine addiction [51] and mood disorders [30]. But these results should be proved in further larger trials.

Neuroprotection

There are many pathophysiological similarities between cerebral ischemia and epilepsy. Both events lead to cell loss and activate autoprotective mechanisms in the brain. Reports suggest that AEDs can be useful not only in epilepsy but also as neuroprotectant agents in ischemic stroke [48]. Most of AEDs have already been tested in animal models of ischemia and produced very promising outcomes. The neuroprotective properties of some of them were evaluated in clinical, randomized trials in humans.

Barbiturates and benzodiazepines reduce energy consumption in the brain, but also decrease brain perfusion. Moreover, they failed to produce any positive effects in two studies [80, 84]. Therefore, these AEDs do not seem to be good neuroprotectants in ischemic conditions.

Phenytoin and fosphenytoin have been tested in an animal model of ischemia and they have been found to reduce mortality [17, 95]. But fosphenytoin (sharing a similar mode of action with phenytoin) decreased cerebral blood flow and has not shown any neuroprotective activity in a clinical trial [70].

Carbamazepine. Data concerning this agent are inconsistent. Its neuroprotective properties in a model of ischemic stroke have been documented [72], but failed in another one [56]. Moreover, carbamazepine reduces cerebral perfusion and is a CNS depressant [31].

Valproate was revealed to be completely ineffective as a neuroprotective agent in ischemia and had similar properties on cerebral blood flow and metabolism as carbamazepine [56, 93].

Lamotrigine has reduced the infarct size and mortality in animal models of ischemia, but also lowers the brain perfusion [72, 82, 93].

All the above-mentioned compounds have narrow therapeutic window (must be administered up to 30 min. from the onset of ischemia), limiting their use in ischemic stroke.

Felbamate, levetiracetam and zonisamide decreased the size of infarct in gerbils, but there are only single studies for each drug [9, 37, 56, 83, 93]. They are very promising drugs in ischemia due to their potential antiischemic properties, but further animal studies are needed prior to their use in clinical trials.

Remacemide significantly limited infarct volumes in animal models of focal ischemia, hypoxia and ischemic stroke [3, 50]. It was also used in humans to protect brain of patients during coronary artery bypass graft (CABG) surgery [1]. It was found to decrease the number of neuropsychological deficits in active drug treated group compared to placebo-group. In another study, remacemide proved to be relatively safe, but the phase 3 of this trial is awaited to determine its neuroprotective efficacy [23].

Topiramate was investigated in several experimental models of cerebral ischemia. These findings revealed its promising effects, i.e. reduction of motor disability and infarct volumes [99]. These investigators showed that the co-administration of topiramate and thrombolytic agent (urokinase) in ischemic stroke produced synergistic results [98]. These positive outcomes were dose-dependent and significant even when the drug was given up to 2 h from the onset of ischemic symptoms.

Tiagabine was evaluated in two studies in animals. It was administered 1 or 2 h after the ischemia onset [41, 42]. This AED reduced the hippocampal cell mortality, infarct size, brain and core temperature. The capability to induce hypothermia can be a very important mechanism in neuroprotection.

Vigabatrin effectively protected the effects of transient global ischemia in gerbils [93].

In conclusion, only two AEDs were applied as neuroprotectants in clinical trials (fosphophenytoin and remacemide). The first one did not show any neuroprotective properties [70] and the second one provided promising results in patients undergoing CABG surgery [1], but further studies are necessary.

Other AEDs – carbamazepine, phenytoin, valproate, barbiturates and lamotrigine have probably no neuroprotective potential in ischemic injury. These drugs reduce cerebral blood flow, have depressing activity on the CNS and very narrow therapeutic window. There are insufficient data to state whether felbamate, levetiracetam and zonisamide may be useful in neuroprotective strategy in ischemic stroke. Oxcarbazepine, vigabatrin and gabapentin have no published evidences for their clinical protective efficacy in cerebral ischemia.

Topiramate and tiagabine are the most promising neuroprotectants of AEDs, because they affect several different antiischemic pathways. Topiramate has anti-excitotoxic and GABAergic activity, while tiagabine acts through its hypothermic effects that probably also reduces excitotoxic and inflammatory damage [93]. Furthermore, these two agents were revealed to have significant efficacy in both global and focal ischemia (in animals) and broad therapeutic window [93]. Valproate, due to its positive effects upon bcl-2 proteins, protein kinase C and neurotrophic factors, may be of importance in the therapy of Parkinson's and Alzheimer's diseases [94].

Other indications

At present, there is only one indication for phenytoin in cardiology. This is ventricular tachyarrhythmia caused by overdosing of digitalis in hypokaliemia [4].

Phenobarbital is widely used for treating hyperbilirubinemia (ex. Gilbert syndrome), because it can lower the serum bilirubin level. Phenobarbital induces the enzyme glucuronyl transferase and increases bile flow [27].

Tab 1. Disorders and symptoms treated with some antiepileptic drugs

	CBZ	FBM	GBP	LEV	LTG	OXC	PHT	PRM	REM	TGB	TPM	VGB	VPA	ZNM
Neuropathic pain syndromes	+/–	0	+	0	+	+	+/–	0	0	0	+/–	0	+/–	0
Migraine and tension-type headache	0	0	+	0	0	0	0	0	0	+/–	+	0	+	0
Essential tremor	0	0	+/–	0	0	0	0	+	0	0	+	0	0	0
Spasticity	0	0	+	0	0	0	0	0	0	0	0	+	0	0
Restless legs syndrome	+	0	+/–	0	0	0	0	0	0	0	0	0	0	0
Bipolar disease	+	0	+/–	+/–	+	+/–	+/–	0	0	0	+/–	0	+	+/–
Schizophrenia and schizoaffective psychoses	+	0	0	0	+/–	0	0	0	0	0	0	0	+/–	0
Social phobia	0	0	+	0	0	0	0	0	0	0	0	0	0	0
Panic disorder	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Binge eating disorder	0	0	0	0	0	0	0	0	0	0	+	0	0	0
Neuroprotection[a]	+/–[b]	+[b]	0	+[b]	+[b]	0	+/–[b]	0	+	+[b]	+[b]	+[b]	+/–[b]	+[b]

CBZ – carbamazepine, FBM – felbamate, GBP – gabapentin, LEV – levetiracetam, LTG – lamotrigine, OXC – oxcarbazepine, PHT – phenytoin, PRM – primidone, REM – remacemide, TGB – tiagabine, TPM – topiramate, VGB – vigabatrin, VPT – valproate, ZNM – zonisamide. (+) action present in at least two trials, (+/–) variable or not sufficient data, (0) not determined or insufficient efficacy, [a] – against ischemia, [b] – only experimental data

Valrocemide, in a rat-model reduced allodynia and hyperalgesia [8]. Interestingly, topiramate is currently extensively tested for a possible treatment of alcoholism [44].

All non-epilepsy uses of AEDs are summarized in Table 1.

Conclusions

The primary indication for AEDs remains certainly epilepsy, but increasing role of this group of drugs in the treatment of other (especially neurological and psychiatric) conditions is observed.

AEDs are recommended especially in these disorders where the available treatment proves to be ineffective. Pathophysiological mechanisms are similar in epilepsy and some other disorders, e.g. bipolar disease, migraine, ischemic stroke. Therefore, perspectives for the use of AEDs (especially novel ones, which have better safety profile than the old ones) in other than epilepsy conditions look promising. It is quite possible that some more AEDs will soon prove effective in this respect.

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