



Anticonvulsants for neuropathic pain and detoxification

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Anticonvulsants have been used for treatment of neuropathic pain almost as long as they have been used for seizures. Bergouignan successfully treated trigeminal neuralgia with phenytoin in 1942.¹ Though it subsequently became a standard agent for this pain disorder, phenytoin use was limited by the fact that it often loses efficacy over time, and the high doses required for therapeutic activity often cause unacceptable side effects. Nonetheless, this was the beginning of the current, widely accepted use of anticonvulsant drugs to treat neuropathic pain. Since the 1960s, anticonvulsant agents have been used extensively for pain management, particularly for lancinating or burning pain of neuropathic origin. Carbamazepine is one of the most effective drugs and often the first-line agent in the treatment of trigeminal neuralgia. But today, two drugs are expanding the utility of anticonvulsant drugs: valproate, which is better tolerated, and the newer agent gabapentin, which has a unique and safer pharmacokinetic profile. Although not officially approved for use in pain therapy, there is substantial documentation for the clinical efficacy of these drugs in the treatment of neuropathic pain syndromes.

Phenytoin also has a long history of use in the treatment of alcohol withdrawal seizures. Although the efficacy of phenytoin in easing alcohol with-

drawal is now in doubt, some of the newer anticonvulsants have been shown to essentially reverse signs and symptoms of alcohol and sedative withdrawal. In this summary, the older drugs phenytoin, carbamazepine, clonazepam, and valproic acid, and two newer agents gabapentin and lamotrigine are discussed and their roles in neuropathic pain management and detoxification are reviewed.

MECHANISMS OF THE AVAILABLE ANTICONVULSANT DRUGS

The use of anticonvulsant drugs to reduce neuropathic pain and to manage sedative withdrawal is based on their ability to decrease membrane excitability (either by interacting with neurotransmitter receptors or ion channels)² and to suppress discharges in pathologically altered neurons. The exact mechanisms by which they alleviate the sensation of pain are not fully understood. *Table 1* summarizes some of the sites of action that have been identified for the anticonvulsants used to treat pain and withdrawal.²

The known mechanisms of anticonvulsant agents² may provide some insight into their function in neuropathic pain and detoxification (the pharmacokinetics of the newer agents are reviewed by Morris elsewhere in this supplement). It is clear, however, that the mechanisms responsible for the anticonvulsant activity of these drugs are not the same as those that alleviate pain. This is evident in the fact that drugs such as barbiturates have no analgesic effect, despite being good anticonvulsants; similarly, phenytoin provides inferior pain control compared with other agents of equivalent or lesser anticonvulsant activity.^{3,4}

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TABLE 1
ANTICONVULSANT AGENTS: SITES OF ACTION

	Na Channel	GABA _A Channel	T-Ca Channel	NMDA Channel
Older agents				
Carbamazepine	++	—	—	
Phenytoin	++			
Valproic acid	++	?/+	?/+	
Barbiturates	+	+	—	
Benzodiazepines	+	++	—	
New agents				
Felbamate	+	—	?	+
Gabapentin	+	—		?
Lamotrigine	++	—	?	?

From MacDonald and Kelly,² with permission

NEUROPATHIC PAIN: CHARACTERISTICS AND DIAGNOSIS

What is neuropathic pain?

It is useful to distinguish “normal” from pathologic pain. The neurologic systems that signal pain function appropriately when there is a close correspondence between the intensity of a mechanical, thermal, or chemical stimulus and the degree of pain as perceived by the individual. Such “normal” pains signal real or potential damage to bodily integrity, and they respond to treatment with the classic analgesic agents, opioids, and nonsteroidal anti-inflammatory drugs (NSAIDs).

When there is damage to this signaling system, signals disproportionate to the provoking stimulus, or absent of any peripheral stimulus, arrive at the central nervous system (CNS). These pathologic pains are often poorly responsive to typical analgesics; instead, they may respond to treatment with antidepressant, anticonvulsant, or antiarrhythmic medications. Significantly, the response of these pains to pharmacotherapy seems less dependent on the etiology of the neuropathology than on underlying pathophysiology of the pain state. For this reason, a clinician seeking guidance in treating a traumatic nerve lesion with allodynia should rely more on drug trials in allodynia than on studies of nerve trauma.

Pathophysiology of neuropathic pain

Virtually any condition that damages neural tissue or impairs its function can be a source of neuropathic pain. Thus, injury, inflammation, ischemia, metabol-

ic derangements, toxins, tumor, and primary neurologic diseases may lead to mononeuropathy, polyneuropathy, or CNS sources of neuropathic pain. In fact, a combination of processes frequently contributes to the symptom of pain following nerve injury. For a thorough review of the pathophysiology of neuropathic pain, refer to Bennett⁵ or Devor.⁶

Identification of neuropathic pain

Neuropathic pain may be suggested first by pain in an apparently healthy body part, such as the electrical pain that shoots down the leg in sciatica. In addition, certain sensations (eg, burning, electrical, paroxysmal, jabbing, squeezing, deep aching, spasmodic, or cold) or sensory perversions (eg, paresthesias, formication, broken glass sensation, or allodynia) are indicative of neuropathic origin. Sensory loss is often present. The pain may be unresponsive to maneuvering, repositioning, etc.

The distribution of pain often is diagnostic. Thus, hemibody pain may result from cortical, internal capsule, or thalamic lesions, while pains that follow the distribution of cranial or somatic nerves suggest damage to these structures. Frequently, a pain drawing created by the patient is nearly diagnostic. Complex regional pain syndrome (reflex sympathetic dystrophy) is marked by allodynia, autonomic changes (temperature, color, sweating), and trophic changes (skin, hair, nails). Furthermore, neuropathic pain is often resistant to treatment with NSAIDs and opioids.⁷⁻⁹

More difficult cases to identify are those in which frequent, intense prior nociception has led to central sensitization causing specific structures to become painful. For example, intraspinal ligament injection with saline may cause chest wall hyperalgesia in humans, and in animal studies, rectal or vaginal inflammation leads to prolonged hyperalgesia in these areas, as well as in their associated somatic referral areas. Visceral hyperalgesia is thought to explain some obscure chronic abdominal pains that follow illnesses or surgeries.¹⁰⁻¹²

ANTICONVULSANT AGENTS: USE IN PAIN MANAGEMENT

It is somewhat remarkable, given the long history of anticonvulsant use in chronic pain, that most of the applications of these agents are based on anecdotal reports in humans, at times bolstered by experience in animal models. Almost every source of neuropathic pain has been treated with anticonvulsants in at least a few patients, but there have been few controlled, blinded, randomized trials.

The best-studied neuropathic pain, and the only one for which anticonvulsants have an approved indication, is trigeminal neuralgia. By extension, however, this use led to testing of anticonvulsants for most neuropathic pains characterized by paroxysms. If the pain description suggested a ganglion or nerve "seizure," anticonvulsants were administered, generally with excellent (anecdotal) results. Glossopharyngeal and other cranial neuralgias were convincingly shown to respond to anticonvulsants, as were lightning pains of tabes dorsalis and similar pain in multiple sclerosis.³ In a review of controlled trials of anticonvulsants for neuropathic pain, McQuay and coworkers¹³ found good evidence that anticonvulsants provided effective treatment for trigeminal neuralgia, diabetic neuropathy, and migraine prophylaxis; other uses have been reported as well (Table 2).

Clinical applications for the various anticonvulsants are reviewed below.

Phenytoin

An animal model for use of phenytoin in neuropathic pain has been described.¹⁴ In rats with sciatic nerve neuromas, systemic administration of phenytoin suppressed spontaneous impulse discharge, which is thought to be a cause of paresthesias and pain following nerve injury. Although phenytoin was the first anticonvulsant used for the treatment of human neuropathic pain, it is often not the best. For example, Swerdlow³ reported that 70% of patients with trigeminal neuralgia responded to carbamazepine, whereas only 20% improved with phenytoin. Kingery⁴ extensively reviewed the literature on drug treatment of neuropathic pain, concluding that carbamazepine was efficacious but the data for phenytoin were contradictory. Phenytoin has been used for many other conditions, including diabetic neuropathy,¹⁵ Fabry's disease, tabetic lightning pain, and thalamic pain; however, newer anticonvulsants are probably better first-line agents.

TABLE 2
SETTINGS IN WHICH ANTICONVULSANTS
HAVE BEEN USED FOR PAIN RELIEF

Trigeminal, cranial neuralgia ³
Postherpetic neuralgia ³
Tabes dorsalis (lightning pain) ³
Myelopathy*
Phantom limb pain ³
Thalamic pain ³
Plexus avulsion ³
Diabetic neuropathy ^{3,44}
Migraine prophylaxis ³
Multiple sclerosis ³
Poststroke pain ³
Traumatic neuropathy ³
Tumor invasion, compression ³

From Swerdlow³ and Backonja⁴⁴

*From Wetzel CH, Connelly JF. Use of gabapentin in pain management. *Ann Pharmacother* 1997; 31:1082-1083.

Carbamazepine

Carbamazepine is perhaps the most studied anticonvulsant for pain management. It is approved for use in trigeminal neuralgia and is promoted as therapy for glossopharyngeal neuralgia. Although carbamazepine was originally primarily used for paroxysmal pains, such as tabetic lightning pains, its use subsequently extended to include such pains as diabetic neuropathy,¹⁶ postherpetic neuralgia,¹⁷ phantom limb pain,¹⁸ and multiple sclerosis.¹⁹

In one study, a minority of patients with brachial plexus avulsion responded to treatment with carbamazepine, suggesting that other agents might be used first for this condition.²⁰ Blom²¹ found carbamazepine to provide superior pain relief in trigeminal neuralgia compared with phenytoin. In a double-blind, controlled crossover trial involving 15 patients with central poststroke pain, Leijon and Boivie²² reported that 10 patients responded to amitriptyline 75 mg/day compared with five who responded to carbamazepine 800 mg/day. The benefit of carbamazepine was not statistically significant when compared with placebo. In addition, carbamazepine caused more side effects than amitriptyline.²² Based on a review of anticonvulsant agents used in the treatment of postherpetic neuralgia, Watson concluded that the activities of carbamazepine, phenytoin, and valproic acid were either unimpressive or difficult to interpret due

to antidepressant coadministration.²³ Carbamazepine was not effective in rat allodynia after cord ischemia, whereas tocainide was efficacious.²⁴ Thus, the human and animal literature confirms that carbamazepine is efficacious for some, but not all, neuropathic pains, and in many clinical situations its use is based more on suggestions of efficacy than on conclusive studies.

The clinical application of carbamazepine may be limited in the long term by some serious, albeit uncommon, adverse effects. Aplastic anemia, agranulocytosis, thrombocytopenia, hepatic abnormalities, and dermatitis may develop during carbamazepine use.²⁵ Furthermore, carbamazepine is a potent enzyme inducer, capable of inducing its own metabolism. It is associated with frequent drug-drug interactions, necessitating cautious administration, especially among patients receiving several concomitant medications.²⁶

Valproic acid

Although used to treat trigeminal neuralgia and postherpetic neuralgia, the best studies of valproic acid use involved patients with headache.²⁷ Rothrock et al²⁸ treated 75 patients with intractable headache with valproic acid and reported response rates of 61%, 51%, and 21% in the treatment of frequent migraine, transformed migraine, and tension-type headache, respectively. In a triple-blind, placebo-controlled, crossover trial, Jensen et al²⁹ found that 65% of 43 migraine patients responded to prophylactic treatment with valproic acid by week 4. The number of days with migraine decreased 43% with active treatment compared with placebo. The severity and duration of those headaches that did occur, however, were unaffected.²⁹

Cutrer and colleagues³⁰ found that valproic acid reduced c-fos expression in guinea pigs given intracisternal capsaicin, an irritant. This effect was blocked by GABA_A antagonists but not by GABA_B antagonists, suggesting that valproic acid blocks neurogenic inflammation within the meninges via a GABA_A receptor-mediated mechanism.

Valproic acid is generally well tolerated, although a number of adverse effects, some serious, complicate its use. The most common side effects involve gastrointestinal disturbances, which are often effectively treated with histamine antagonists. The most serious adverse effects are potentially fatal hepatotoxicity which occurs most often in children and individuals with prior liver disease and, rarely, pan-

creatitis. Of more concern are frequent endocrinological effects including polycystic ovaries.³¹

Clonazepam

Clonazepam is used to alleviate pain due to cranial neuralgias, postlaminectomy, phantom limb, amputation stump, postherpetic neuralgia, multiple sclerosis, and peripheral neuropathy.^{32,33} Caccia found it to be effective in five of seven patients with trigeminal neuralgia,³⁴ and Smirne and Scarlato reported benefit in 64% of patients with sphenopalatine neuralgia.³⁵ In an open study of deafferentation pain, Bouckoms and Litman³⁶ found that patients with allodynia responded better to clonazepam than those without allodynia.

The use of benzodiazepines in pain management is complicated by adverse effects on mood and cognition, and risk of addiction among individuals with a history of chemical dependency. There has been concern as well that benzodiazepines may increase pain during chronic use; in the acute situation, postoperative pain was reduced by administration of flumazenil, a benzodiazepine antagonist, among individuals who had been given preoperative diazepam.³⁷ For these reasons, benzodiazepines are rarely drugs of first choice for the treatment of pain.

Gabapentin

Despite few controlled studies on the efficacy of gabapentin in human pain management, this new drug has become the anticonvulsant of choice among many pain specialists. This popularity probably reflects promising studies in animals showing efficacy in disparate pain states, a low side effect profile, and lack of drug interactions in patients with pain, who often are subject to extensive polypharmacy.

Animal models provide strong support for the analgesic efficacy of gabapentin in several types of pain. Mechanical allodynia in rat models of causalgia was relieved by gabapentin administration.³⁸ Gabapentin's efficacy was reported as well by Hunter et al,³⁹ who compared lamotrigine, felbamate, and gabapentin in rat models of acute and neuropathic pain (chronic constriction injury and spinal nerve ligation). Lamotrigine, felbamate, and gabapentin reversed cold allodynia; however, only gabapentin ameliorated tactile allodynia. Interestingly, carbamazepine and phenytoin were ineffective in both models. The gabapentin doses required for antiallodynic activity had virtually no

effect on acute nociception and did not affect locomotion. Shimoyama et al⁴⁰ found that gabapentin administered intrathecally prevented hyperalgesia from occurring after intraplantar formalin administration. Thus, in animal models gabapentin is analgesic in various types of neuropathic pain, suggesting wide clinical applicability.

There are several reports of gabapentin's efficacy in mixed neuropathic pain.^{41,42} In addition, Mellick and Mellick⁴³ reported six cases of intractable complex regional pain syndrome that responded well to gabapentin therapy. In a double-blind study, gabapentin effectively alleviated pain from diabetic neuropathy.⁴⁴ It has been tried with some success, as well, in postherpetic neuralgia, thalamic pain, and erythromelalgia.⁴⁵

Gabapentin is notable for its lack of drug interactions, simple elimination pathway, and lack of adverse reactions. It does not require monitoring via hematologic or liver studies. Although it produces ataxia, sedation, and cognitive slowing, these effects generally do not occur at clinically appropriate doses. Weight gain and constipation may be problematic.⁴⁶

Lamotrigine

Lamotrigine, like gabapentin, effectively relieves pain of varying neurophysiologic causes. Nakamura-Craig and Follenfant⁴⁷ found that in rats, lamotrigine blocked the hyperalgesia induced by plantar injections of prostaglandin E₂ as well as by diabetes. This contrasts with the results of Chapman et al,⁴⁸ who compared the effects of lamotrigine and bupivacaine on central sensitization produced by electrical stimulation of C fibers. Lamotrigine was found to enhance windup and postdischarge, which occur in dorsal horn neurons in this model; bupivacaine reduced both. As a result, lamotrigine facilitated C fiber-evoked responses, raising questions about the potential of lamotrigine as an analgesic. This remains to be clarified by future research or clinical reports.

The clinical applications of lamotrigine have included trigeminal neuralgia, postherpetic neuralgia, and central pain. In a double-blind, crossover trial, Zakrzewska et al⁴⁹ continued carbamazepine or phenytoin therapy among patients with refractory trigeminal neuralgia and added lamotrigine 400 mg/day or placebo. Eleven of fourteen patients achieved significant benefit from the addition of lamotrigine, as assessed by pain scores and use of

escape medications.⁴⁹ In another trial, Canavero and Bonicalzi⁵⁰ successfully treated four patients with central pain (two from cerebrovascular accident, one due to brain tumor, and one from cervical syring) with lamotrigine up to 600 mg/day. Lamotrigine provided relief of burning, lancinating, electrical, and allodynia pain among these patients who had been refractory to treatment with carbamazepine and valproic acid. In addition, Canavero and colleagues⁵¹ reported 90% relief of trigeminal neuralgia among four patients treated with lamotrigine in an open-label design.

SPECIAL CONSIDERATIONS

Due to the novel use of drugs normally indicated for seizure disorders in the treatment of neuropathic pain, several adaptations from standard practice must be observed. Patients should be advised of the fact that this is an off-label use of these medications in order to avoid confusion with the pharmacist, who might assume a seizure disorder. It is also necessary to explain that, since response to these agents is not predictable, serial trials may be required to ensure optimal relief. Furthermore, dose requirements for pain treatment are not established, making it necessary to start at a minimum dose and titrate to optimal response or toxicity. In cases for which combination therapy is necessary involving antidepressant, anticonvulsant, and/or antiarrhythmic medications, it is important to titrate one drug at a time.

ANTICONVULSANT AGENTS: USE IN SEDATIVE DETOXIFICATION

Anticonvulsant agents have been investigated as treatment for sedative withdrawal since 1976.⁵² Results from early studies suggested a trend toward efficacy in managing withdrawal symptoms (Table 3),⁵³⁻⁵⁹ and subsequent studies established the value of valproic acid, carbamazepine, gabapentin, and clonazepam in specific withdrawal settings. The accumulated literature on anticonvulsant use during detoxification is reviewed below.

Carbamazepine

In 1986, Klein and coworkers⁶⁰ reported three cases in which carbamazepine attenuated alprazolam withdrawal symptoms. In a case review series, Ries and colleagues⁶¹ reported that carbamazepine permitted rapid detoxification among patients tak-

TABLE 3
EARLY EXPERIENCE WITH USE OF ANTICONVULSANT AGENTS DURING SEDATIVE WITHDRAWAL

Drug	No. Pts.	Control	Results	Comments
Carbamazepine				
Bjorkqvist et al ⁵³	105	Placebo	CBZ > P	More returned to work with CBZ
Riitola, Malinen ⁵⁴	68	CMT	Equivalent	70% response
Agricola et al ⁵⁵	60	Tiaprider	Equivalent	CBZ faster acting
Flygenring et al ⁵⁶	60	Barbital	Equivalent	Both well tolerated
Malcolm et al ⁵⁷	86	Oxazepam	Equivalent	Psych symptoms improved more rapidly with CBZ
VPA				
Lambie et al ⁵⁸	48	CMT±VPA	VPA group needed	No statistical analysis
Carbamazepine + VPA				
Hillbom et al ⁵⁹	138	VPA vs CBZ	Side effects frequent	High incidence of side effects with both due to rapid dose

CBZ=carbamazepine; P=placebo; CMT=clonmethiazole; VPA=valproic acid
From Keck et al,⁵² with permission

ing high doses of those benzodiazepines that cause severe abstinence syndromes (eg, alprazolam 10 mg/day). Although supplemental benzodiazepines were available as needed for withdrawal symptoms, none was required.

In a double-blind study involving 40 patients with difficulty discontinuing daily benzodiazepine use, Schweizer et al⁶² found that the addition of carbamazepine 200 to 800 mg/day permitted comfortable detoxification over 5 weeks. In addition, more carbamazepine-treated patients remained free of benzodiazepines at 5 weeks, suggesting that subtle symptoms of protracted withdrawal also may be reduced. Carbamazepine treatment appeared most beneficial for patients receiving dosages equivalent to > 20 mg diazepam.

Malcolm and colleagues⁵⁷ compared the efficacy of carbamazepine 800 mg/day with oxazepam 120 mg/day in detoxifying 86 men with severe alcohol withdrawal. The drugs were equally effective, but global psychologic distress increased among those taking oxazepam, whereas it declined in those taking carbamazepine. These findings suggest that carbamazepine is as effective and safe as benzodiazepine treatment for alcohol withdrawal syndrome. It, of course, offers a significant advantage if symptoms of protracted withdrawal require treatment, as patients can be maintained on nonaddicting medication.

Valproic acid

Valproic acid has been successfully used in the treatment of benzodiazepine withdrawal, as described in case reports and one small series.^{63,64} Roy-Byrne et al⁶⁵ described a patient who had been unable to discontinue alprazolam intake, even at extremely slow rates, but who was comfortably withdrawn with the addition of valproic acid. In 1980, Lambie et al⁵⁸ randomly assigned alcohol-dependent individuals to treatment with valproic acid 400 mg vs no treatment as add-on to conventional medications for detoxification. Withdrawal symptoms decreased more rapidly and less conventional medication for withdrawal was required by those patients receiving valproic acid.

Hillbom and colleagues⁵⁹ found that treatment with carbamazepine and valproic acid produced a high incidence of side effects, perhaps hampering their utility as treatment for alcohol withdrawal symptoms; however, this may have resulted from aggressive dose titration.

Gabapentin

Animal models. Watson and associates⁶⁶ found that gabapentin, in doses that did not impair locomotion or coordination, reduced anxiety and induced an anticonvulsant response in alcohol-dependent mice experiencing withdrawal. By contrast, phenytoin failed to provide benefit, carba-

TABLE 4
RESPONSE AMONG SEVEN PATIENTS TO GABAPENTIN THERAPY DURING SEDATIVE WITHDRAWAL

Age/sex	Diagnosis	Dependence	Baseline Diazepam Equivalents (mg/day)	Maximum Dose (mg/day)	Discontinuation Dose (mg/day)
66/F	Mixed headache	BZD	50	1200	400
34/M	Atypical face pain	BZD	40	2400	2400
32/F	Pelvic pain	BZD	80	1200	None
32/F	Mixed headache	PB	20	1200	600
38/M	Lumbar canal stenosis	BZD	40	1600	1200
76/F	Postherpetic neuralgia	BZD	25	2400	2400
51/F	Fibromyalgia, headache	BZD	80	3600	1000

BZD=benzodiazepine; PB=phenobarbital
From Covington et al⁶⁸

mazepine reduced symptoms only at intoxicating doses, and valproic acid was effective only at sedating doses. Based on this finding, it was theorized that the gabapentin binding site may be selectively affected by alcohol withdrawal, because the dose required for withdrawal control is lower than that required to prevent seizures from other causes.

Bailey et al⁶⁷ studied alcohol withdrawal response in hippocampus slices from rats. As compared with controls, brain slices from animals undergoing alcohol withdrawal had reduced thresholds for production of single- and multiple-population spikes by electrical stimulation, as well as “reverberative firing patterns.” These changes were prevented in large by gabapentin and isradipine (a calcium channel antagonist). Neither drug altered thresholds in normal (not undergoing alcohol withdrawal) brain slices.

Clinical use. We have found gabapentin to be effective in the treatment of benzodiazepine and sedative withdrawal in a group of patients with chronic pain.⁶⁸ This trial was prompted by the following anecdotal experience. A 66-year-old patient with intractable headache who was being withdrawn from butalbital and alprazolam was unsuccessfully treated with clonazepam. Switching to valproic acid was effective, but resulted in SIADH (sodium of 119 mmol/L). A subsequent trial of carbamazepine 800 mg/day caused severe pruritic rash requiring discontinuation. A test dose of 300 mg gabapentin relieved the withdrawal symptoms and

the patient continued therapy at 300 mg qid with good control.

In six of seven subsequent patients it was found that gabapentin successfully controlled sedative withdrawal symptoms (Table 4).⁶⁸ The single failure probably resulted from inadequate dosing of gabapentin, an inference drawn from our current practice, which is to abruptly stop all benzodiazepines and barbiturates on admission and replace with gabapentin administration. Typically, treatment is started with a 300–800-mg test dose, depending on the patient’s estimated degree of physical dependence and severity of predicted withdrawal syndrome. An additional 300–400 mg is given in an hour if there are no adverse effects and signs of withdrawal persist. Typically, patients are comfortable and free of significant withdrawal on gabapentin doses of 1800–4800 mg/day.

Phenytoin

Most studies of phenytoin in alcohol withdrawal address only the issue of seizure treatment or prophylaxis and not other components of the withdrawal syndrome. One group found that in alcohol-dependent mice phenytoin increased body tremor and other withdrawal signs, although it slightly ameliorated withdrawal from barbitol.⁶⁹ The American Society of Addiction Medicine Committee on Practice Guidelines has taken the stand that phenytoin is not effective for alcohol withdrawal, even in the presence of a seizure.⁷⁰ The use of phenytoin is

reserved for cases in which there is an independent seizure disorder for which phenytoin is indicated, or to abort status epilepticus. In alcohol-dependent individuals with a history of withdrawal seizures, the evidence is considered inconclusive.

SUMMARY

It is now well demonstrated that several anticonvulsants have a role in the treatment of neuropathic pain and also in withdrawal from benzodiazepines, sedatives, and perhaps alcohol. Valproic acid, carbamazepine, gabapentin, clonazepam, and lamotrigine are appropriate treatments for neuropathic pain,

effective to a degree dependent on the underlying pathophysiology. While less effective than newer agents, there are situations in which phenytoin remains useful. Currently, a limited understanding of both the processes responsible for pain and the specific effects of each agent prevents prediction of individual response to these drugs, often necessitating trials of several drugs before the best one is found. It is interesting that the anticonvulsant drugs most useful for neuropathic pain are the same ones effective in sedative withdrawal, bipolar disorder, and several anxiety disorders. Issues of neural hypersensitivity and kindling, therefore, may prove to be unifying concepts for these conditions.

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