Tolerance to the Beneficial Effects of Prophylactic Migraine Drugs: A Systematic Review of Causes and Mechanisms

Paul Rizzoli, MD; Elizabeth W. Loder, MD, MPH

Loss of benefit of a previously effective treatment regimen, also known as tolerance, can be an important barrier to the successful preventive treatment of migraine. We undertook a systematic review of the literature to identify the prevalence and possible mechanisms of drug tolerance in migraine prophylaxis. Results demonstrate that the frequency of tolerance to prophylactic migraine treatment is unknown, but available data support an estimate that it occurs in 1-8% of patients receiving prophylaxis. Four broad types of tolerance were identified that are likely to be relevant to migraine prophylaxis. These are pharmacokinetic, pharmacodynamic, behavioral, and cross tolerance. The mechanisms that underlie these types of tolerance determine whether their effects can be overcome or minimized. For example, certain forms of tolerance may be affected by manipulation of environmental cues associated with drug administration, by the order in which drugs are used, and by the concomitant use of other medications. Many medications used for migraine prophylaxis exert their effects through the endogenous opioid system. The implications of this finding are explored, particularly the parallels between medication overuse headache and tolerance to migraine prophylaxis. Given the many ways in which tolerance to migraine medications may develop, in some ways it is not surprising that migraine-preventive drugs stop working; it is more surprising that in many cases they do not.

From John R. Graham Headache Center and Division of Headache and Pain, Department of Neurology, Brigham and Women's/Faulkner Hospitals, Boston, MA, USA (P. Rizzoli and E.W. Loder).

Address all correspondence to P. Rizzoli, 1153 Centre Street, Suite 4970, Boston, MA 02130, USA.

Loss of benefit from a previously effective treatment regimen is not uncommonly reported by migraine patients. It has been described with both acute and preventive treatments for migraine, and in some patients it is an important barrier to successful treatment. The term tolerance is commonly used to describe this situation and refers "to the relatively common observation that during chronic drug treatment the effect(s) of some drugs may progressively reduce in magnitude."[1]

By definition, tolerance is a reduction in response to a drug after repeated administration.[2] Since it can occur only after an initial period of drug response, it must be distinguished from pharmacoresistance, a situation in which there is no response at all to treatment of adequate dose and duration[3] (Box). The problem of pharmacoresistance is often due to innate resistance or insensitivity to a treatment. It has been extensively studied in epilepsy patients who have failed to respond to multiple medications. A number of physiological explanations for pharmacoresistance have been identified, ranging from abnormalities of drug transporter mechanisms to faulty receptor binding, but few of these mechanisms seem likely to be relevant to the phenomenon of tolerance.[3]

Box.—Distinguishing Drug Tolerance From Pharmacoresistance.

Tolerance: A reduction in the effects of a drug with repeated administration. Requires an initial period of drug response before effects wane. Sometimes referred to as neuroadaptation.[2]

Pharmacoresistance: No effect from a drug, even with repeated administration or escalation of dose. Multiple causes, often innate, which include such things as drug transporter dysfunctions or congenital absence of drug receptors.[3]

The problem and mechanisms of drug tolerance in migraine treatment have not been systematically examined. The goals of this review are to identify available evidence about frequency of this pattern of treatment response and to examine possible explanatory physiologic and drug-dependent mechanisms. In the linked clinical review, we describe expected clinical patterns of
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drug response for each identified mechanism of tolerance, and review the implications for clinical treatment. These papers focus on the development of tolerance to beneficial effects of prophylactic drug treatments for migraine, although many of the concepts discussed also apply to the development of tolerance to non-pharmacologic treatments, to adverse effects of treatments, and to therapies intended for treatment of acute attacks of migraine.

METHODS

Literature Search
The search strategy was intended to identify a wide array of potentially relevant research on the mechanisms of tolerance in migraine. We aimed to find pertinent research on the 4 main categories of preventive drugs used in migraine (β-blockers, antiepileptic drugs, calcium channel antagonists, and tricyclic antidepressants). We also intended to locate applicable research in other therapeutic areas that share obvious similarities to migraine. In particular, we sought to identify related work in the epilepsy field since epilepsy, like migraine, is a paroxysmal neurological disorder and some treatments are effective for both conditions.

We searched PubMed from 1960 to January 2011 without language restrictions. We used a wide array of search terms in an attempt to capture the largest number of possibly relevant papers. The MeSH terms of *tolerance* (*loss of effect*), *drug tolerance*, *resistance*, *drug resistance*, *tachyphylaxis*, or *placebo effect* were combined with the following groups of words using the AND command: *headache*, *migraine* or terms indicating individual drug classes of interest: *antiepileptic drugs*, *topiramate*, *divalproex*, *gabapentin*, *calcium channel blockers*, *tricyclic antidepressants*, or *beta blockers*. Previous reviews of relevant literature and the reference lists of retrieved articles were also searched.

Inclusion and Exclusion Criteria
We included fully published clinical and experimental studies that evaluated the property of tolerance in relation to agents commonly used in the management of migraine. Papers describing experimental animal models of tolerance were included. Since mechanisms involved in the development of tolerance to opioids are also relevant to the development of tolerance to some migraine drugs, we also selected papers describing mechanisms of opioid tolerance. We excluded articles in which the term tolerance was used to refer to tolerability, and we excluded the large literature on the development of tolerance to the effects of alcohol, with the exception of papers in which the anticonvulsant properties of alcohol were studied. We excluded papers discussing mechanisms of tolerance to medications that are not used for migraine prophylaxis, or that discussed other topics we judged unlikely to be relevant to migraine.

Selection of Relevant Papers and Extraction of Themes and Data
P. R. reviewed the titles of papers identified in the initial search to identify those relating to drug tolerance. He then eliminated papers whose titles indicated they dealt with tolerance but which were judged irrelevant to migraine. The abstracts of selected titles were then reviewed for relevance and papers meeting inclusion and exclusion criteria were retrieved for full review. Relevant information and themes were extracted from these papers by one author (P. R.), who reviewed and discussed themes and findings with the second author (E. L.). In areas of disagreement, consensus was reached through discussion. Papers relevant to the development of drug tolerance and its management in clinical practice were saved for the linked clinical review.

RESULTS
The initial search returned titles for 2388 papers, 2030 of which remained after initial review of title and 981 of which remained after review of the title for relevance to detailed review selection criteria. After review of the abstracts for these papers, 509 were further evaluated for relevance, and of these, 140 were retrieved for review. The Figure shows the flow of studies through the review.

Prevalence
We did not identify any studies that examined the prevalence of tolerance to the beneficial effects of migraine prophylaxis. Lipton and Bigal have reviewed the epidemiology of refractory migraine and refractory chronic migraine.[4] Implicit in the definitions of these conditions is the notion of the failure of prior adequate trials of acute and preventive medications. Based on several epidemiologic studies, they estimate that chronic migraine affects roughly 2% of the adult population.[4-6]

Data from the American Migraine Prevalence and Prevention study show that roughly 40% of patients with chronic migraine have tried preventive drugs, many of whom reported trying several agents.[7] Thirty-two percent had tried topiramate or amitriptyline, 22% had tried propranolol or gabapentin, and 20% had tried divalproex. Only 9% had tried verapamil, lower than the roughly 10% who had tried feverfew, magnesium, and vitamin B2.

Participants in the American Migraine Prevalence and Prevention study were not, however, queried about whether multiple trials of medication were related to loss of benefit or nonpersistence of benefit (tolerance), although tolerability and side effects were investigated as reasons for discontinuation. Agents reported as most satisfactory by the chronic migraineurs in this study included divalproex, gabapentin, topiramate, amitriptyline, propranolol, and verapamil. Of note, although 40% of those with chronic migraine had ever used a preventive treatment, only 33% were currently using preventive medications. It
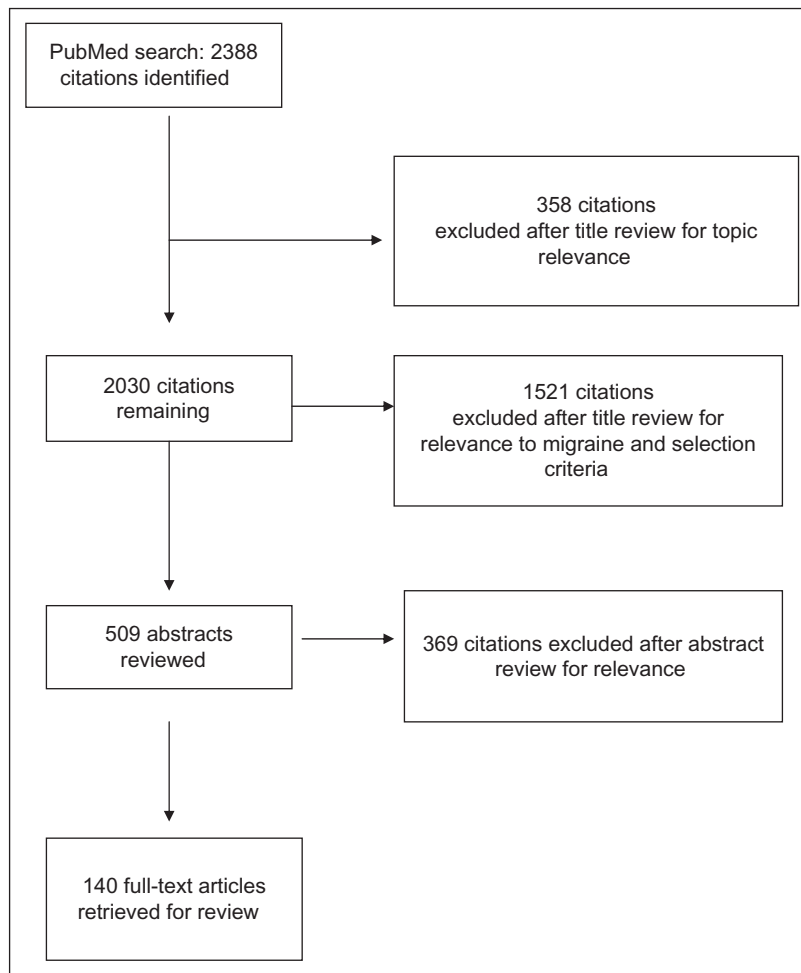
Figure.—Flow of studies through the review.

is unknown what proportion of the 7% who discontinued use of preventive treatment may have done so because of the development of tolerance.

As part of his clinical practice in a tertiary referral headache center, the first author (P. R.) routinely records whether patients spontaneously and without prompting report problems with "medications wearing out." He estimates that over the course of 1 year, roughly 4 of 400 patients, or 1%, have without prompting disclosed this problem.

Given the overlap in mechanisms and treatments between epilepsy and migraine, estimates of the prevalence of tolerance to seizure control with antiepileptic drugs might provide some indication of the possible magnitude of the problem in migraine. One study found an 8% seizure relapse rate in a large group of epileptic patients receiving antiepileptic therapy after a 12-month period of control, but did not evaluate tolerance as a possible explanation for loss of control.[8]

Possible Mechanisms of Drug Tolerance in Migraine
Our review identified 4 broad explanations for the development of drug tolerance that seem likely to apply to migraine prophylaxis. These are listed in Table 1. They are: (1) pharmacokinetic tolerance; (2) pharmacodynamic tolerance; (3) behavioral tolerance; and (4) cross tolerance (see Table 1).

Pharmacokinetic Tolerance
Pharmacokinetic tolerance (sometimes referred to as dispositional tolerance) occurs when metabolic adaptations cause more efficient metabolism or excretion of a medication.[2] In pharmacokinetic tolerance, it is the drug level itself that changes with time. Pharmacokinetic tolerance can result from changes in drug distribution among different tissues or bodily compartments, or alterations in metabolic rates. An example of the latter is the induction of hepatic enzymes that can occur with chronic use of barbiturates. Pharmacokinetic tolerance can be identified

Table 1.—Mechanisms of Tolerance Relevant to Migraine Prophylaxis†

Type of Tolerance	Description	Clinical Example
Pharmacokinetic†	The drug level is altered, for example, through the induction of hepatic enzymes	A patient taking clonazepam daily to improve sleep altered by chronic migraine reports that over the course of a month the drug is working less well
Pharmacodynamic†	The drug effect at a given concentration is modified, for example, through alterations in receptor function	A patient on a stable dose of divalproex for 6 months reports that the medication "just stopped working"
Behavioral†	The drug effect on behavior is modified	
Learned	Involves both learning and physiologic changes in response to drug effect	For example, development of tolerance to the cognitive effects of topiramate
Conditional	Classic Pavlovian conditioning	For example, reaction to the bitter taste of a medication while simply holding the pill
Contingent	Change in response to drug effect in relation to timing of drug administration	For example, the weight loss effect of topiramate may be shown to relate to when the medication is used in relation to a meal
Cross tolerance	Development of tolerance to 1 drug that then extends to a second drug. May be uni- or bi-directional	For example, it may be that tolerance to 1 tricyclic might extend to another, influencing choice of the next migraine medication

†Not mutually exclusive; may occur together.
Table modified after Loscher and Schmidt[2] with permission.

through the use of drug blood levels when such monitoring is possible. This form of tolerance is generally easily recognized and can be overcome through dosage adjustment.

Pharmacodynamic Tolerance
Pharmacodynamic tolerance (sometimes referred to as functional tolerance) is "mediated by changes in the sensitivity of neuronal, receptor, or neurochemical systems, which may limit a drug's actions."[1] Thus, with pharmacodynamic tolerance, it is the *effect* of a drug that changes with time and not its level or concentration. Tachyphylaxis, the rapid development of complete tolerance to the effect of a medication based on rapid receptor desensitization, may be a special form of pharmacodynamic tolerance.[9]

Mechanisms of pharmacodynamic tolerance are likely to be multiple.[10,11] Structural and/or functional changes to CNS drug target sites or defects in drug transporter systems are among the many changes felt by some to underlie antiepileptic drug tolerance.[10,12] Other proposed mechanisms, characterized as the oppositional models,[12,13] suggest that tolerance develops due to activation of pathways that then function in opposition to the pathway being modulated by the drug, ultimately producing an equal and opposite response to the drug thus nullifying its efficacy.

Behavioral Tolerance
Behavioral tolerance results from behavioral adaptations that occur and that counteract the effects of a drug. In experimental situations, this is best identified with the use of easily observed outcomes such as seizure activity, performance in a maze, or response to painful heat exposure, for example. Behavioral tolerance can be divided into 3 subtypes: learned, conditional, and contingent tolerance.

Learned tolerance we propose is a subtype of behavioral tolerance.[2] It may develop when behaviors are repeated or practiced while under the effects of a treatment. For example, both humans and rats that are regularly exposed to intoxicating doses of ethanol are observed to become tolerant to its gait-altering effects; that is, they learn how to walk in spite of the ethanol.[1,2] This learned tolerance may involve physiologic mechanisms, that is, acquisition of motor skills, in addition to learning, that is, adjustment to the awareness of a deficit.[1,2] Learned tolerance can be enhanced with rewards, but typically is not transferable. A person who learns to navigate a familiar driving route under the influence of alcohol, for example, will not necessarily be able to navigate a new route.[14-16]

Conditional tolerance is another subtype of behavioral tolerance. Conditional tolerance implies a special form of learning that incorporates principles familiar to anyone who has studied classical Pavlovian theories of conditioning.[2,17] In this model, 2 stimuli are paired. One, referred to as the *unconditional stimulus*, is something such as food which produces a typical *response*. In the case of a food stimulus, the usual response is salivation.

For conditional tolerance to develop, the unconditional stimulus is paired with a *conditional* stimulus that ordinarily does not provoke the response of salivation. In Pavlov's classic experiment, the conditional stimulus was a bell that was rung each time the experimental subjects (in his case, dogs) were presented with

food.[17,18] Eventually, the conditional stimulus alone (ringing a bell) will elicit salivation. The neutral stimulus of the bell has been conditioned through learning.

As applied to the development of drug tolerance, conditional tolerance is a conditioned anticipatory compensation to some expected drug effect. The organism learns, for example, that certain environmental cues are followed by certain drug effects, and that mounting a compensatory response in advance may be a useful adaptive response which can attenuate those drug effects and more quickly restore the organism to its baseline function. This has been demonstrated in a number of experimental settings.[18,19] For example, rats have been shown to develop compensatory hyperthermia in response to the anticipated hypothermic effect of ethanol. After conditioning, this response can also be triggered when the rats are exposed to conditions associated with alcohol administration but not to alcohol itself.

As applied to drug tolerance in migraine prophylaxis, conditional tolerance suggests that over time the response to a drug may become conditioned to environmental cues or other aspects of drug administration which may impact efficacy. For example, whether a person typically experiences a headache, nausea, or other environmental cue or not at the time of drug administration may influence the response to the drug.

Contingent tolerance is a third form of behavioral tolerance. Although noted for many years before, contingent tolerance was first reported in a seizure model in 1985 with a study of tolerance to the anticonvulsant effects of ethanol in kindled rats.[20] Substantial tolerance to the anticonvulsant effects of ethanol could be produced but only if the drug was administered in a specific relationship to the test procedure, that is, the stimulation of a seizure. Tolerance developed if rats were stimulated to seize after each of 5 ethanol injections given every other day, but not if they were stimulated before each ethanol injection. Overall, the 2 groups received that same amount of drug over the same time period; however, something about the ethanol being present at the time of the stimulation produced more complete and rapid tolerance than if the ethanol was administered after the stimulation procedure. This difference indicated to researchers that this form of tolerance involved "a reaction to the expression of a drug's effect rather than to the mere presence of the drug in the body . . . (thus) drug exposure alone (was) not sufficient for maximal tolerance development."[2] Contingent tolerance then is "any tolerance that develops specifically as a consequence of drug treatment being administered so that the drug interacts with a specific assay procedure."[1]

Contingent tolerance is not well explained by the multiple models of the mechanism of behavioral tolerance. One influential model by Baker and Tiffany,[21] for example, proposes that behavioral tolerance be viewed simply as a form of habituation, that is, a decrement in behavioral response that results from repeated stimulation.[22] Another model that is able to incorporate contingent tolerance is the homeostatic theory of tolerance.

The homeostatic theory of drug tolerance[23] is but a specific example of a more general theory of physiological adaptation of the organism to homeostatic disturbances. In essence, it claims that a functional disturbance or demand must be placed on a system in order to drive the physiologic responses necessary to restore homeostasis. Thus, it is the demand placed on the system by the drug effect that determines the development of tolerance. The mere presence of the drug is not sufficient; it is the presence of the drug in relation to a specific disturbance that determines the organism's resulting response. As an analogy, a presbyope will not develop tolerance to the disorienting effects of new bifocals by simply wearing them in the dark or with eyes closed (simple presence of drug). They must be worn in lighted conditions with eyes open (disturbance or stimulus + drug) in order for tolerance to develop. With regard to contingent tolerance, turning the light on and then off (stimulus) and then putting on the glasses (drug administered after stimulus) will not speed the development of tolerance; the drug must be present with the stimulus.

The homeostatic theory links the development of tolerance not only to the homeostatic state of the organism but also to feedback from the environment and thus provides a much wider context in which to view tolerance. Weiss et al in 1995[24] provided strong support for the homeostatic theory of drug tolerance and hinted at the possible treatment implications: "One of the primary determinants of the behavioral and physiological effects of a drug is the organism's history with respect to that drug." "Not only does (contingent tolerance) powerfully demonstrate the importance of temporal contingencies in a wide range of organismic functions—it also suggests a reconsideration of the role that associative processes, traditionally related to learning and memory, might play in pharmacotherapeutics. To the extent that contingent tolerance is a factor in clinical situations of tolerance development, new avenues for reversing or preventing tolerance may be investigated."

Cross Tolerance

Tolerance that develops to the effect of 1 drug can sometimes carry over and lead to tolerance to the same effect, that is, anticonvulsant effect, of another, usually mechanistically similar, drug. This situation can be difficult to detect in clinical practice but is more easily identified in research settings where the timing of drug exposure can be manipulated. Such cross tolerance in epilepsy was first demonstrated for the benzodiazepines and other antiepileptic drugs that work through the benzodiazepine site on gamma-amino-butyric acid (GABA) A receptors.[2] Table 2 summarizes information about cross tolerance between selected antiepileptic agents.

It seems likely that the physiological basis of cross tolerance is related to shared mechanisms of action of drugs. For many antiepileptic drugs, however, the mechanism(s) of action are uncertain and possibly multiple, which makes it difficult to draw firm

Table 2.—Cross Tolerance to the Anticonvulsant Effect of Selected Antiepileptic Drugs in Rodent Models

First Drug	Second Drug	Cross Tolerance Demonstrated?	Comments
Benzodiazepine	Benzodiazepine	Yes	Shown in more than 1 model.[62]
Benzodiazepine	Valproate	Yes	Unidirectional,[25] not present in reverse, from valproate to benzodiazepine
Benzodiazepine	Phenobarbital	No	25
Lamotrigine	Carbamazepine	Yes	Complete in this direction but incomplete in reverse, from carbamazepine to lamotrigine[63]
Lamotrigine	Gabapentin	No†	†Sensitization or synergy when used together[64]
Lamotrigine	Valproate	No	63
Levetiracetam	Carbamazepine	Yes	Unidirectional[65]
Phenobarbital	Carbamazepine	Yes	66
Valproate	Phenobarbital	No	25

Adapted with permission from Loscher and Schmidt.[2]

conclusions. Further complicating the matter is that cross tolerance may be partial rather than complete.

Interestingly, in some cases, cross tolerance is unidirectional. For example, an animal treated first with benzodiazepines may display tolerance to the anti-seizure effects of subsequently administered valproic acid, but not the converse. In other words, animals treated first with valproic acid do not then display tolerance to the anti-seizure effects of benzodiazepines.[25]

A phenomenon sometimes called reverse tolerance has also been described, in which increased, rather than reduced, drug effect is seen after chronic exposure. Technically, this is not a form of true tolerance, since tolerance is described as a *loss* of drug effect, and perhaps this is better termed sensitization. Variations of sensitization have also been described, including cross sensitization where, for example, pretreatment with valproic acid improved the antiepileptic effects of later administration of phenobarbitone.[25]

DRUG-SPECIFIC ASPECTS OF TOLERANCE IN MIGRAINE PROPHYLAXIS

Antiepileptic Drugs

Tolerance to an antiepileptic drug was first reported for acetazolamide in 1955.[26] By the mid-1980s, pharmacodynamic tolerance had been documented experimentally to the anticonvulsant effects of phenobarbital, diazepam, clonazepam, carbamazepine, and valproic acid. Multiple other first through third generation antiepileptic drugs have also been studied with regard to tolerance. Table 3 summarizes the results of this work for antiepileptic drugs that may be relevant to headache prophylaxis.

It is difficult to summarize the results of research into tolerance to the desirable effects of antiepileptic drugs. Results vary depending upon the animal studied, on seizure type, and on whether seizures were induced (eg, with a substance such as pentylenetetrazole) or natural (eg, amygdala-kindled seizure animal models).[27] Grouping antiepileptic drugs based on their

mechanisms of action is appealing but in fact does not greatly simplify the interpretation of data on tolerance and cross tolerance. In many cases, the mechanisms of action for these drugs are putative or uncertain, and it seems likely that many work through mechanisms that have not yet been identified. For these reasons, considerable caution should be exercised in generalizing the results of tolerance research done in the epilepsy field to the problem of migraine.

Nonetheless, 2 themes emerge from a review of existing evidence. First, from a mechanistic standpoint, benzodiazepines and barbiturates exert anti-seizure effects by potentiating GABAergic inhibition through effects on the GABA A receptor.[19] Thus, a likely mechanism of pharmacodynamic tolerance for these antiepileptic drugs is a reduction in brain glutamic acid decarboxylase (GAD). This reduces the amount of GABA available at the receptor, perhaps through a feedback suppression of GAD synthesis due to accumulation of brain GABA with continued antiepileptic treatment.[10] Such effects seem likely to also apply to these drugs when used for migraine prophylaxis. Second, the existence of cross tolerance with various antiepileptic drugs has been clearly demonstrated in animal models, and these effects can operate in 1 direction only.

Other seizure drugs, such as carbamazepine, lamotrigine and zonasamide, affect predominantly voltage-dependent ion channels.[28-31] The 2 drugs that have US Food and Drug Administration (FDA) approval for use in the prophylaxis of migraine, topiramate, and valproic acid, have mixed or complex mechanism of actions.[32] Gabapentin, also used in migraine prophylaxis although without an FDA approval for that indication, affects both ion channels and GABA metabolism.[29]

Non-Antiepileptic Drugs

The anti-migraine mechanisms of action of the β-adrenergic antagonists (β-blockers), calcium channel antagonists and tricyclic antidepressants are not completely understood. β-blockers have effects on adrenergic systems but also on sero-

Table 3.—Strength of Evidence for the Development of Tolerance to Selected Antiepileptic Drugs Relevant to Migraine Prophylaxis

Simplified Mechanism	Antiepileptic Drugs	Strength of Evidence†
GABA receptor	Benzodiazepines	Strong[67-72]
GABA receptor	Phenobarbital	Strong[66,73-76]
Ion channel	Carbamazepine	Good[69,70,77]
Ion channel/?mixed	Lamotrigine	Good[63,64]
Ion channel	Zonisamide	Fair[78]
Mixed	Gabapentin	Unknown
Mixed	Valproate‡	Strong[10,32,69,70,78,79]
Mixed	Topiramate‡	Unknown
Unknown	Levetiracetam	Good[2,64]

Adapted with permission from Loscher and Schmidt.[2]
†The strength of evidence of tolerance for each drug was determined as follows based on the number of studies identified in the review, the consistency of their results and the presence of studies in more than 1 animal model: Strong = consistent findings in 2 or more studies and in more than 1 animal model; Good = consistent findings in 2 or more studies in a single animal model *or* evidence that would be rated strong but with inconsistent results among studies; Fair = 1 study in a single animal model or equal numbers of conflicting findings from multiple studies or animal models; Unknown = no studies.
‡US Food and Drug Administration approved for the prophylactic treatment of migraine.

tonergic systems.[33,34] Calcium channel antagonists interfere with the entry of calcium into smooth muscle cells and prevent muscle contraction; they are theorized to work through effects on blood vessel tone.[35,36] The tricyclic antidepressants block reuptake of various neurotransmitters such as serotonin and norepinephrine.[37,38]

All of these drugs were developed for the treatment of chronic conditions other than migraine. In our review of the literature, we did not find evidence of the development of pharmacologically mediated tolerance to these non-migraine effects of these classes of drugs, although we did not specifically search for such evidence. In the authors' clinical experience, however, patients do report the development of tolerance to the anti-migraine effects of these classes of drugs.

If tolerance does not develop through mechanisms related to non-migraine effects of these drugs, that is, for the treatment of other chronic conditions, it is possible that their anti-migraine activity stems from other mechanisms of action that might be susceptible to the development of tolerance. Our review identified a wide array of evidence that many drugs used for migraine prophylaxis have effects on pain that are mediated through endogenous opioid systems. These findings are summarized in Table 4. Considered together, this evidence suggests that mechanisms involved in the development of tolerance to opioids may also play a role in tolerance to some anti-migraine drugs. Tolerance to the analgesic effects of both the acute and chronic administration of opioids has been well documented both clinically and experimentally.[39-41] Additionally, as discussed below and as listed in Table 4, a number of drugs commonly used for migraine prophylaxis can suppress the development of tolerance to the analgesic effects of opioids.

It would not be surprising if many of the drugs used for migraine prophylaxis exert at least some of their effects through direct or indirect effects on the opioid system. A large number of naturally occurring substances are capable of interacting with the relatively small number (4) of identified opioid receptors, which is not the case for most other neurotransmitter systems. This "apparent paradox" is felt by some to underlie the enormous complexity of the opioid system and the large number of possible patterns of response that might result from varying degrees of stimulation of opioid receptors.[41] One expert has cautioned against a simplistic, "on-off" view of opioid receptor function, suggesting that it is better viewed as "a sophisticated sensor that responds in different ways, depending on the local environment and how the sensor is manipulated."[39]

Propranolol
Possible cross tolerance between morphine and propranolol has been investigated but study results are conflicting.[42,43] α- or β-blockers used alone or together have been shown to suppress the development of tolerance to the analgesic effects of morphine. However, once this effect had developed with use of a single drug, for example, the α-blocker, it was lost when that drug was withdrawn and replaced by the other one, for example, the β-blocker. Similarly, if tolerance had been suppressed with a combination of the 2 drugs, the effect was lost when one was removed, and then only if the medications had been given together from the outset and not in some sequential fashion. Thus, there was a specificity to the resulting tolerance that very much depended on how the drugs were administered. These findings suggest that the effects of β-blockers, particularly if used

Table 4.—The Effects of Drugs Relevant or Possibly Relevant to Migraine Prophylaxis on the Opioid Pain System

Drug	Delays Development of Tolerance to Opioids	Intrinsic Analgesic Effect	Concomitant Use Increases Analgesic Effects of Opioids	Blocks Effects of Opioid Withdrawal	Reference
Amitriptyline	Yes	Yes	Yes	?	44-46
Gabapentin	Yes	Yes	Yes	?	51,80
Lamotrigine	Yes	Yes	Yes	Yes	31,52,58
Magnesium	Yes	?	Yes	No	52,58
Melatonin‡	Yes	?	Yes	?	55
Minocycline§	Yes	?	Yes	?	53
Propranolol	Yes	?	No	?	42
Riluzole¶	Yes	?	Yes	?	47,50,53
Verapamil	Yes	?	Yes	Yes	

‡Although these drugs are not commonly used in migraine prophylaxis, there has been some preliminary work suggesting that tetracyclines might have a role in headache treatment,[54] and by extension riluzole. Also, there is fair evidence for melatonin in migraine prophylaxis.[81-84]

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? = not assessed in the reviewed studies but may be present.

with opioids or other drugs that might work through opioid mechanisms, may depend on when and how the drug is administered in relation to other drugs.

Amitriptyline

Administration of amitriptyline to rodents potentiates the intensity and duration of the analgesic effect of opioids in both naïve and tolerant animals. This augmentation does not appear to result from any changes in the concentration or metabolism of morphine.[44] Rather, it is speculated that it is due to "an alteration of neurotransmitters at the receptor sites, resulting in increased CNS sensitivity to morphine analgesia."[44,45]

Further work demonstrated a striking potentiation of the analgesic effect of morphine after amitriptyline administration in morphine-tolerant animals, with an almost 5-fold leftward shift of the dose–response curve.[46] This work provided some evidence that the mechanism involved the increase in the activity of glutamate transporters, which would lead to faster removal of glutamate from receptors.[45] Stimulation of glutamate receptors is suspected of mediating opioid-induced tolerance, hyperalgesia, and neurotoxicity.

Verapamil

Calcium channel antagonists are known to enhance analgesia produced by morphine[47] as well as to exert their own antinociceptive effect.[48] When the various L-type calcium channel antagonists were compared they all, including verapamil, enhanced morphine-induced analgesia in a rat model and all blocked naloxone-induced withdrawal.[47] These effects occurred without notable cardiovascular side effects and were thought possibly clinically significant. Additionally, the chronic use of

verapamil attenuated the development of tolerance to the analgesic effects of morphine. Previously, verapamil had been noted to attenuate the development of tolerance to the motor effects of ethanol.[49] This effect has been attributed to the interaction between the kappa opioid receptor and the calcium channel.[50]

Miscellaneous Anti-Migraine Drugs

Gabapentin

Gabapentin is an analogue of GABA. It has known analgesic effects and reduces features of nociceptive pain including hyperalgesia and allodynia.[51] It enhanced the analgesic effect of morphine in a rat model and also prevented the development of tolerance.[51] It has been suggested that these results support a possible clinical role for gabapentin and opioid combinations for the treatment of pain, or for the addition of gabapentin to opioids to reduce the development of tolerance to their analgesic effects.

Magnesium

N-methyl-D-aspartate (NMDA) or glutamate receptors are thought to be involved in the development of tolerance to the analgesic effects of opioids. Although the exact mechanism of such tolerance is unclear, NMDA receptor activation leads to multiple changes such as calcium ion influx and enzyme activation that result in enhanced glutamate activity and possible neurotoxicity. Some or all of these things may be important in the development of tolerance. An NMDA receptor antagonist known as MK 801 blocks such tolerance to opioid-induced analgesia and so does magnesium, which is a noncompetitive

NMDA antagonist.[52] It has been theorized that the addition of magnesium to morphine might clinically potentiate its analgesic effect, although magnesium side effects such as diarrhea may make this impractical.

Tetracyclines

The tetracycline derivative minocycline has been evaluated in a rodent hotplate model of pain.[53] The drug riluzole, a benzothiazole sodium channel blocker that interferes with stimulation of glutamate receptors, has also been studied. Both delay the development of tolerance and increased the analgesic response to morphine, presumably through interference with the effects of glutamate, even though achieved through different mechanisms. Case reports have suggested a possible benefit for the use of another tetracycline derivative, doxycycline, in the management of new daily persistent headache, a possible variant of chronic migraine.[54]

Melatonin

In rodents, melatonin suppresses the development of tolerance to the analgesic effects of morphine. This may be due to its suppression of nitric oxide synthase.[55] Other nitric oxide synthase inhibitors have been shown to prevent the development of tolerance to the motor impairing effects of diazepam.[56] The nitric oxide donor L-arginine facilitated the development of tolerance to diazepam. This suggests that the role of nitric oxide activity may bear scrutiny as a possible cause of resistance to anti-migraine drugs, at least those suspected of having effects on nitric oxide. In another study, however, nitric oxide synthase inhibitors did not suppress development of tolerance to the analgesic effects of the nonsteroidal anti-inflammatory drug, dipyrone.[57] Thus, the complete story is not yet clear.

Lamotrigine

Lamotrigine is another drug sometimes used for migraine prophylaxis that seems to suppress tolerance to the antinociceptive effects of opioids while itself displaying an intrinsic antinociceptive effect.[31,58]

DISCUSSION

This systematic review aimed to identify the prevalence and possible mechanisms of tolerance in the preventive treatment of migraine. We found no studies that have directly assessed the proportion of patients likely to develop tolerance during migraine prophylaxis. Despite this, we believe that information identified by this review supports a very conservative estimate that from 1% to 8% of patients using migraine prophylaxis will develop tolerance to medication. The lower boundary of this range is based on the fact that roughly 1% of patients seeking specialty headache care spontaneously report the development of such tolerance; the upper boundary is based on the reported 8% of patients who experienced seizure relapse when response to antiepileptic treatment was monitored.

For multiple reasons, this approximation is likely to be an underestimate. For one thing, tolerance can only be reliably identified when there has been careful scrutiny of treatment response to adequate trials of medication over a relatively long period of time. In clinical practice, it is often unclear whether patients have had treatment trials of adequate dose or duration. Additionally, migraine naturally waxes and wanes; this variability in disease activity makes it difficult to distinguish the effects of tolerance from those of the underlying natural history of the disorder. Finally, patients may incorrectly report that the medication is not now and never was effective when a careful review of contemporaneous medical records or headache calendars in fact discloses an initial period of benefit. We have just begun a systematic study of medication tolerance in our clinic, using standardized criteria that are applied to consecutive patients and verified where possible by review of medical records and headache diaries.

We identified 4 broad explanations that may underlie the development of medication tolerance. Pharmacokinetic tolerance is best understood and is particularly applicable to tolerance that develops to the effects of benzodiazepines, barbiturates, and certain antiepileptic drugs such as divalproex.

The role of pharmacodynamic tolerance in loss of effect from migraine prophylaxis has not been systematically explored. Mechanisms important in pharmacodynamic tolerance, such as changes in receptor density or sensitivity, however, are thought to underlie the development of tolerance to opioids and may be important in tolerance to anti-migraine drugs that work through opioid mechanisms. They may also play a role in the development of medication overuse headache, a condition that occurs with use of acute medication for migraine but which has many fascinating parallels to tolerance to migraine prophylaxis, as outlined in Table 5.

It is tempting to speculate that medication overuse headache and tolerance to preventive medication are 2 sides of the same coin, a conclusion reached by another author who suggested that "[Opioid tolerance] has been well described in the general pain literature and may be similar, if not identical, to the descriptions of analgesic rebound found in the headache literature."[11]

Behavioral mechanisms of tolerance have been carefully explored in animal models but are difficult to study in humans and under conditions that approximate real-world treatment. The role of learning in development of tolerance to migraine treatment deserves future study, and may be particularly important in the development of tolerance to unintended or adverse effects of treatment, such as fatigue.

The identified experimental literature also provides ample reason to suppose that the outcomes of migraine treatment may be strongly influenced by the environmental circumstances and cues that are associated with drug prescribing and administration. It is worth considering the extent to which they may also influence the outcome of clinical trials of migraine medications.

Table 5.—Comparison of the Clinical Features of Medication Overuse Headache and Tolerance to Migraine Prophylaxis

Clinical Feature	Medication Overuse Headache[85]	Tolerance
Associated with daily headache?	Yes, by definition, patients have headache 15 or more days/month	Likely in view of the fact that patients are using prophylaxis in the first place, but there may be exception, eg, patients taking prophylaxis for menstrual migraine
Typical scenario?	Frequent, often daily, use of acute or symptomatic medication for headache	Daily use of prophylactic medication for headache. May also occur with frequent or daily use of some classes of abortive agents, eg, opioids
Threshold of use to develop?	Yes, regular exposure needed to develop but susceptibility may vary among individuals and drugs. Diagnostic criteria specify regular use >3 months and differ depending upon the drug involved	Yes, regular exposure needed to develop but susceptibility may vary among individuals and drugs. There is insufficient evidence at present to speculate on the time required for tolerance to develop
Initial benefit from medication?	Yes, implied by continued use of the drug	Yes, by definition
Headache worsens with medication use?	Yes, there is loss of response and worsening of headaches (presumably beyond baseline pre-drug state)	Yes, there is loss of response and worsening of headaches (presumably reversion to baseline pre-drug state)
All patients at risk?	Uncertain but probably not	Uncertain but probably not
Effect of medication withdrawal?	Headache improves	Headache unchanged
Occurs when used for other reasons?	Yes. Patients taking NSAIDs/opioids for arthritis who have pre-existing headache experience worsening of headache. No evidence of reverse	Unstudied but plausible, for example, that a tricyclic used for another condition might engender tolerance to the anti-migraine effect

NSAID = nonsteroidal anti-inflammatory drug.

Further study of such cues may inform the design and interpretation of clinical trials. Because some environmental circumstances can be manipulated, identification of cues associated with treatment response might also be exploited to improve response to migraine treatment.

Although cross tolerance can occur with drugs that share mechanisms of action, we did not identify any information to suggest that tolerance to 1 category of medication predicts tolerance to unrelated medications. A period of abstinence from opioids or benzodiazepines results in a return of drug response when those medications are re-introduced.[59,60] This suggests that drug holidays or drug rotation to medications working through non-opioid mechanisms may be beneficial in patients who become tolerant to migraine medications that work opioid mechanisms. We did not identify any information about whether drug holidays or drug rotation is true for drugs with other mechanisms of tolerance.

The fact that cross tolerance to some of the antiepileptic drugs used in migraine can work in 1 direction only suggests the order in which drugs are used might affect the outcome of treatment. This interesting possibility should be explored in future research.

Our findings demonstrate that many commonly used migraine-preventive drugs have important effects on the endogenous opioid system. Many of them diminish the development of tolerance to opioid analgesia and this suggests that they may

facilitate or augment drugs that work through these mechanisms. It is far from clear, however, that this means they should be used with opioids for the treatment of migraine. There is strong evidence to suggest that in the long run, the pain facilitation effects of opioid administration (as reflected in the development of opioid-induced hyperalgesia) generally outweigh their pain-suppressive effects. Still, it remains plausible that combinations of prophylactic agents may thwart the development of tolerance.

A fascinating related question is whether the use of prophylactic medication for migraine might, as is the case with opioids, eventually make the underlying condition worse. Because most studies of migraine prophylaxis occur over relatively short periods of time, this possibility has not been carefully evaluated. While it might seem far-fetched, this is one plausible explanation for the findings of a recent study of chronic migraine which showed that ongoing preventive medication use during the period of observation was a significant variable predicting a lower, not higher, remission rate from chronic to episodic migraine.[61] This provocative and counter-intuitive result may well be due to confounding by indication, since patients with the poorest prognosis are more likely to receive migraine prophylaxis. Nonetheless, the possibility of long-term hyperalgesia caused by migraine prophylaxis probably deserves further exploration, especially in light of the prominent effects on the opioid system exerted by many migraine drugs.

CONCLUSION

The identified mechanisms of tolerance apply broadly to all categories of migraine drugs examined in this review. The generality of the findings across such a wide range of drug treatments provides strong support for the importance of both behavioral and physiological explanations for loss of effect in migraine prophylaxis. At the neurochemical level, they reflect a limited range of underlying processes likely acting upon receptor sites within the pain system, but at the behavioral level they are much more complex. Given the many ways in which tolerance to migraine medications may develop, in some ways it is not surprising that migraine-preventive drugs stop working; it is more surprising that in many cases they do not.

References

1. Goudie AJ. Behavioral techniques for assessing drug tolerance and sensitization. *Psychopharmacology (Berl)*. 1989;13:565-622.
2. Loscher W, Schmidt D. Experimental and clinical evidence for loss of effect (tolerance) during prolonged treatment with antiepileptic drugs. *Epilepsia*. 2006;47:1253-1284.
3. Remy S, Beck H. Molecular and cellular mechanisms of pharmacoresistance in epilepsy. *Brain*. 2006;129:18-35.
4. Lipton RB, Bigal ME. Toward an epidemiology of refractory migraine: Current knowledge and issues for future research. *Headache*. 2008;48:791-798.
5. Scher AI, Stewart WF, Liberman J, Lipton RB. Prevalence of frequent headache in a population sample. *Headache*. 1998;38:497-506.
6. Castillo J, Munoz P, Guitera V, Pascual J. Kaplan Award 1998. Epidemiology of chronic daily headache in the general population. *Headache*. 1999;39:190-196.
7. Bigal ME, Serrano D, Reed M, Lipton RB. Chronic migraine in the population: Burden, diagnosis and satisfaction with treatment. *Neurology*. 2008;71:559-566.
8. Monhanraj R, Brodie MJ. Pharmacological outcomes in newly diagnosed epilepsy. *Epilepsy Behav*. 2005;6:382-387.
9. Blumenthal DK, Garrison JC. Chapter 3. Pharmacodynamics: Molecular mechanisms of drug action. In: Brunton L, Chabner B, Knollmann BS, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 12th edn. Available at: http://www.accessmedicine.com.ezp-prod1.hul.harvard.edu/content.aspx?aID=16658452.
10. Loscher W. Development of tolerance to the anticonvulsant effect of GABAmimetic drugs in genetically epilepsy-prone gerbils. *Pharmacol Biochem Behav*. 1986;24:1007-1013.
11. Biondi DM. Opioid resistance in chronic daily headache: A synthesis of ideas from the bench and bedside. *Curr Pain Headache Rep*. 2003;7:67-75.
12. Bonavita CD, Bisagno V, Bonelli CG, Acosta GB, Rubio MC, Wikinski SI. Tolerance to the sedative effect of lorazepam correlates with a diminution in cortical release and affinity for glutamate. *Neuropharmacology*. 2002;42:619-625.
13. Fernandes C, Arnot MI, Irvine EE, Bateson AN, Martin IL, File SE. The effect of treatment regimen on the development of tolerance to the sedative and anxiolytic effects of diazepam. *Psychopharmacology (Berl)*. 1999;145:251-259.
14. Sdao-Jarvie K, Vogel-Sprott M. Response expectancies affect the acquisition and display of behavioral tolerance to alcohol. *Alcohol*. 1991;8:491-498.
15. Siegel S, Sdao-Jarvie K. Attenuation of ethanol tolerance by a novel stimulus. *Psychopharmacology (Berl)*. 1986;88:258-261.
16. Tsibulsky VL, Amit Z. Role of environmental cues as Pavlovian-conditioned stimuli in enhancement of tolerance to ethanol effects: 1. Lethal effects in mice and rats. *Pharmacol Biochem Behav*. 1993;45:473-479.
17. Pavlov IP. *Conditioned Reflexes* (Anrep GV, trs.). London: Oxford University Press; 1927.
18. Siegel S. Environmental modulation of tolerance: Evidence from benzodiazepine research. In: Frey HH, Froscher W, Koella WP, Meinardi H, eds. *Tolerance to the Beneficial and Adverse Effects of Antiepileptic Drugs*. New York: Raven Press; 1986:89-97.
19. File SE. Tolerance to the behavioral actions of benzodiazepines. *Neurosci Biobehav Rev*. 1985;9:113-121.
20. Pinel JP, Mana MJ, Renfrey G. Contingent tolerance to the anticonvulsant effects of alcohol. *Alcohol*. 1985;2:495-499.
21. Baker TB, Tiffany ST. Morphine tolerance as habituation. *Psychol Rev*. 1985;92:78-108.
22. Rankin CH, Abrams T, Barry RJ, et al. Habituation revisited: An updated and revised description of the behavioral characteristics of habituation. *Neurobiol Learn Mem*. 2009;92:135-138.
23. Poulos CX, Cappell H. Homeostatic theory of drug tolerance: A general model of physiological adaptation. *Psychol Rev*. 1991;98:390-408.
24. Weiss SR, Clark M, Rosen JB, Smith MA, Post RM. Contingent tolerance to the anticonvulsant effects of carbamazepine: Relationship to loss of endogenous adaptive mechanisms. *Brain Res Brain Res Rev*. 1995;20:305-325.
25. Gent JP, Bentley M, Feely M, Haigh JR. Benzodiazepine cross-tolerance in mice extends to sodium valproate. *Eur J Pharmacol*. 1986;128:9-15.
26. Frey H. Experimental evidence for the development of tolerance to anticonvulsant drug effects. In: Koella WP, ed. *Tolerance to the Beneficial and Adverse Effects of Antiepileptic Drugs*. New York: Raven Press; 1986:7-14.
27. File SE, Aranko K. Sodium valproate decreases exploratory behaviour in mice: Development of tolerance and cross-tolerance with chlordiazepoxide. *Eur J Pharmacol*. 1988;151:293-299.
28. Beck H. Plasticity of antiepileptic drug targets. *Epilepsia*. 2007;48(Suppl. 1):14-18.
29. Avanzini G. Is tolerance to antiepileptic drugs clinically relevant? *Epilepsia*. 2006;47:1285-1287.
30. Mann MW, Pons G. Various pharmacogenetic aspects of antiepileptic drug therapy: A review. *CNS Drugs*. 2007;21:143-164.
31. Saberi M, Chavooshi B. Suppressive effects of lamotrigine on the development and expression of tolerance to morphine-induced antinociception in the male mouse. *Brain Res*. 2009;29:32-39.
32. de Angelis L. Effects of valproate and lorazepam on experimental anxiety: Tolerance, withdrawal, and role of clonidine. *Pharmacol Biochem Behav*. 1995;52:329-333.

33. Kaniecki RG. A comparison of divalproex with propranolol and placebo for the prophylaxis of migraine without aura. *Arch Neurol.* 1997;54:1141-1145.

34. Frances H, Monier C, Debray M. Behavioral effect of beta-blocking drugs resulting from the stimulation or the blockade of serotonergic 5-HT1B receptors. *Pharmacol Biochem Behav.* 1994;48:965-969.

35. Solomon GD. Verapamil in migraine prophylaxis—a five-year review. *Headache.* 1989;29:425-427.

36. Solomon GD. Comparative efficacy of calcium antagonist drugs in the prophylaxis of migraine. *Headache.* 1985;25:368-371.

37. Couch JR, Ziegler DK, Hassanein R. Amitriptyline in the prophylaxis of migraine. Effectiveness and relationship of antimigraine and antidepressant effects. *Neurology.* 1976;26:121-127.

38. Gomersall JD, Stuart A. Amitriptyline in migraine prophylaxis. Changes in pattern of attacks during a controlled clinical trial. *J Neurol Neurosurg Psychiatry.* 1973;36:684-690.

39. Walwyn WM, Miotto KA, Evans CJ. Opioid pharmaceuticals and addiction: The issues, and research directions seeking solutions. *Drug Alcohol Depend.* 2010;108:156-165.

40. Bagley EE, Chieng BC, Christie MJ, Connor M. Opioid tolerance in periaqueductal gray neurons isolated from mice chronically treated with morphine. *Br J Pharmacol.* 2005;146:68-76.

41. Gutstein HB, Akil H. Chapter 23. Opioid analgesics. In: Hardman JG, Limbird LE, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 10th edn. New York: McGraw-Hill; 2001: 569.

42. Cowan A, Macfarlane IR. Effect of propranolol on antinociceptive, tolerance- and dependence-producing properties of morphine in rodents and monkeys. *Eur J Pharmacol.* 1975;34:87-94.

43. Kihara T, Inoue M, Kaneto H. Adrenergic function and the development of analgesic tolerance to morphine. *Jpn J Pharmacol.* 1989;50:397-401.

44. Liu SJ, Wang RI. Increased sensitivity of the central nervous system to morphine analgesia by amitriptyline in naive and morphine-tolerant rats. *Biochem Pharmacol.* 1981;30:2103-2109.

45. Tai YH, Tsai RY, Wang YH, et al. Amitriptyline induces nuclear transcription factor-kappaB-dependent glutamate transporter upregulation in chronic morphine-infused rats. *Neuroscience.* 2008;153:823-831.

46. Tai YH, Wang YH, Tsai RY, et al. Amitriptyline preserves morphine's antinociceptive effect by regulating the glutamate transporter GLAST and GLT-1 trafficking and excitatory amino acids concentration in morphine-tolerant rats. *Pain.* 2007;129:343-354.

47. Michaluk J, Karolewicz B, Antkiewicz-Michaluk L, Vetulani J. Effects of various Ca^{2+} channel antagonists on morphine analgesia, tolerance and dependence, and on blood pressure in the rat. *Eur J Pharmacol.* 1998;352:189-197.

48. Wong CH, Zbuzek VK, Wu WH. Tolerance-like phenomenon of nifedipine-induced antinociception. *Life Sci.* 1996;59:PL277-PL281.

49. Sullivan JT. Effects of verapamil on the acquisition of ethanol tolerance. *Life Sci.* 1993;52:1295-1300.

50. Gullapalli S, Ramarao P. L-type Ca^{2+} channel modulation by dihydropyridines potentiates kappa-opioid receptor agonist induced acute analgesia and inhibits development of tolerance in rats. *Neuropharmacology.* 2002;42:467-475.

51. Gilron I, Biederman J, Jhamandas K, Hong M. Gabapentin blocks and reverses antinociceptive morphine tolerance in the rat paw-pressure and tail-flick tests. *Anesthesiology.* 2003;98:1288-1292.

52. McCarthy RJ, Kroin JS, Tuman KJ, Penn RD, Ivankovich AD. Antinociceptive potentiation and attenuation of tolerance by intrathecal co-infusion of magnesium sulfate and morphine in rats. *Anesth Analg.* 1998;86:830-836.

53. Habibi-Asl B, Hassanzadeh K, Charkhpour M. Central administration of minocycline and riluzole prevents morphine-induced tolerance in rats. *Anesth Analg.* 2009;109:936-942.

54. Rozen TD. Doxycycline for treatment resistant new daily persistent headache. 2008;70(Suppl. 1):A348.

55. Raghavendra V, Kulkarni SK. Possible mechanisms of action in melatonin reversal of morphine tolerance and dependence in mice. *Eur J Pharmacol.* 2000;409:279-289.

56. Talarek S, Listos J, Fidecka S. Role of nitric oxide in the development of tolerance to diazepam-induced motor impairment in mice. *Pharmacol Rep.* 2008;60:475-482.

57. Yilmaz I, Ulugol A. The effect of nitric oxide synthase inhibitors on the development of analgesic tolerance to dipyrone in mice. *Int J Neurosci.* 2009;119:755-764.

58. Habibi-Asl B, Hassanzadeh K, Vafai H, Mohammadi S. Development of morphine induced tolerance and withdrawal symptoms is attenuated by lamotrigine and magnesium sulfate in mice. *Pak J Biol Sci.* 2009;12:798-803.

59. Azar NJ, Lagrange AH, Wang L, Song Y, Abou-Khalil BW. Transient improvement after brief antiepileptic drug withdrawal in the epilepsy monitoring unit—possible relationship to AED tolerance. *Epilepsia.* 2010;51:811-817.

60. Weiss SR, Post RM. Development and reversal of contingent inefficacy and tolerance to the anticonvulsant effects of carbamazepine. *Epilepsia.* 1991;32:140-145.

61. Manack A, Buse DC, Serrano D, Turkel CC, Lipton RB. Rates, predictors, and consequences of remission from chronic migraine to episodic migraine. *Neurology.* 2011;76:711-718.

62. Rosenberg HC. Differential expression of benzodiazepine anticonvulsant cross-tolerance according to time following flurazepam or diazepam treatment. *Pharmacol Biochem Behav.* 1995;51:363-368.

63. Krupp E, Heynen T, Li XL, Post RM, Weiss SR. Tolerance to the anticonvulsant effects of lamotrigine on amygdala kindled seizures: Cross-tolerance to carbamazepine but not valproate or diazepam. *Exp Neurol.* 2000;162:278-289.

64. Zhang ZJ, Russell S, Obeng K, et al. Coadministration of gabapentin or MK-801 with lamotrigine slows tolerance to its anticonvulsant effects on kindled seizures. *Pharmacol Biochem Behav.* 2003;74:565-571.

65. Zhang ZJ, Xing GQ, Russell S, Obeng K, Post RM. Unidirectional cross-tolerance from levetiracetam to carbamazepine in amygdala-kindled seizures. *Epilepsia.* 2003;44:1487-1493.

66. Kim CK, Pinel JP, Hudda MM, Wong DJ, Yung A. Tolerance to the anticonvulsant effects of phenobarbital, trimethadione, and clonazepam in kindled rats: Cross tolerance to carbamazepine. *Pharmacol Biochem Behav.* 1992;41:115-120.

67. De Sarro G, Di Paola ED, Aguglia U, de Sarro A. Tolerance to anticonvulsant effects of some benzodiazepines in genetically epilepsy prone rats. *Pharmacol Biochem Behav.* 1996;55:39-48.

68. Loscher W, Schwark WS. Development of tolerance to the anti-convulsant effect of diazepam in amygdala-kindled rats. *Exp Neurol.* 1985;90:373-384.

69. Mana MJ, Kim CK, Pinel JP, Jones CH. Contingent tolerance to the anticonvulsant effects of carbamazepine, diazepam, and sodium valproate in kindled rats. *Pharmacol Biochem Behav.* 1992;41:121-126.

70. Mana MJ, Kim CK, Pinel JP. Tolerance to the anticonvulsant effects of carbamazepine, diazepam, and sodium valproate in kindled rats. *Pharmacol Biochem Behav.* 1992;41:109-113.

71. Rundfeldt C, Wlaz P, Honack D, Loscher W. Anticonvulsant tolerance and withdrawal characteristics of benzodiazepine receptor ligands in different seizure models in mice. Comparison of diazepam, bretazenil and abecarnil. *J Pharmacol Exp Ther.* 1995;275:693-702.

72. Young NA, Lewis SJ, Harris QL, Jarrott B, Vajda FJ. The development of tolerance to the anticonvulsant effects of clonazepam, but not sodium valproate, in the amygdaloid kindled rat. *Neuropharmacology.* 1987;26:1611-1614.

73. Brezenoff HE, Mycek MJ. Prevention and reversal of tolerance to barbiturates by intraventricular injection of hemicholinium-3. *Eur J Pharmacol.* 1976;37:125-132.

74. Gay MH, Ryan GP, Boisse NR, Guarino JJ. Phenobarbital tolerance and physical dependence: Chronically equivalent dosing model. *Eur J Pharmacol.* 1983;95:21-29.

75. Ito T, Suzuki T, Wellman SE, Ho IK. Pharmacology of barbiturate tolerance/dependence: GABAA receptors and molecular aspects. *Life Sci.* 1996;59:169-195.

76. Kim CK, Pinel JP, Roese NR. Bidirectional contingent cross tolerance between the anticonvulsant effects of pentobarbital and ethanol. *Pharmacol Biochem Behav.* 1992;41:127-132.

77. Weiss SR, Post RM, Sohn E, Berger A, Lewis R. Cross-tolerance between carbamazepine and valproate on amygdala-kindled seizures. *Epilepsy Res.* 1993;16:37-44.

78. Hamada K, Song HK, Ishida S, Yagi K, Seino M. Contrasting effects of zonisamide and acetazolamide on amygdaloid kindling in rats. *Epilepsia.* 2001;42:1379-1386.

79. Wahle H, Frey HH. Development of tolerance to the anticonvulsant effect of valproate but not to ethosuximide in a rat model of absence epilepsy. *Eur J Pharmacol.* 1990;181:1-8.

80. Pakulska W, Czarnecka E. The effect of gabapentin on antinociceptive action of analgesics. *Acta Pol Pharm.* 2004;61:393-400.

81. Peres MF. Melatonin, the pineal gland and their implications for headache disorders. *Cephalalgia.* 2005;25:403-411.

82. Peres MF, Zukerman E, da Cunha Tanuri F, Moreira FR, Cipolla-Neto J. Melatonin, 3 mg, is effective for migraine prevention. *Neurology.* 2004;63:757.

83. Miano S, Parisi P, Pelliccia A, Luchetti A, Paolino MC, Villa MP. Melatonin to prevent migraine or tension-type headache in children. *Neurol Sci.* 2008;29:285-287.

84. Alstadhaug KB, Odeh F, Salvesen R, Bekkelund SI. Prophylaxis of migraine with melatonin: A randomized controlled trial. *Neurology.* 2010;75:1527-1532.

85. Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders: 2nd edition. *Cephalalgia.* 2004;24(Suppl. 1):9-160.