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

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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.

Key words: tolerance, migraine, migraine prevention, chronic migraine, medication overuse headache

Abbreviations: FDA US Food and Drug Administration, GABA γ-aminobutyric acid, GAD glutamic acid decarboxylase

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 duration³ (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
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. 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.

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. 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 non-persistence 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
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...
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.9

**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.2

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

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

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

†Not mutually exclusive; may occur together. Table modified after Loscher and Schmidt2 with permission.
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. 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.” 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.”

Contingent tolerance is not well explained by the multiple models of the mechanism of behavioral tolerance. One influential model by Baker and Tiffany, 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. Another model that is able to incorporate contingent tolerance is the homeostatic theory of tolerance.

The homeostatic theory of drug tolerance 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. 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 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-aminobutyric acid (GABA) A receptors. 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
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 reverse. 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.

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

<table>
<thead>
<tr>
<th>First Drug</th>
<th>Second Drug</th>
<th>Cross Tolerance Demonstrated?</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepine</td>
<td>Benzodiazepine</td>
<td>Yes</td>
<td>Shown in more than 1 model.62</td>
</tr>
<tr>
<td>Benzodiazepine</td>
<td>Valproate</td>
<td>Yes</td>
<td>Unidirectional,25 not present in reverse, from valproate to benzodiazepine</td>
</tr>
<tr>
<td>Benzodiazepine</td>
<td>Phenobarbital</td>
<td>No†</td>
<td>25</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Carbamazepine</td>
<td>Yes</td>
<td>Complete in this direction but incomplete in reverse, from carbamazepine to lamotrigine65</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Gabapentin</td>
<td>No†</td>
<td>63</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Valproate</td>
<td>No</td>
<td>63</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Carbamazepine</td>
<td>Yes</td>
<td>Unidirectional65</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Carbamazepine</td>
<td>Yes</td>
<td>66</td>
</tr>
<tr>
<td>Valproate</td>
<td>Phenobarbital</td>
<td>No</td>
<td>25</td>
</tr>
</tbody>
</table>

Adapted with permission from Loscher and Schmidt.2
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. 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. 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.”

**Propranolol**

Possible cross tolerance between morphine and propranolol has been investigated but study results are conflicting. Propranolol 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 3.—Strength of Evidence for the Development of Tolerance to Selected Antiepileptic Drugs Relevant to Migraine Prophylaxis

<table>
<thead>
<tr>
<th>Simplified Mechanism</th>
<th>Antiepileptic Drugs</th>
<th>Strength of Evidence†</th>
</tr>
</thead>
<tbody>
<tr>
<td>GABA receptor</td>
<td>Benzodiazepines</td>
<td>Strong (^67-72)</td>
</tr>
<tr>
<td>GABA receptor</td>
<td>Phenobarbital</td>
<td>Strong (^65-75,76)</td>
</tr>
<tr>
<td>Ion channel</td>
<td>Carbamazepine</td>
<td>Good (^66,73-76)</td>
</tr>
<tr>
<td>Ion channel/mixed</td>
<td>Lamotrigine</td>
<td>Good (^63,64)</td>
</tr>
<tr>
<td>Ion channel</td>
<td>Zonisamide</td>
<td>Fair (^8)</td>
</tr>
<tr>
<td>Mixed</td>
<td>Gabapentin</td>
<td>Unknown</td>
</tr>
<tr>
<td>Mixed</td>
<td>Valproate‡</td>
<td>Strong (^35,32,65,70,78,79)</td>
</tr>
<tr>
<td>Mixed</td>
<td>Topiramate‡</td>
<td>Unknown</td>
</tr>
<tr>
<td>Unknown</td>
<td>Levetiracetam</td>
<td>Good (^2,64)</td>
</tr>
</tbody>
</table>

†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.
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. 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." 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. 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. 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 as well as to exert their own antinociceptive effect. 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. 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. This effect has been attributed to the interaction between the kappa opioid receptor and the calcium channel.

**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. It enhanced the analgesic effect of morphine in a rat model and also prevented the development of tolerance. 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
Tetracyclines
The tetracycline derivative minocycline has been evaluated in a rodent hotplate model of pain. The drug riluzole, a benzothia-zole 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.

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. 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.

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. Other nitric oxide synthase inhibitors have been shown to prevent the development of tolerance to the motor impairing effects of diazepam. 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 antimigraine 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. Thus, the complete story is not yet clear.

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.”

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.
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. 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. 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


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