

Tolerance and Loss of Beneficial Effect During Migraine Prophylaxis: Clinical Considerations

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A familiar situation in migraine treatment is the patient with an initial positive response to prophylactic drug therapy who later experiences relapse. The goals of this paper are to provide a theoretical framework to help doctors think about this problem, to evaluate factors and response patterns that may be associated with different causes of relapse, and to suggest clinical strategies that may aid in its management. Six key explanations for loss of benefit from prophylactic therapy are: (1) pharmacokinetic, pharmacodynamic, and behavioral drug tolerance; (2) non-specific or placebo effects; (3) natural variability in disease activity; (4) disease progression; (5) inaccurate recall of treatment effects; and (6) drug delivery problems. Current options for patients who experience loss of benefit from prophylactic therapy include traditional techniques such as switching, re-trying, rotating, or combining drugs. Selected behavioral and environmental treatment techniques might also be useful. We describe a practical, structured approach to evaluation and management of relapse with migraine prophylaxis.

Key words: migraine, preventive treatment, loss of effect, tolerance, relapse, adherence

“I’ve been on like five or six different medications to prevent migraines in the last 5 years or so, the most recent one being an antidepressant . . . It worked fine at preventing the migraines with minimal side-effects for a few months and then it stopped preventing and started triggering the migraines, so I haven’t taken it since December. This is nothing new to me; every medication I’ve been on to prevent migraines eventually does this to me, stops working and starts giving me migraines . . .”¹

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THE CLINICAL PROBLEM

A familiar situation in migraine treatment is the patient with an initial positive response to prophylactic drug therapy who later experiences relapse. The usual response to this loss of beneficial effect is to increase the dose, try a different drug, or use a combination of treatments in an effort to regain therapeutic benefit. Sometimes, as in the vignette above, this pattern of initial encouraging but ultimately non-persistent response to treatment occurs repeatedly. It may happen with different classes of drugs or even with non-pharmacologic treatments. This can have important negative clinical consequences if patients or their doctors develop expectations of treatment futility.

In the linked systematic review, we discussed physiological mechanisms that might explain the development of tolerance to the beneficial effects of migraine prophylaxis. We estimated that true tolerance to preventive treatment may occur in from 1% to 8% of patients receiving migraine prophylaxis. From a clinical standpoint, however, the problem is much broader, because in addition to tolerance there are many other possible explanations for relapse.

There have been no previous efforts to systematically identify possible explanations and treatment approaches for this common clinical scenario. The goals of this paper are to provide a theoretical framework to help doctors think about this problem, to evaluate factors and response patterns that may be associated with different causes of relapse, and to identify clinical strategies that may aid in its management.

EXPLANATIONS FOR LOSS OF TREATMENT EFFECT

Patients who initially respond to migraine prophylaxis and then report a reduction in drug response are not a homogeneous group. Rather, they are a mixture of those who had an actual response to treatment and those who had an apparent response. Symptom return does not always indicate a true loss of drug effectiveness. Inaccurate recall of drug effects, poor adherence to treatment regimens, drug delivery problems, disease progression, and naturally occurring fluctuations in disease activity can also result in perceptions of reduced treatment benefit. True loss of response may be somewhat less common than it appears clinically, since some proportion of those who relapse were not

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Conflict of Interest: None

Table.—Key Explanations for Loss of Beneficial Effect of Migraine Prophylaxis

Mechanism	Clinical Example and Pattern	Treatment Implications	Comments
Tolerance Pharmacokinetic Pharmacodynamic Behavioral	Loss of benefit from valproate treatment when patient begins an enzyme-inducing treatment such as phenobarbital	Depending upon circumstances, consider an increase in dose; switch to a different drug; discontinue interacting drug	Pharmacologic causes of tolerance are more likely when loss of drug effect correlates with what is known about a drug's pharmacology. Drug rotation schedules may be considered for patients with well-established patterns of tolerance to multiple medications
Non-specific or placebo effects	Report of immediate, dramatic benefit from an intervention such as onabotulinum toxin type A injections which just as quickly wanes	Appreciate the patient's sensitivity to environmental cues. Consider treatments that harness such non-specific effects such as biofeedback-assisted relaxation. Encourage careful evaluation of objective treatment responses with a headache calendar or other semi-objective measures of benefit	Non-specific treatment responses are unlikely to correlate with known pharmacologic properties of the drug; may be more likely with dramatic interventions such as injections, surgery, or devices compared with pills
Natural variability in disease expression	Inconsistent response to multiple adequate trials of preventive therapy	Re-trials of the same treatment may produce different effects; to avoid over-interpretation of small random fluctuations in headache activity set the threshold for treatment success fairly high	The definition of treatment "response" typically used in controlled trials of preventive medications is a reduction of 50% or more in headache frequency. This high threshold increases the chance that headache changes are due to treatment
Disease progression	Limited if any response to multiple adequate trials of preventive therapy; careful history and review of headache calendars is likely to establish a progressive deterioration in headache control independent of treatment attempts	In truly refractory patients, temporary benefit to prophylaxis may reflect non-specific factors or small random fluctuations in headache activity. They may benefit from combination therapy or rehabilitative approaches to headache management	Disease progression may occur naturally but might also be influenced by environmental events. The possibility that some forms of prophylactic treatment might worsen headache over time has not been systematically explored
Inaccurate recall or perception of drug effects	Inconsistencies between patient report and contemporaneous records of treatment effect	Re-trials of the same treatment may demonstrate benefit; conversely a drug holiday or dose reduction for a drug the patient is currently on may reveal the drug's benefit	Reliance on patient global impression to judge response to treatment is unwise; great emphasis should be placed on more objective measures of headache activity such as calendars
Drug delivery problems "Bad batch" Non-adherence Confusion	With drug quality problems or pharmacy mistakes, may see sudden loss of effect. Suspect when there has been a change in pharmacy, drug brand or supplier, or directions for use. Adherence problems may be more subtle. They may be more common in those on multi-drug regimens or with regimens requiring greater than once daily dosing	Check drug levels where appropriate; ask patient to bring in medication containers for pill counts. Inquire about adherence in a non-judgmental manner	Available evidence suggests that poor adherence is a major cause of treatment failure or loss of effect in migraine prophylaxis. It is likely to be an underappreciated explanation for relapse

true drug responders. The Table outlines 6 key explanations for a reduction over time in the perceived benefits of drugs used for migraine prophylaxis. These are: (1) the various forms of tolerance described in the linked systematic review; (2) non-specific or placebo effects; (3) natural variations in disease

activity; (4) disease progression; (5) inaccurate recall of treatment effects; and (6) drug delivery problems. It is important to note that these causes are not mutually exclusive. These explanations can be divided into drug-dependent and drug-independent mechanisms.

Treatment-Dependent Mechanisms

Treatment-dependent mechanisms are related to specific characteristics of the drug and include the development of pharmacokinetic or pharmacodynamic forms of tolerance, as described in the linked systematic review. The possibility of drug-induced progression of disease was touched on briefly in that paper, and is another potential explanation for loss of effect from both acute and prophylactic treatments for migraine.

Pharmacokinetic and Pharmacodynamic Tolerance and Drug-Induced Disease Progression

With pharmacokinetic tolerance, such things as changes in metabolic processing of a drug or induction of liver enzymes occur that reduce the drug's effect. These problems can generally be overcome by adjustment of the dose of the drug or the removal of competing medications. Drug–drug interactions and other pharmacokinetic factors that affect response to migraine prophylaxis have been reviewed elsewhere and will not be covered in detail in this review.² An example of pharmacokinetic tolerance is the patient whose headaches are well-managed on valproate but worsen when the patient begins to use a barbiturate-containing medication. Barbiturates increase the clearance of valproate, which may result in sub-therapeutic drug levels.³

Another example of a treatment-dependent cause of relapse would be a patient with an initial good response to onabotulinum toxin type A injections for chronic migraine who developed antibodies to the drug with repeated treatments.⁴ Patients who experience repeated loss of benefit from treatment often ascribe the problem to “becoming immune” to drugs. With the exception of onabotulinum toxin type A, however, the physiologic mechanisms of immunity such as antibody production are unlikely to account for relapse to migraine prophylaxis.

Pharmacodynamic tolerance is another possible cause of reduction of benefit from migraine prophylaxis. One way to think about pharmacodynamic tolerance is that it results from “adaptive changes in . . . target systems” as a result of drug exposure.⁵ These adaptive changes represent an interaction between a drug and a susceptible patient, and might include up- or down-regulation of receptors in response to chronic use of a drug. In discussing epigenetic changes and gene induction that may lead to drug tolerance, Wang and colleagues concluded that “tolerance to drugs that affect neural activity is mediated, in part, by adaptive mechanisms that attempt to restore normal neural excitability. Changes in the expression of ion channel genes are thought to play an important role in these neural adaptations.”⁶

Pharmacodynamic tolerance has not been well studied with regard to the drugs that are in common use to prevent migraine. In contrast, a substantial body of research exists regarding pharmacodynamic changes that occur with the use of opioids and other drugs typically used for acute or symptomatic treatment of migraine.^{7,8}

Behavioral Tolerance

Behavioral tolerance occurs when behavioral alterations caused by a drug gradually diminish over time for reasons that cannot be explained by pharmacologic changes in drug activity. It is thought to result from adaptations to drug effects that occur through learning or conditioning, although not necessarily at the conscious level. Headache-related behaviors include such things as remaining in bed, missing work, pain complaints, taking medication, and use of healthcare resources such as emergency department or physician visits. These behaviors are targets of most preventive treatments for migraine, and their changes over time can be tracked using headache calendars, diaries, or routine healthcare database information.

Drug-Induced Disease Progression

There has been no systematic study of the possibility that other preventive drugs used for migraine may over time worsen the condition. This phenomenon has, however, been well described in the case of medication overuse headaches from frequent use of symptomatic migraine medications such as combination analgesics and triptans. It may also explain the generally disappointing long-term treatment benefits of opioids for prophylaxis of chronic headache disorders.⁹ Research suggests, for example, that long-term treatment with opioids may produce opioid-induced hyperalgesia.¹⁰

In any case, the distinction between acute and prophylactic medications for migraine is blurred and arbitrary, and a number of drugs are used for both purposes. This raises the question of whether mechanisms commonly thought to produce disease progression with overuse of acute medications might also operate with prophylactic drugs. Medications that have been used for both acute and prophylactic treatment of migraine include opioids, ergot-based drugs, non-steroidal anti-inflammatory drugs and even triptans.^{9,11-14} Thus, drug-induced progression of disease is another plausible although speculative explanation for apparent loss of treatment effect that may well involve (or represent an extension of) some of the same mechanisms responsible for pharmacodynamic tolerance.

Treatment-Independent Mechanisms

Treatment-independent mechanisms generally do not depend on the drug; instead, they may be related to patient, disease, or environmental characteristics.

Non-Specific or Placebo Effects

The patient characteristics of expectation and belief are known to influence perceptions of treatment benefit in many illnesses including migraine, a phenomenon sometimes referred to as placebo or non-specific treatment effects. Five components of the placebo effect have been described: patient, practitioner, patient–practitioner interaction, nature of the illness, and treatment and setting.¹⁵

In migraine, treatment effects are subjective and patient-reported, both factors that appear to increase the likelihood of non-specific placebo responses to treatment.¹⁶

The durability of non-specific treatment effects is uncertain. Some studies have suggested that placebo effects wear off more quickly than do specific treatment effects, but it is unlikely that duration of benefit would be a useful way of distinguishing waning placebo effects from other possible explanations of relapse.¹⁷

A full discussion of placebo effects is beyond the scope of this paper, but several matters may be particularly relevant to the interpretation of possible placebo effects from migraine prophylaxis in clinical practice. The first is that more dramatic interventions such as injections generally produce higher placebo responses than less striking treatments such as pills.¹⁸ Second, a high level of patient confidence in the physician is correlated with a higher placebo response, as is a good doctor–patient relationship. And finally, placebo effects can co-exist with specific biological responses to drugs.¹⁹

Augmentation of the specific response to a treatment can occur when practitioners are friendly and supportive. This augmented response is enhanced in females and in patients who have a friendly, agreeable, and open personality style. Research also shows that healthcare practitioners differ greatly in their ability to elicit this non-specific enhanced response to treatment, leading 1 group of researchers to comment that “We propose that the quality of the patient–practitioner interaction accounts for the significant difference between the groups in placebo response.”²⁰ The influence of the therapeutic relationship on treatment outcomes has been appreciated for a long time. Balint, for example, formulated this idea as “the doctor is the drug.”²¹

Two studies have produced estimates of the average placebo response to migraine prophylaxis. In a meta-analysis of 22 randomized placebo controlled trials of preventive treatment, the overall proportion of subjects who responded to placebo with a 50% or greater reduction in headache frequency was 23.5 ± 8.0 (95% CI 18.3–28.8%). In a later meta-analysis of 32 trials, the proportion was 21%. Placebo response was higher in studies conducted in Europe compared with North America. It also was higher in parallel than in crossover studies, perhaps because in crossover studies, subjects are aware that at some point they will definitely receive placebo, whereas in crossover studies they are unsure.^{22,23} Included studies were not long enough to characterize the durability of placebo responses to migraine prophylaxis.

Natural History and Variability of Disease Expression

The fluctuating course of migraine is another treatment-independent factor that may explain some cases of diminishing benefit from migraine prophylaxis. Migraine is a disorder that naturally waxes and wanes; even those with very frequent headaches have a high rate of spontaneous improvement. In the Frequent Headache Epidemiology study, subjects who at baseline reported more than 180 headaches per year were followed for a

year. Over the course of the subsequent year, 14% of them experienced a reduction in headache frequency to less than 1 headache per week, and 57% had less than 180 headaches per year.²⁴

The authors pointed out that even with these improvements, headache frequency remained high. These subjects presumably are very likely to later experience spontaneous worsening of headaches. Factors associated with a higher likelihood of remission included higher educational status, non-white race, being married, and having diabetes.

In the population-based American Migraine Prevalence and Prevention study, 26% of subjects with chronic migraine at baseline had reverted to episodic migraine at 2 years. Predictors of remission were lower baseline headache frequency and absence of allodynia at baseline. Interestingly, use of preventive medication was associated with a lower remission rate but this was not statistically significant when results were adjusted for headache frequency. In any case, it is unlikely that preventive medication had much impact on the overall rate of remission since only a small proportion of subjects were using preventive medication. Thus, these findings seem likely to reflect the underlying natural variability of disease expression over time.²⁵

The dynamic and changing nature of headache activity makes it difficult to distinguish the effects of treatment from the naturally variable course of the underlying headache problem. Migraine also tends to improve with age, and this spontaneous recovery may complicate interpretation of drug response in older patients. If a drug happens to be started when the disorder is improving anyway, the drug will appear to be effective. Conversely, if a drug is started during a period of spontaneous worsening, or if that worsening occurs at some later point after a drug is begun, the drug will appear to be ineffective or to lose effectiveness.

Disease Progression

Disease progression is another treatment-independent factor that can influence perceptions of treatment benefit. It can be difficult to distinguish from the temporary fluctuations in disease activity described previously, but it is not the same thing. Background variability of migraine results in alternating periods of both increased and decreased headache frequency or severity, while with disease progression there is a steady or stepwise, inexorable worsening trajectory of headache.

Disease progression can be related to innate characteristics of the disorder itself, presumably genetic factors that influence severity of the disorder and render it progressive and treatment-resistant. Acquired characteristics such as head injury may also lead to inexorable worsening of headaches. Finally, environmental aggravating or trigger factors such as obesity, medication overuse, severe work demands, or sleep difficulties can contribute to disease progression. The latter may work through epigenetic as well as structural mechanisms.^{24,26–28}

Inaccurate Recall of Treatment Effects

Headache diaries, calendars, or other contemporaneous records of headache characteristics are the gold standard for headache diagnosis and for making treatment decisions. Patient compliance with diaries, however, is less than ideal. Compliance with paper diaries might be poor because such diaries are not always accessible and are easily misplaced.

Even when diary keeping is made easier, however, as with online headache diaries provided to motivated patients, compliance is suboptimal. In 1 study of migraine patients recruited from websites and Internet chat rooms, 24 of 101 people dropped out before completing the 4-month electronic diary study. Only 68% completed at least half of their diary entries within 24 hours of the day for which they were recording information; 25% of pages were not completed within 2 days. Seventeen percent of patients did not keep written notes on days when they were unable to access the Internet.²⁹

Poor compliance with headache diaries and calendars means that for many patients who take prophylactic migraine therapies assessment of treatment response will be based on patient recall. Patient recall is not very accurate. In 1 study, 209 headache patients kept a daily diary of headaches over a 4-week period. Then, without having the diary to consult, they completed a questionnaire about headache frequency and severity during the period covered by the diary. The average headache severity reported by patients in this questionnaire was statistically significantly worse than that demonstrated in prospectively kept diaries.³⁰

A similar study was conducted among 181 children aged 8-16 with migraine. Again, patients overestimated headache severity and duration on the questionnaire compared with diary results.³¹ A study that used comparable methods but included just 40 patients showed a modest positive correlation between the headache diary and patient reports of frequency and duration of headaches, with Spearman's rank coefficients of 0.80 and 0.72, respectively. For headache intensity, there was only mild positive correlation, with a Spearman's rank coefficient of just 0.51.³²

Drug Delivery Problems

Drug delivery problems can lead to a perception of decline in benefit from migraine prophylaxis. It is always possible that the patient is no longer receiving the drug or dose that was previously effective. This could happen if a pharmacy has mistakenly dispensed another drug or a lower dose of the drug. The most common dispensing errors are "dispensing the wrong drug, strength, form or quantity, or labeling medication with the incorrect directions."³³

Drug quality problems may also result in apparent loss of drug effect. Problems with manufacturing processes may lead to variability in drug activity; 1 study estimated that pharmaceutical manufacturing results in approximately 35 000 defective "prod-

ucts" for each million produced. The US Food and Drug Administration has embarked on efforts to improve manufacturing standards for drugs.³⁴⁻³⁶ Similarly, a drug past its expiration date or one that has been stored improperly may have reduced pharmacologic activity.

Poor adherence (non-compliance) to medication regimens may also result in loss of treatment effect. Not all adherence problems are deliberate: patients may not understand dosing directions for a drug, particularly when moving from 1 tablet strength to another. Consider, for example, a patient who takes a single 100-mg amitriptyline tablet daily who is instructed to move to a daily dose of 150 mg by taking 3 50-mg tablets. Accustomed to taking a single tablet of amitriptyline daily, she may well continue to do this when she receives the new, lower-dose amitriptyline tablets.

In 1 study of migraine prophylaxis, compliance rates averaged 66% when evaluated with pill bottle lids that stored information about when medication containers were opened.³⁷ Interestingly, when compliance in this group of patients was assessed using counts of returned pills, it appeared to be higher (91%). Medication compliance was highest for once daily regimens compared with regimens that required doses 2 or 3 times daily, but even then was not perfect. With a once daily regimen, compliance with taking the medication on schedule was 66%, with an estimation that "therapeutic coverage" levels were achieved 81% of the time. The authors comment that ". . . in the drug prophylaxis of migraine, dosing frequency is better if lower, to the extent that anything above [once daily] seems doomed to failure in many patients. In the routine management of migraine patients, more elaborate methods of compliance measurement have a role. They may avoid much wasted effort, especially in cases of unexplained multiple drug resistance."

Another study of adult migraineurs attending a Swedish headache clinic showed that 35% were non-adherent with migraine prophylaxis as assessed with the Medication Adherence Report Scale. This is a 5-statement questionnaire that patients fill out to assess treatment compliance. This and other self-report measures of adherence are reasonably well correlated with other measures of adherence such as pill counts.³⁸ Interestingly, in this population, beliefs about medications, as measured by the Beliefs about Medicines Questionnaire, did not predict non-adherence.³⁹

Adherence to medication for migraine prophylaxis has also been examined in a large Dutch prescription database. This analysis indicated that over half of patients discontinued prophylaxis within 3 months and only 25% were still taking the medication after 1 year.⁴⁰ Patient characteristics or clinical features have been examined as possible predictors of adherence, but none appear to be significantly associated with compliance.⁴¹

CLINICAL MANAGEMENT

Although there is good-quality evidence for several plausible treatment-dependent and -independent effects that might cause

relapse during migraine prophylaxis, it can be difficult to determine which are relevant to an individual patient. This is an important clinical management problem because the appropriate treatment response differs depending upon the underlying cause.

Clinically, patterns of response to treatment as well as responses to drug re-challenge and other related information may be helpful in distinguishing among causes of relapse. The Table contains some information on treatment patterns that might be observed in selected causes of treatment relapse, as well as suggestions about treatment strategies that might be helpful in each case.

Patterns of Treatment Response

For some causes of relapse, there may be characteristic patterns of drug response. In many cases, these are difficult to identify in the context of a single drug trial. In patients who repeatedly experience initial response and subsequent loss of drug effect, however, certain patterns may emerge.

If loss of drug effect is due to the development of tolerance, the time course will be consistent with established pharmacologic parameters for the individual drug. Examination of treatment records or reconstruction of an accurate drug history may demonstrate concomitant use of medications likely to produce known drug–drug interactions or to produce cross-tolerance. Re-challenge with the drug in the absence of interacting medications, along with efforts to ensure an adequate dose and level of the drug, may well restore benefit.

With non-specific or placebo effects, the temporal course of benefit and subsequent loss of effect is likely to be independent of medication class or mechanism of action. It may be more pronounced with dramatic interventions such as injections or surgery. It may wane over time as the patient develops negative expectations of treatment benefit, for example, “nothing worked before so this won’t either.” This pattern of response might also be recognized in a patient who tends to have strong “nocebo” or negative non-specific responses to many different classes of drugs.

A good response to re-challenge with the drug is unlikely, unless accompanied by strong suggestions or cues that previous dose was too low or that some other augmentative technique might restore benefit. In our practice, we sometimes suggest to the patient that a short “booster” course of scheduled anti-inflammatory drugs or steroids, for example, might help restore benefit to a drug. If this strategy is successful, it may not be necessary to discontinue the treatment. It is helpful to remember that non-specific responses to treatment, which can co-exist with and augment true drug effects, are affected by situational factors such as a good relationship with the doctor and strong cues suggesting that treatment will be effective.

In cases where apparent loss of drug benefit is due to the natural variability of migraine activity, there might be a history of variable response to treatment trials. Some might appear effective initially, with effects wearing off over time as the disease worsens

temporarily; others, started when disorder is worsening, might conversely appear to worsen headaches initially and then, if continued, be perceived to have a beneficial effect. Retrials should produce inconsistent, sometimes contradictory results compared with initial trials. The underlying variability of migraine is a good reason to set the threshold for a “positive” trial of prophylaxis at a convincingly high level; in our practice, we often use the 50% reduction in headache frequency that is employed in clinical trials of migraine prophylaxis, for example.

In cases where disease progression is responsible for apparent loss of treatment benefit, it is likely that all drugs will appear to be ineffective or even to make things worse. If progression is occurring in a discontinuous manner, a patient may see initial slight improvement (perhaps due to placebo or natural history effects) but then apparent lack of effect or worsening. Re-challenge with the drug will not be effective.

When inaccurate recall of drug effects is responsible for apparent loss of treatment benefit, careful review of headache calendars, previous medical records or interviews with family members might prove helpful. In this case, a re-challenge with the drug is likely to produce benefit. This is most likely to be noticed and remembered by the patient if a careful record of treatment response is maintained.

Similarly, relapse due to drug delivery problems might be recognized by a sudden loss of effect that coincides with changes in pharmacy, a prescription refill, or a change in medication directions. Re-challenge or continuation of treatment with a new supply of the drug, careful review of prescription instructions and dosage, and efforts to ensure adherence should be considered in such cases.

An Algorithmic Treatment Strategy for Loss of Effect With Migraine Prophylaxis

A standardized approach to the problem of relapse is outlined in the algorithm in the Figure. This algorithm suggests that clinicians begin by evaluating factors that are easiest to appraise and for which treatment strategies are relatively straightforward. This includes a careful history and focused laboratory or physical examination to judge adherence, drug delivery, and the existence of possible environmental aggravating or trigger factors. Clinicians might look for physiologic signs that indicate a drug is being taken, such as checking the pulse and blood pressure of a patient on a β -blocker. They might also obtain laboratory tests such as drug levels, or ask the patient to bring in bottles for pill checks and counts. Once these things are ruled out as possible root causes of relapse, it is appropriate to put progressively more effort into an examination of explanations that are more complex or difficult to ascertain.

Review of Previous Treatment Trials to Verify Relapse

A reasonable next step might be a review of previous treatment and pharmacy records in an effort to more precisely reconstruct the effects of previous drug trials. This is a time-consuming but

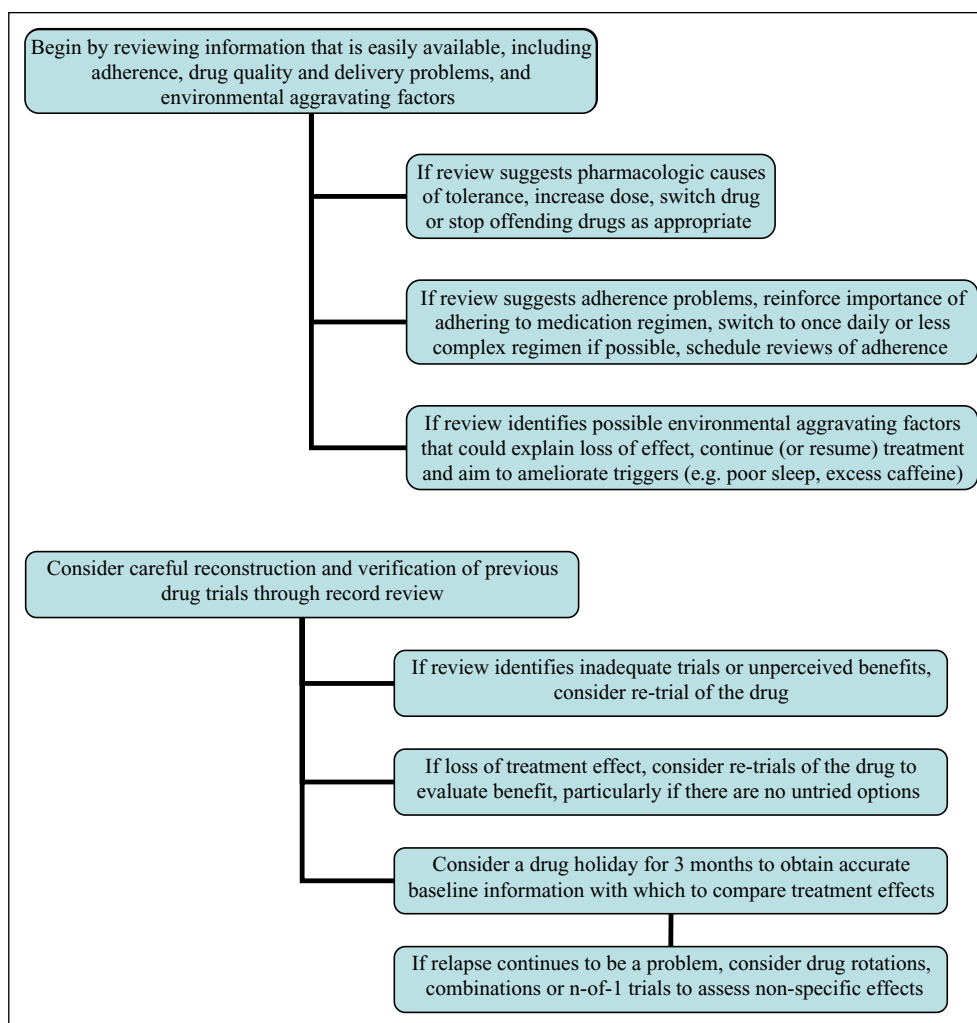


Figure.—An algorithmic evaluation and management strategy for loss of effect with migraine prophylaxis.

particularly important exercise in patients who report repeated loss of benefit from many different trials of medication. Patients are often willing to invest time in obtaining and abstracting their own records, and this can be a useful exercise for them as it prompts their memory about the circumstances and details of past treatment efforts.

In the authors' experience, accounts of repeated relapse are not always verified when medical and pharmacy records are carefully reviewed and compared to headache calendars and other information. In some cases, it becomes clear that the dose and duration of previous prophylactic trials were not adequate. In other cases, it is apparent that drug–drug interactions or pharmacokinetic factors may have been responsible for treatment problems. It is not uncommon for contemporaneous records to show that there was in fact sustained treatment benefit with the drug but that treatment was switched because of side effects or the hope

that other drugs might be even more effective. The patient may incorrectly recall that the switch was prompted by loss of effect.

Drug Holidays and n-of-1 Treatment Trials

When it is difficult to be certain that relapse has occurred because of inadequate information about the underlying pattern of headaches, a 2- or 3-month drug holiday should be considered. This provides a period of time during which baseline headache activity can be carefully tracked. The outcome is an accurate measure of baseline disease activity to which the effects of subsequent treatment trials can be more accurately compared.

In addition to drug holidays, n-of-1 treatment trials might also be considered in cases where the effects of treatment are difficult to distinguish from the natural history of waxing and waning headaches, or where disease progression or placebo effects seem possible. With n-of-1 trials, periods of active drug administration

are interspersed with periods during which an identical or similar-appearing inert pill is given, so that the patient is uncertain when active drug is being used.⁴² Careful records of treatment response are kept, and compared with use of active and inert medications in order to distinguish the effects of natural history, placebo, and true drug effect. Because of practical difficulties in implementing them, such trials have not been widely used in clinical practice. They probably should be, however, since they provide high-quality evidence of treatment effects that are relevant to an individual patient. Although they involve placebo, there is no patient deception involved since patients are aware of and consent to the fact that placebo will be used.⁴³

Drug Rotation and Combination Treatments

Drug rotation can also be considered in cases where few alternative treatments remain to be tried. In cases where patients have identified temporal patterns of relapse, as, for example, a patient who reports that most drugs lose benefit around 4 to 6 months after treatment initiation, an empirical approach might be to plan to rotate from 1 drug to the next at the 4-month mark. In other words, instead of waiting for loss of effect to occur, it is anticipated and treatment is changed before it occurs. With this approach, there might be a 1-month or so period of overlap of the 2 drugs, in order to establish a therapeutic level of the second drug before the first is tapered or discontinued. Drug rotation has been used successfully to optimize treatment response in patients who develop tolerance to opioid therapy for chronic pain.⁴⁴

The use of combination therapy is another strategy to consider in patients who have experienced repeated loss of benefit from single drugs. There is little evidence from randomized trials or other high-quality study designs to guide such treatment, but it is commonly used in patients with chronic, difficult-to-treat headache problems.⁴⁵ Drug combinations are chosen empirically based on theoretical hopes of synergy or in an effort to treat not only headache but also co-morbid disorders. Although the mechanisms of action of prophylactic migraine drugs are in most cases putative, it makes sense to choose combinations of drugs that (presumably) work in different ways.

AREAS OF UNCERTAINTY

It seems likely that the order in which drugs are used or the drugs they are given with may influence the chance of treatment success or failure, but high-quality evidence about this matter is lacking. There is also little solid information about behavioral and contingent forms of tolerance that might occur with migraine prophylaxis. For example, if, as suggested in the linked review, biological detection of drug effects is necessary for tolerance to occur, it might make sense to minimize this by starting with a low dose of treatment and working up gradually to a target level in an effort to minimize drug side effects or other cue properties of drugs that could cause tolerance to develop.

In the case of behavioral tolerance, it seems possible that some patients may be conditioned by previous failures or attitudes to

physicians to experience repeated loss of treatment benefit. Perhaps they have unconsciously come to associate a physician offer of drug treatment with the outcome of non-persistent treatment benefit. It seems worthwhile to explore whether this might be prevented or reversed with treatment strategies such as shared decision making or other forms of patient control over treatment.

Little work has been done on how to best exploit non-specific factors in headache treatment. It is likely that what the doctor says about prophylactic treatment and how she says it might substantially influence treatment outcomes. For example, in discussing possible side effects of topiramate, a physician might manipulate expectations by formulating them as evidence of drug effects, perhaps by saying “A common non-dangerous side effect of this drug is tingling in the fingers or toes . . . that is a sign that the drug is working.” Enhancement of non-specific benefits might also imply that it is worthwhile to start with treatments most likely to be effective, so that patients do not develop expectations of treatment failure.

From a behavioral point of view, it is also worth noting that response to prophylactic therapy for migraine is usually assessed using treatment diaries and calendars that inadvertently emphasize the occurrence of headaches (treatment failure) rather than days without headache (treatment success). There is little reinforcement that a prophylactic drug is working, but substantial attention is drawn to evidence that it might not be. In other words, every headache that is recorded represents a treatment failure, and “headaches that don’t happen” are not easily recognized.

Overly detailed headache calendars or diaries may also promote a focus on somatic symptoms that is counterproductive. There is evidence that at least in some cases the more frequently patients are asked to rate and attend to pain, the higher the pain ratings become.⁴⁶ Calendars and diaries usually require patients to pay close attention to each episode of headache, recording details about disability, pain levels and associated symptoms. Perhaps headache calendars should be reformulated to obtain the minimum necessary information about headaches and to draw more attention to days without headache. In graphic calendars that ask patients to record headache intensity each day of the month, this could be accomplished simply by inverting the usual 0-10 pain scale so that the low levels of headache intensity are at the top of the chart. The eye would be drawn to these peaks, which represent good rather than bad days.

This focus on treatment success rather than failure has been successfully used in other chronic waxing and waning disorders. One expert describes it as follows: “The goal is to encourage active participation in symptom improvement . . . I encourage the patient to keep a daily diary of symptoms, focusing on a “good days” count . . . The focus of the diary would be an increase in the days with moderate or less distress. The diary should be the focus of review at each planned visit, and it adds an objectivity that is instructive to both patient and physician.”⁴⁷

CONCLUSIONS

Despite clinical impressions that loss of beneficial effect can occur during prophylactic migraine treatment, little has been written about the possible causes or management of this problem. Our review has identified 6 main explanations for loss of effect and the likely patterns of response that may be seen for each. Based on this, we have developed a proposed algorithmic approach to evaluation and management.

A complete understanding of relapse during migraine prophylaxis requires an appreciation not only of pharmacologic principles but also of environmental and behavioral influences on treatment response. Managing patients who experience repeated loss of benefit from treatment is a challenge. A structured approach to evaluation and management is most likely to identify treatment strategies that best suit an individual patient.

Current options for patients who experience loss of benefit from prophylactic therapy include traditional techniques such as switching, re-trying, rotating, or combining drugs. Perhaps the most important recommendation to emerge from this review, however, is that it is important to pay close attention to behavioral and environmental aspects of treatment response. Accurate records of headache activity are important, but should not reinforce treatment failure. Efforts to enhance patients' expectations and beliefs about treatment effects, and careful management of environmental cues that can influence perceptions of benefit should also reduce the likelihood of treatment relapse.

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