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Expert Opinion

Adherence to Prophylactic Migraine Medication

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One of the more frustrating aspects of treating migraineurs are those who prematurely discontinue preventive medications for no clear reason or because of nuisance side effects they were advised of or take their medications intermittently. Some may bitterly complain that their headaches persist, nothing works, and what are you going to do about it?

CASE

This 33-year-old woman is seen in headache consultation with a 15-year history of migraine without aura occurring about 8 times monthly with an inconsistent response to triptans. She was tried on amitriptyline 25 mg at bedtime by her primary care physician but stopped on her own after 1 week because she was no better even though she was aware that the medication may take 6 weeks to work and that the dose may need to be higher. A neurologist placed her on topiramate, which she took inconsistently because she "forgot" and reported that the medication was not effective.

Questions: What is the difference between compliance and adherence? How often are migraineurs non-adherent with preventive medications and why? What can physicians do to improve adherence?

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EXPERT COMMENTARY

There is no commonly accepted indication for starting a prophylactic treatment. According to European Federation of Neurological Societies Task Force guidelines,[1] prophylactic drug treatment should be considered and discussed with the patient when important life domains are severely impaired, the frequency of attacks is 2 or more per month, acute treatment fails, or when auras are very disturbing. However, in daily migraine care, one cannot simply expect the same efficacy of drugs as in clinical trials, because prophylactic treatment is not uncommonly prematurely discontinued by the migraineur for no apparent clinical reason.[2]

The term "compliance" is still commonly used to indicate a patient's correct following of medical advice. Non-compliance has thus sometimes been regarded as a manifestation of irrational behavior or willful failure to observe instructions. Nowadays, health care professionals prefer to talk about "adherence" to a regimen, a less authoritarian term proposed for the extent to which patients follow agreed recommendations regarding treatment. It emphasizes the importance of the patient's participation. Regardless of the nomenclature, this poorly understood phenomenon is a significant problem in headache care, because it prevents achievement of the full benefits of medications. It is possible that most evaluations of efficacy and tolerance of migraine prophylactics to date have been biased in this respect.[3-5] A large number of studies have addressed the degree of patient non-adherence to medication in other medical conditions,

but the methodological quality is generally poor, which poses obstacles to meta-analyses.[6,7]

In a retrospective analysis of a large prescription database in the Netherlands, more than half of the population had terminated treatment with migraine prophylactic drugs within 3 months, and poor patient adherence with the treatment regimen was probably a major contributing factor.[8] Only a few publications examine adherence to prophylactic migraine treatment. Between a quarter and half of patients are non-adherent with prophylactic medications.[4,9-11]

The problem is that there are no known predictors to help the clinician anticipate non-adherence among migraineurs today. In a logistic regression analysis, we found no significant association regarding adherence and sex, age, or educational level.[12] The patient's decision-making is a complex, dynamic, and continuous process that develops over time. Characteristics of the headaches *per se* are the starting point of this process.[13] You would think that the more severe disease, the more adherent someone would be to their therapy. We therefore explored whether a selection of clinical features, apparent to the physician, influenced adherence in a typical migraine population. However, neither attack frequency, duration of attacks, degree of recovery between attacks nor cardinal symptoms during attacks were significantly associated with adherence.[11] Thus, non-adherence is also a problem among patients with severe migraine.

So how do you identify them? The simplest is to ask them nonconfrontationally if they take their medicines. You can also incorporate a routine in your practice that helps identify them. For example, while the patient is in the waiting room, they can fill out a questionnaire. Self-reported questionnaires in general have been found to have a moderate-to-high concordance with other measures of adherence, such as pill count or plasma drug concentration analysis.[14,15] There is no golden standard among instruments, but it has been shown that persons who report non-adherence are indeed non-adherent.[16] For research purposes, we have used the Medication Adherence Report Scale (MARS), which consists of 5 statements about the use of medicines.[17-20] They concern forgetfulness, altering dosage, stopping taking medicines, missing out on a dose, and taking less than instructed. For each statement, respondents mark their degree of agreement on a 5-point scale (1 = always, 2 = often, 3 = sometimes, 4 = seldom, 5 = never). An example of non-adherence (score of 22) according to the MARS would be to "often" miss taking the daily dose of a prescribed beta-blocker. A patient "sometimes" forgetting it is, on the other hand, defined as adherent as long as the drug is taken according to the given recommendations in other aspects, eg, in the prescribed dose (score of 23). A potential weakness is that patients returning to the clinic might be those satisfied with the treatment given, leading to a selection bias. Self-report should therefore be supplemented with objective data like the refill rate or frequently missing appointments. Look also for those who are not responding to their medicines or not having expected side effects, for example, diminished heart rate when using a beta-blocker.

At our center, beliefs about medicines in general did not contribute significantly to adherence in a typical migraine population receiving standard care.[12] To a limited degree, there are, however, more specific treatment predictors, such as the cost. As in other illnesses, a satisfactory efficacy/tolerance ratio is an essential determinant.[21-24] This may in part explain why our users of beta-blockers were significantly more adherent than users of amitriptyline. It is also interesting to note from our material that patients with a superior educational level expressed more concern about medications and they had a lower necessity-concern differential, compared with those with primary school as highest level of education.[12] Adherence declines with more frequent and complex dosing regimens.[25] One reason may be simple forgetfulness. In a study on migraine prophylaxis, once-daily treatment was associated with better used-on-schedule rate than multiple daily dosing, but still only 66% were adherent.[10]

New strategies to improve adherence with existing therapeutic regimens might yield greater benefits than will new pharmacologic agents. Various approaches can be used to achieve this in clinical practice. It is crucial not to overlook the patient's own desire to play an active role as decision maker. Greater insight into individual needs and fulfillment of expectations increases the likelihood of adherence.[26] Therefore, it is most important to understand

the benefits and disadvantages of the current therapies from the patients' perspective.[27] One must consider the patient's stage of readiness for change, help the patient relate to the clinical trial data, and realize the potential value of the treatment.[28] Motivation for change is increased when patients make decisions themselves rather than being passive recipients of instructions. Partner with the patient and negotiate rather than dictate a plan.[9] The benefits of care must outweigh costs. Put the price of prophylactic medication into the context of the indirect expenses. If you recommend a less costly medicine, patients are likely to be more adherent.

In a busy clinic, it is sometimes easy to give out a prescription with little or no explanation. Verbal recommendations can be supplemented with standardized written instructions. Patients often like the idea of fewer pills. Explain the importance of reporting their current dosage when calling for a new prescription, so that you can choose the appropriate strength of tablets. When possible, simplify the treatment regimen by using sustained release preparations with fewer dosages during the day. A variety of packaging solutions, such as blister packs or just a pillbox, have been developed to remind the patient if they have missed the most recent dose.

Communicate balanced information about potential side effects outweighing the risks. Select treatments with few concerns for long-term use. The drug has to fit within the patient's lifestyle. For example, amitriptyline in the evening may be unsuitable for patients working nights. Give advice on minimizing or coping with the most common adverse events. When there is a risk for dose-dependent side effects, explain that titration should not continue above the highest tolerable dose. It is reassuring for the patient to be in control.

Tell patients you are monitoring them. Such attention can be very helpful. Involve the patient in being responsible for this evaluation and reporting back to the team. A migraine diary is mandatory. Explain that prophylaxis is regarded as successful if the frequency of attacks is decreased by at least 50% within 3 months. People may perceive that the drug is ineffective if their migraine manifestations are not completely eradicated. Provide continuous reinforcement to assure the patient's persistence, ie, continuing with the medication as long as it is prescribed. Always take care to maintaining an emphatic and nonjudgmental atmosphere.[28] Patients may otherwise not accurately report back because of fear of possible embarrassment.

Migraine also tends to cause distress and frustration for significant others such as the migraineur's family and friends, and non-adherence is a problem for them too. It is often they who have brought the patient to the office, and we should therefore involve them in the decision-making progress and ask them to support the patient in taking their medication.[29]

It is important to find ways around potential barriers within the health care system. Problems with adherence have been associated with a long wait time to return visits after consultation.[30] Contacting patients in advance of their scheduled appointments and recalling those who miss an appointment are interventions that may increase long-term adherence.[29] For patients with a lower income status, it may be hard to get to the doctor more regularly. Does the patient have other access to the clinic staff? Asking a nurse to call the patient between visits to see how they are doing is a positive reminder.

Despite all efforts, a number of patients do not wish to commence or continue a course of treatment. The reason is often a stigma for taking medications in general which might be very difficult to overcome. Self-care measurements other than medication should always be part of a consultation, but it should be particularly emphasized in these cases. Have them work on their lifestyle habits and put in plain words that they must avoid migraine triggers.[31,32]

In this particular case, I would consider non-pharmacological treatment because it may be equally viable to drugs in prophylaxis for migraine.[33] Many patients appreciate and prefer "low-tech-high-touch" medicine, not necessarily because they reject drugs as is often thought, but because non-pharmacological treatment is considered to activate endogenous, positive mechanisms, and because it offers "empowerment" – an opportunity to be an active participant and influence the recovery. Along with the positive findings in clinical trials, this supports the notion that non-pharmacological therapies are a first choice for

patients in need of prevention, either in monotherapy or as an adjunct to drugs.[31]

In summary, a prerequisite for successful outcome of prophylaxis emanates from awareness of the patient's expectations. Furthermore, the prescribing physician must offer continuous reinforcement to maintain adherence.

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