

Prophylaxis: Headaches That Never Happen

Elizabeth Loder, MD, MPH

The discovery of preventive drugs for headache involved both serendipity and design. Despite modest efficacy and uncertainty about mechanisms, prophylaxis has transformed the lives of countless headache sufferers in the last 50 years. Realizing its full potential will be the work of the next half-century.

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Elizabeth Loder, MD, MPH, Chief, Division of Headache and Pain, Department of Neurology, Brigham and Women's/Faulkner Hospitals, Associate Professor of Neurology, Harvard Medical School, Boston, Massachusetts.

The word “serendipity” appears repeatedly when the history of pharmacologic prophylaxis of headache is recounted. That is not surprising, since only one of the major headache preventive drugs of the last 50 years was found through concerted, purposeful effort; the rest were incidentally discovered to be useful following their development to treat other medical problems. Despite this, prophylactic drugs for headache and the idea for which they stand – headache prevention – constitute the most important headache breakthrough of the last 50 years. The realization that headaches could be stopped before they began had a profound impact on thinking about headache. Until then, acute rather than preventive treatment had been the means of control, and little thought had been given to the possibility that the underlying vulnerability to headache might be altered. Since then, prophylactic drugs have prevented millions of headaches.

Some important milestones in pharmacologic prophylaxis of headache

Methysergide and the Antiserotonin Drugs

Methysergide, approved by the United States Food and Drug Administration (FDA) in 1962, was the first prophylactic drug to be introduced to headache practice. For that reason, it remains iconic despite subsequent restrictions on use due to fibrotic side effects. Its introduction was the cul-

mination of years of deliberate research by the Swiss pharmaceutical company Sandoz to purify and synthesize ergot derivatives for use as pharmaceuticals. The first report in the general medical literature on methysergide, then known as UML-491, was by Federigo Sicuteri and appeared in 1959.

It is difficult at the remove of almost half a century to fully appreciate the excitement that accompanied the arrival of methysergide on the headache scene. Writing in the October 1963 issue of *Headache*, Dr. Leonard Lovshin of the Cleveland Clinic reported that this was the first “advance made in the therapy of migraine and related forms of head-

Table 1.—Drugs Approved by the United States Food and Drug Administration for Headache Prophylaxis

Drug	FDA approval date*
Methysergide maleate	1962
Propranolol	1979
Timolol	1990
Divalproex sodium delayed-release tablets	1996
Divalproex sodium extended-release tablets	2000
Topiramate	2004

*Approval for a headache indication.

ache” since the introduction of ergotamine tartrate some 30 years earlier, and that its advent “aroused considerable interest” because “no satisfactory preventive measure had previously been developed.” The prophylactic potential of other antiserotonin drugs, including pizotifen and cyproheptadine, was also investigated during the 1960s. It seems more than coincidental that interest in forming the American Headache Society coalesced just as the medical literature was full of news about a class of drugs that might be effective for a problem long regarded as psychiatric. The era of truly biological headache treatment had begun, and with it came a surge of organized professional interest in headache.

Tricyclic Antidepressants

In the mid and late 1960s, case reports and small studies appeared in medical journals suggesting the efficacy of amitriptyline and several other tricyclic antidepressants in the treatment of headache and pain syndromes. The results of controlled trials showing a benefit for amitriptyline in the treatment of migraine, tension, posttraumatic and “mixed” headache

syndromes were published throughout the decade and into the 1970s. Tricyclic drugs, especially amitriptyline, remain a mainstay of preventive treatment for migraine, tension-type headache, and other forms of head pain. The efficacy of these drugs in headache focused attention on the connection between psychiatric disorders and headache. Decades of research have subsequently established the bidirectional nature of the association between many psychiatric problems, especially affective disorders, and headache.

Beta-Adrenergic Blockers

The beta-blockers were next. In the late 1960s, propranolol was already in use for the treatment of angina pectoris. Sporadic reports appeared describing its beneficial effects in patients with coexistent migraine, and the first results from a large controlled trial of propranolol for migraine were published in the early 1970s. Spurred by developments in the field, the United States National Institute of Neurological Disease and Blindness (NINDB) issued a 1968 monograph on the conduct of “controlled clinical trials of drugs for use in the prophylaxis of migraine.”

In the January 1973 issue of *Headache*, Dr. John Graham reported results from his double-blind trial of propranolol for migraine and made a point of noting the trial’s adherence to the NINDB recommendations. In discussing the results of the study, Dr. Graham made 2 prescient observations: first, that the drug seemed to work better in “some patients” – an early formulation of the idea that subgroups might exist whose response to treatment differed from that of the overall group of trial participants. Second, Dr. Graham noted that propranolol worked less well in patients who “were consuming very much larger quantities of analgesic and especially ergot drugs during the trial” – an early formulation of the idea that medication

overuse might interfere with response to prophylaxis.

These observations have stood the test of time and continue to influence the design and conduct of clinical trials in headache. Renowned for his powers of clinical observation, Dr. Graham might well have reached these conclusions in any case. It seems likely, though, that adherence to reporting requirements of the NINDB guidelines made plain patterns of treatment response that might otherwise have remained hidden. The need to develop and test drugs for migraine provided on the job training in the proper conduct of clinical trials for an entire generation of headache doctors, and exposed them to sophisticated statistical concepts. Science was coming to headache.

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Lithium

Migraine and tension headache were not the only recurrent headache problems to attract the attention of researchers. The value of lithium for prophylaxis of cluster headache was established in the mid 1970s by Karl Ekblom, and the drug remains widely used for this purpose.

Calcium Antagonists

A variety of calcium antagonists were investigated for headache prophylaxis in the 1980s, mostly for migraine. The first double-blind, placebo-controlled trial of verapamil in migraine prophylaxis appeared in the *Journal of the American Medical Association* in 1983. Other calcium antagonists tested were nimodipine, flunarazine, and diltiazem. Verapamil and flunarazine have had particular staying power; flunarazine has never been commercially available in the USA but is a mainstay of treatment

for migraine in Europe. The modest preventive benefits of verapamil in migraine stand in contrast to its impressive efficacy in the prevention of cluster headache, which was also established in the 1980s.

Antiepileptic Drugs

In 1988, the first report appeared suggesting that valproate might be useful in migraine prophylaxis. Studies of the drug’s effects on “intractable” headaches and migraine appeared through the early 1990s, and FDA approval for valproate for migraine was gained in 1996. Its success bolstered theories of cortical hyperexcitability in migraine and led to many studies evaluating the possible benefits of other antiepileptic drugs in migraine. Results for many were disappointing, but a notable exception was topiramate. Originally expected to have hypoglycemic effects, it failed as an antidiabetic agent but showed unexpected potential as an antiseizure medication. Once approved for that indication, it did not take long for enterprising researchers to investigate its antimigraine effects. FDA approval for migraine prevention came in 2004.

Investigation Expands

A critical mass of headache-interested researchers, physicians, and pharmaceutical companies has developed over the last 50 years. It is now common for certain types of newly released drugs, particularly antiepileptic drugs, to be studied to see if they are also effective in headache prophylaxis. Pharmaceutical companies often provide small “investigator-initiated grants” that allow researchers to perform proof-of-concept or pilot studies; further large-scale trials might then be pursued if initial results are promising. Space precludes a full discussion of the wide variety of compounds that have entered practice in this way: drugs such as lisinopril, candesartan, and botulinum toxin are among them. The size and unmet needs of the headache-prone population also

make it likely that the next 50 years will bring us new drugs specifically designed for headache prophylaxis, in addition to a continuing parade of those borrowed from other therapeutic areas.

The importance of prophylactic treatment

It is common to decry the modest therapeutic benefits of currently available headache preventive drugs. Certainly, many of them barely meet the commonly used “50/50” minimum standard of efficacy (a 50% reduction in headache frequency in 50% of users). Most have undesirable side effects.

Yet, these imperfect drugs have transformed the lives of countless headache sufferers and substantially reduced the public and personal health burden of chronic, recurrent headaches. The use of acute treatment alone to treat very frequent headaches is impractical and costly. It may worsen the situation by producing medication overuse headache or other medical complications. In this setting, therapies that reduce the number of headaches, even if they do

not eliminate all of them, can make the difference between going to work and going on disability.

However, like the dog that did not bark in the night, headaches that never happen do not get noticed. Prophylactic drugs for headache belong to a distinguished group of underappreciated preventive medical interventions, such as vaccination and antihypertensive treatment. The side effects and failures of these treatments loom large, particularly at the level of the individual, while their benefits are far less apparent and appreciated. Few, though would argue that the health results of these imperfect treatments have been anything less than profound. The real failures of headache prophylaxis are those of access and application, and it will be the work of the next half-century to redress them.

Only a small proportion of patients who would benefit from headache prophylaxis receive it, and in only some of those patients are the dose and length of therapy adequate. Further work is needed to understand which subgroups of patients will benefit from particular treatments,

and the optimal timing and duration of prophylactic treatment.

Even with its full potential not yet realized, headache prophylaxis remains the most significant achievement of the last 50 years in the headache field. Patients with cluster headache are routinely rendered headache-free in a matter of days or weeks with use of the appropriate drugs. The difficult-to-treat headache syndromes found in specialty headache clinics often respond to careful, systematic use of existing preventive drugs. And we must not overlook the large number of headache patients who never appear in specialty care because prophylaxis in primary care has been successful. *Prophylactic treatment has prevented millions of headaches.*

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