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Headache (JR Couch, Section Editor)

Editor's Note: a Brief History of Preventative Antimigraine Therapy (PAMT)

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The idea of PAMT has been a concept sought by physicians treating headache and migraine since antiquity and has spawned a number of unique approaches ranging from trepanation in ancient societies to implanting garlic pods under the skin of the forehead as described in the tenth century by *abou l'ouasim*, to feverfew and application of poultices of millipedes and woodlice by Thomas Willis in the seventeenth century [1]. In the modern era, PAMT begins with methysergide and the work done by Sicuteri [2], Friedman, Graham, and others beginning in the 1950s. Methysergide was found to have a preventative antimigraine effect but was also found to have many acute and subacute side effects as well as the longer term complications of retroperitoneal, pleuropulmonary, and cardiac fibrosis. These complications limited the use of methysergide as other PAMT agents were identified [3].

In the late 1960s and 1970s, work by Lance and his group began to test other agents of antihistamine and antidepressant origin. Papers by Lance, Diamond, and Couch noted a PAMT effect of amitriptyline [4] which was followed by testing of virtually all antidepressant agents for this purpose. Of these, amitriptyline and its first-order metabolite, nortriptyline, appeared to be the most effective agents. The reports by Ekbom and Lundberg [5] and by Weber and Reinmuth [6] in 1972 dealing with propranolol stimulated much research on beta-blocking agents finding that agents without intrinsic sympathomimetic activity were effective in PAMT. These agents are still in common use for PAMT.

The classification of headache was not well articulated until the introduction of the ICDH 1 in 1988 [7]. Education in headache during medical school was rudimentary in many places prior to this time. Publishing on migraine usually meant that the author had to define the criteria for diagnosing migraine or tension-type headache instead of simply referring to an accepted definition. In particular, dealing with frequent headache and when to use PAMT presented

difficult. Mathew et al. introduced the concept of "transformed migraine" [8] which, along with the work of many others, eventually evolved into the term "chronic daily headache" [9, 10] which is now divided into "chronic migraine" and "chronic tension-type headache" as defined today [11]. Medication overuse headache, closely related to chronic daily headache and chronic migraine, became well-defined entities in this period [9, 12]. This terminology as laid out in ICDH 3 [11] and its predecessors have been very important in communicating among headache medicine specialists and very important in carrying out and communicating results in trials of headache therapy.

Valproic acid was introduced as an antiepileptic drug in 1975. Trials of valproate as PAMT were carried out in the 1980s by multiple investigators, and approval for PAMT occurred in the early 1990s. [13] This led to trials of multiple antiepileptic agents with varying levels of success. Topiramate was found to be effective in PAMT in the later 1990s and received FDA approval in 2004. Topiramate has achieved very good success of the antiepileptic agents and currently is often a first choice for PAMT [14, 15].

Botulinum toxin (Botox) joined the PAMT scene in the 1990s as a result of the beauty industry. Women who received Botox for temporary removal of forehead wrinkles at times reported relief from migraines. Clinical trials subsequently demonstrated that onabotulinum toxin A (OBA) was effective for chronic migraine [16, 17].

Currently, topiramate, onabotulinum toxin A, amitriptyline, valproate, and beta-blocking agents are the most commonly used PAMT. These are reviewed and referenced extensively in the following articles. There are certainly other agents employed with varying levels of success. Except for amitriptyline, which has been rated a having level II effectiveness, others have achieved FDA approval. The patent expired on amitriptyline in 1980, and consequently, no attempts at gaining FDA approval were initiated after that point.

In evaluating headache, the usual parameters employed include frequency, usually in terms of headache days/month; intensity (severity), usually on a pain scale of 1–10; and duration, usually in terms of hours. These may be used individually or in some type of scoring system employing combinations of these parameters to measure the effectiveness of headache treatments. In older trials, improvement by at least 50%, using the measurement employed by that study, was often reported as an end point. In recent years, however, decrease in the number of headache days has been a popular measurement as a primary end point. Often, the rate of subjects receiving at least 50% improvement is also reported as a secondary end point. This latter measurement also allows comparison of the newer to the older agents. In general, in placebo-controlled trials employing this criterion, usually 50–60% of subjects on active drug reach this level of response while only 20–30% of placebo subjects do so. To date, the anti-CGRP agents that are available seem to produce similar levels of overall response.

A second major aspect of PAMT agents is tolerability. The agents noted all have side effects (adverse effects—AED) that limit their use. These AED are well known and will not be recounted here. There are both acute and longer-term AED that may affect the PAMT patient. For amitriptyline, for instance, the early effect may be excessive drowsiness while a longer-term AED for a patient with successful headache relief may be weight gain, sexual dysfunction, or even worse depression. These symptoms, along with anxiety, hair loss, apathy cardiac

problems, and a number of other AEDs often limit the usefulness of these current and older PAMT agents. To date, the anti-CGRP agents have had very few short-term AEDs. The possibility of longer-term AED will not be known until usage has continued for several years. Migraine is a long term problem and this perspective will be a critical one in headache medicine. A similar situation exists for the therapy of multiple sclerosis, another long term disease.

Cost of therapy is another major problem. Amitriptyline and propranolol are used heavily throughout the world as they are relatively inexpensive drugs. The cost for the anti-CGRP agents is projected at > $6000.00 per year and onabotulinum toxin A may be in the same range depending on the situation. Whether these therapies can be considered for any individual patient will depend on the financial state of the patient or his/her insurance coverage.

The anti-CGRP agents represent a radically new approach to PAMT and have been hailed as a "game changer" in headache medicine similar to or greater than the introduction of the triptans for acute headache therapy. The purpose of these reviews of older PAMT is to allow the reader to have a basis for comparison of the "old" versus the "new" PAMT. The older PAMT are reviewed in individual articles by class. The editorial by Drs. Jain and Silberstein presents a perspective on the newer agents. A major question for consideration is as follows: Are the anti-CGRP agents a "game changer" that will render older PAMT obsolete, or do they represent another "bullet in the holster" of PAMT options and a much-needed addition? Clearly, answering this question will have a major impact upon the practice of headache medicine.

In this commentary, I have tried to present the rationale for this group of articles and presented very few references. This was intentional as the following articles are extensively referenced. There are many other individuals working in the field of headache that have made significant contributions to the area of PAMT. I would like to apologize to these colleagues in this field for my minimal citations. I have tried to keep the length of the commentary to a minimum as the important material follows.

As the Editor for the Headache Section of Current Treatment Options in Neurology, I would like to thank the authors of the ensuing reviews for their efforts and hard work in preparing their articles. Preparing reviews of subjects is difficult and time-consuming. I am very pleased with the material presented here. I hope our readers find the information presented will provide useful assistance in managing their patients with severe headache problems.

Compliance with Ethical Standards

Conflict of Interest

Dr. James Couch is currently serving as section editor for the Headache section of the Current Treatment Options in Neurology journal.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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