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Pathophysiological basis of migraine prophylaxis

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ABSTRACT

Several cellular and molecular mechanisms have been implicated in migraine pathophysiology including abnormal neuronal excitability and vascular events. Drugs from different pharmacological classes are used for migraine prophylaxis. These agents may normalize neuronal excitability by modulating distinct ionic channels and various neurotransmitter systems. They can also block cortical spreading depression, prevent peripheral and/or central pain sensitization, and normalize brainstem function. Most of the drugs recently used in migraine prophylaxis have been identified by serendipidy and they have been originally approved for other indications. Subsequently, their use has been extended to migraine prevention, according to their putative mechanisms of action. More recently, trials on adequate samples of migraine patients have been conducted for several drugs. In the present review, we will present and discuss the pathophysiological bases for the use of antidepressants, β-adrenergic blockers, calcium channel blockers and antiepileptic drugs in migraine prevention. Currently, the major classes of conventional migraine preventive drugs include the antidepressant amitriptyline, the β-adrenergic blocker propranolol, and the antiepileptic drugs topiramate and valproic acid. Promising results have recently been obtained for angiotensin converting enzyme inhibitors and angiotensin II type 1 receptor blockers. Some limited clinical findings have also been reported for atypical antipsychotic agents, nutritional supplements and also botulinum toxin. Targets of migraine preventive treatment are to reduce frequency and intensity of attacks and to decrease disability related to chronic headache.

Contents

Abbreviations: ACE, angiotensin converting enzyme; AEs, adverse effects; AEDs, antiepileptic drugs; AMT, amitriptyline; ARB, angiotensin II type 1 receptor blockers; AT1, angiotensin II type 1; BABs, β-adrenergic blockers; BTX-A, botulinum toxin type A; Ca^{2+}, calcium; CCBs, calcium channel blockers; CGRP, calcitonin gene-related peptide; CoQ10, coenzyme Q10; CSD, cortical spreading depression; DA, dopamine; FHM, familial hemiplegic migraine; GPT, gabapentin; 5-HT, serotonin; ICHD-II, The International Classification of Headache Disorders, 2nd edition; K^+, potassium; LTG, lamotrigine; MELAS, Mitochondrial Myopathy, Encephalopathy, Lactic Acid, Stroke-Like Episodes Syndrome; Mg^{2+}, magnesium; MwA, migraine with aura; MwoA, migraine without aura; NA, noradrenaline; Na^+, sodium; NO, nitric oxide; NOS, nitric oxide synthase; PAG, periaqueductal grey matter; NF-kB, nuclear factor-kB; PUFAs, polyunsaturated fatty acids; RAS, renin–angiotensin system; SSRIs, selective serotonin reuptake inhibitors; TNC, trigeminal nucleus caudalis; TPM, topiramate; VPA, valproic acid; VEP, visual evoked potential; VTA, ventral tegmental area.

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1. Introduction

Migraine is a disabling brain disorder affecting around 12% of the general population (Stewart et al., 1996). It recurs as attacks of unilateral throbbing headache, worsened by movements and routine daily activities, lasting from 4 to 72 h. Associated symptoms include nausea, vomiting and increased sensitivity to light and sounds according to The International Classification of Headache Disorders, 2nd edition (ICHD-II) (Headache Classification Subcommittee of the International Headache Society, 2004). In 15% of cases, migraine headache is preceded by the "aura", a transient neurological dysfunction, which is usually characterized by visual and/or sensory symptoms.

In a significant percentage of migraineurs, headache becomes chronic and occurs on a daily basis (Scher et al., 1998; Castillo et al., 1999). Migraine has a strong social impact, influencing both quality of life and work productivity (Bigal et al., 2004). Symptomatic drug abuse and psychological disturbances are the most important risk factors for chronic headache (Bigal and Lipton, 2006). The goals of prophylactic treatment are to reduce the incidence and severity of migraine attacks, as well as to prevent the development of chronic daily headache and symptomatic drug overuse (Dodick and Silberstein, 2007) (Fig. 1).

Thus, migraine preventive treatment has to be considered in patients with:

(a) two or more attacks per month that significantly interfere with the patient's daily routine activity and produce disability for 4 or more days per month;
(b) an unsatisfactory or scarce response to acute therapy;

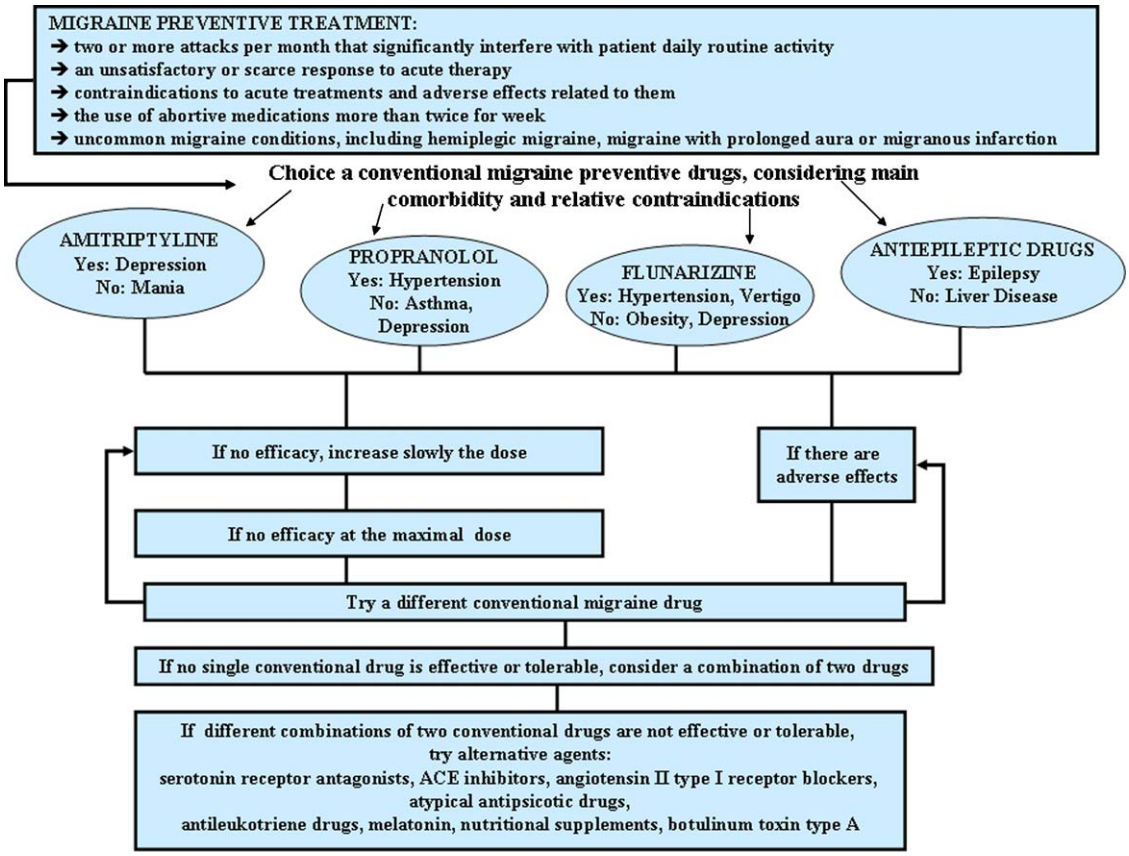

Fig. 1. Algorithm for migraine prophylaxis. For further details see Silberstein (2006).