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Beta-Blockers for Migraine Prevention: a Review Article

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Abstract

Purpose of review This review seeks to establish the role of beta-blockers (B-adrenergic receptor antagonists) in the pathophysiology of migraine prophylaxis, compare the efficacy of this group of medications with other common prophylactic agents, and also explore the relative benefits of using individual beta-blockers compared with others.
Recent findings New evidence supports beta-blockers having several mechanisms of action in migraine prophylaxis. Numerous trials reveal significant clinical differences between various beta-blockers in migraine prophylaxis and that commonly used doses of beta-blockers are not optimal. There are also updated guidelines regarding beta-blocker use in migraine prophylaxis.
Summary Beta-blockers appear to have several mechanisms of action in migraine prophylaxis. We found extensive evidence supporting beta-blockers being effective in migraine prophylaxis. These are often not used at optimum doses; however, when they are, they compare generally favorably compared with other classes of medications. More recent evidence appears to show a relatively favorable side effect profile of beta-blockers compared with previous reports (Barron et al. IJC 163:3572–3579, 2013).

Introduction

Beta-blockers (B-adrenergic receptor antagonists) were the first class of prophylactic medications used for migraine prophylaxis that are still extensively used today, since methysergide which was first used for this purpose in 1959 has widely been discontinued due to its risk profile [1]. As with all medications used for migraine prophylaxis until recently, this was a chance finding during a trial in 1966 looking at the effects of propranolol on angina [2]. Ever since, beta-blockers have been used with good effect for migraine prophylaxis. We aim to clarify how beta-blockers act to reduce migraine frequency, the differences amongst

medications within this class, appropriate use of the various beta-blockers, and their side effect profiles. This should give the reader a better understanding in choosing an appropriate beta-blocker for migraine prophylaxis. As our understanding regarding the pathophysiology of migraine has progressed, there are several mechanisms of action through which beta-blockers are thought to be effective in preventing migraines. Although beta-blockers are thought to be primarily an anti-hypertensive class of medication, it is interesting to find that even this effect was an incidental finding in patients being treated for angina [3]. The first beta-blocker pronethalol was introduced in 1962 and shortly thereafter, in 1965, propranolol was launched. The latter remains the most commonly used beta-blocker for migraine today [4].

Putative mechanisms of action in relation to migraine prophylaxis

Prior to looking at the mechanism of action of beta-blockers on the central nervous system (CNS), it is worthwhile looking at their relative affinity for penetrating the CNS. There are major differences in the level of lipid solubility between various medications within this class which affect their ability to cross the blood-brain barrier (BBB). Most of the beta-blockers with efficacy in migraine prevention, including propranolol, metoprolol, and timolol, have good CNS penetration; nadolol, however, does not cross the BBB and is still effective in reducing migraine activity. It is unclear however if this is because CNS penetration is not necessary in the efficacy of beta-blockers in migraine or whether nadolol has a different mechanism of action to the other beta-blockers used in migraine prophylaxis.

As our understanding of migraine has developed, it has become increasingly apparent that the underlying pathophysiology is predominantly neurogenic rather than vascular, involving changes in neurotransmitter levels. Beta-blockers appear to be exerting their effects mainly centrally by modifying neuronal excitability [5•]. Blockade of beta-1 receptors attenuates the effects of adrenaline and noradrenaline and thereby inhibits the stimulating effect of the sympathetic nervous system [6]. This inhibition has been demonstrated in several measures of cortical information processing that have been shown to be abnormal in migraineurs. This is evidenced by changes in visual evoked potentials (VEP), contingent negative variation (CNV), and auditory evoked potentials (AEP). VEP amplitudes represent the number of retinal receptors stimulated and the excitability of the visual cortex. Several studies have found increased VEP amplitudes in patients with migraine; this has been interpreted as evidence of increased occipital cortex excitability [7]. In patients treated with beta-blockers, the VEP amplitude is seen to decrease to within normal levels [8]. There is mixed data on whether decreased VEP amplitudes caused by beta-blockers correlate with their clinical effects [9]. However, even in trials when the decreased VEP amplitudes did not correlate with clinical benefits of beta-blockers, it was noted that decreased amplitudes were correlated with higher serum level of beta-blockers, suggesting that although the raised serum level of beta-blockers levels were obviously high enough to affect VEP, they were still too low to decrease frequency of migraine re-occurrence [10••, 11]. In untreated migraine patients, increased CNV, an event-related, slow cerebral potential following activation in the striato-thalamo-cortical loop, shows that an

increased amplitude and lack of habituation which implies altered neuronal excitability [12]. Two studies found that the beta-blockers metoprolol and propranolol both normalize CNV and further note that normalization of high CNV was positively correlated with treatment response [13, 14]. Another study found that beta-blockade with metoprolol and bisoprolol decreased the dependence of evoked cortical potentials on the intensity of auditory stimuli in migraine patients and that this decrease was related to clinical improvement [15]. These studies suggest that the therapeutic benefit of beta-blockers relates to a general effect on cortical excitability and abnormal cortical information processing in migraine. However, the aforementioned studies used methods with a focus on specific network activity rather than a focus on the location where beta-blockers potentially exert their actions in the brain. A plausible explanation for the described abnormalities in sensory processing in migraineurs is a dysfunction of processing by thalamo-cortical neurons [16, 17]. Evidence that preventive action of beta-blockers is mediated through beta-1 adrenoceptor inhibition in nociceptive neurons in the thalamus comes from an electrophysiological animal study showing that thalamo-cortical activity evoked by superior sagittal sinus stimulation was inhibited after locally applied propranolol [18].

In addition to their beta-adrenergic blocking effects, there are other pathways affected by beta-blockers that are thought relevant to migraine prevention. Propranolol and timolol have high affinity for 5-hydroxytryptamine (serotonin or 5-HT) receptors, specifically $5HT_{2B}$ and $5HT_{2C}$ in the CNS, whereas metoprolol and nadolol do not, yet all are effective in treating migraine. Since $5HT_{2B}$ is involved in cortical excitability, it suggests that the antagonist effects of beta-blockers on this would lead to migraine prophylaxis [19]. Conversely beta-blockers do not appear to have a profound effect on $5HT_{1B}$ and $5HT_{1D}$ receptors at blood vessels in the CNS [20]. This is perhaps not surprising since the beta-blockers are no longer thought to exert their effects through inhibiting the vasodilatory phase of migraine with the vascular theory of migraine having been largely dismissed [21]. Also, certain beta-blockers inhibit nitrous oxide production by blocking inducible nitric oxide synthase, an effect that is thought to be mediated by their beta-2 antagonist action; this appears to be a plausible mechanism since nitrous oxide transmission plays a key role in migraine through several mechanism, including activation of the trigeminovascular complex [22].

Although the effects of beta-blockers appear to be central, with particularly involvement of the VPM of the thalamus and trigeminovascular signaling, there is still some data suggesting that their effects are primarily through peripheral blockade [16, 23•]. This appears not to be the consensus in the literature we reviewed however and is outside the scope of this review to be discussed in detail.

Guidelines

There is consensus as well as disparity with regard to the role of various beta-blockers when comparing the three recognized guidelines for migraine prophylaxis: those of the American Headache Society/American Association of Neurology (AAN/AHS), the Canadian Headache Society (CHS), and the European

Federation of Neurological Societies (EFNS). The guidelines differ in how they rate treatment categories. AHS/AAN guidelines (2012) were based on level of evidence of existing trials [24]. CHS based its guidelines (2012) on the "principles of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group"; in addition, a general literature review and expert consensus were used for aspects of prophylactic therapy for which randomized controlled trials are not available [25]. EFNS based its guidelines (2009) on literature search performed by its committee members; these were subsequently discussed amongst its members, drafts were written up by the chairman and subsequent consensus amongst all members was reached before final recommendations [26]. A comparison between the guidelines can be made if one supposes the top-rated category for each to be comparable and so on. Therefore, based on judgements about the balance of benefits and harm, "level A" in the AAN/AHS guidelines was equal to "high" level of evidence in the Canadian guidelines and "drugs of first choice" in the European guidelines. Similarly, "level B" on the AHS/AAN was equivalent to "moderate" level of evidence in the Canadian guidelines and "drugs of second choice" in European guidelines, and "level C," "low" level of evidence and "drugs of third choice," was deemed equivalent between the three guidelines respectively. Below is a summary of the three mentioned guidelines for beta-blocker prophylaxis (see Table 1). With regard to pregnancy categories, FDA has published pregnancy categories for all relevant beta-blocker, all of which fall either into categories "B," "C," or "D" (see Table 2). None are "of no risk to human controlled studies" (category A). Pindolol is the only "category B" medication which suggest "No risk in other studies" indicating that animal studies have failed to show a risk to the fetus and there are no adequate studies in pregnant women (https://chemm.nlm.nih.gov/pregnancycategories.htm).

Propranolol

The discovery that beta-blockers were effective in migraine prophylaxis was an accidental one involving propranolol. It is one of the two medications together with metoprolol that are given the highest rating by the AHS/AAN, CHS, and EFNS guidelines. Propranolol is a non-selective beta-blocker that is highly lipid soluble, meaning it can freely cross the BBB to reach the CNS to modulate its

Table 1. Beta-blockers and their ratings for migraine prophylaxis based on the AHS/AAN, CHS, and EFNS guidelines. Other classes of medication have been excluded [23•, 24, 25]

	Top-tier evidence	Second-tier evidence	Third-tier evidence
AHS/AAN	Metoprolol Propranolol Timolol	Nadolol Atenolol	Nebivolol Pindolol
CHS	Metoprolol Nadolol Propranolol	–	–
EFNS	Metoprolol Propranolol	Bisoprolol	–

Table 2. The US FDA pregnancy categories for the beta-blockers which are rated for migraine prophylaxis by the AHS/AAN, CHS, and EFNS

Category B	Pindolol
Category C	Bisoprolol Metoprolol Nadolol Nebivolol Propranolol Timolol
Category D	Atenolol

We will discuss the advantages and disadvantages of the four beta-blockers with top-tier level of evidence according to the guidelines mentioned above

effects. Propranolol is hepatically cleared which may be a limiting factor in patients with liver pathology. It is largely protein-bound which should be considered if used together with other medications that are highly protein-bound such sodium valproate, amitriptyline, and nortriptyline. It has a short half-life of 4–5 h and has therefore traditionally been used on a BID schedule which can limit compliance; however, it should be noted that propranolol is available in a long-acting form. Because of its high pharmacokinetic variability, propranolol needs to be titrated up slowly in order to avoid side effects [27••]. There are several trials that show propranolol to be superior to placebo in preventing migraine. Due to a lack of evidence, it is not clear if the effects are stable after propranolol has been stopped [28]. It is recommended in a dose range of 40–160 mg daily. Comparing 80 mg daily with 120 mg daily and 160 mg daily, it appears that as the dosage increases, there is an increase in the effectiveness of propranolol in migraine prophylaxis, without causing significantly more side effects [29–31].

Comparative effectiveness trials

Studies comparing propranolol with the other medications with "level A" evidence for migraine prophylaxis in the AAN/AHS guideline indicate that it performs favorably. A trial comparing propranolol with sodium valproate showed that propranolol had a slightly greater effect in reducing the mean headache days per month and also caused fewer side effects; these differences, however, were not statistically significant [32]. When compared with topiramate, at relatively low doses of each drug (50 mg topiramate vs 80 mg propranolol daily), it appears that topiramate is more effective than propranolol [33]. However, a higher dose of propranolol (160 mg) was the same as 1–2 mg/kg daily of topiramate with regard to reductions in migraine frequency, responder rate, migraine days, and daily rescue medication usage [34]. Pediatric studies looking at ages ranging from 5 to 18 showed equivalent efficacy for propranolol and topiramate in migraine prophylaxis [35, 36]. When comparing propranolol with metoprolol, it does not appear better at controlling migraines; however, the side effect profile of metoprolol appears favorable [28, 37]. It should be noted,

however, that the benefits of propranolol are dose-dependent and that the trials comparing it head with head with metoprolol used relatively low doses of propranolol, ranging from 80 to 120 mg daily. Compared with timolol, propranolol was equally effective and with a similar CNS side effect profiles [38].

Metoprolol

The other beta-blocker to have the highest level of evidence across the three major guidelines is metoprolol. In the USA, however, unlike propranolol and timolol, it is not FDA-approved for migraine prophylaxis. Pharmacologically, it is highly lipid soluble with good penetration into the CNS. Unlike propranolol, however, it has poor affinity for 5-HT receptors. Unlike the other three beta-blockers that are examined in this review, metoprolol is a selective beta-blocker, inhibiting beta-1 receptors rather than both beta-1 and beta-2 receptors. Metoprolol is also primarily hepatically cleared; however, it is only minimally protein-bound. It has a half-life of 3–7 h. Similar to propranolol, it has high pharmacokinetic variability and requires slow titration; otherwise, it can result in high plasma concentrations in a minority of patients with potentially dangerous effects [27••]. Metoprolol has been shown to be more effective than placebo in migraine prophylaxis two studies [39, 40]. Its effects are dose-dependent, with 100 mg bid being more effective than 50 mg bid [41]. As mentioned above, metoprolol appears to have similar efficacy to propranolol with a lower side effect profile; there are have been no studies comparing the efficacy of metoprolol with other "level A" migraine prophylactic medications in the AAN/AHS guidelines.

Timolol

The only other medication with "level A" grade of evidence in the AAN/AHS guidelines is timolol. It is not recommended by the other two guidelines at any level. Similar to propranolol and metoprolol, it is highly lipophilic and therefore can cross the BBB to assert its effects on the CNS. Similar to propranolol, but unlike metoprolol, it has good affinity for 5-HT_{2B} and $5HT_{2c}$. A serotonergic effect could be relevant when combined with other serotonergic medications; however, this theory has not been tested. Timolol is hepatically cleared; however, it is not largely protein-bound. It has a half-life of 2–5 h. It has low pharmacokinetic variability and can therefore be titrated relatively quickly [27••]. Timolol is effective when compared with placebo and about equally effective as propranolol in decreasing headache frequency with similar side effect profile [42, 43]. It appears effective at a dose of 10–15 mg bid [22].

Nadolol

Although nadolol does not have the same level of evidence across the guidelines as propranolol and metoprolol, it has a "high" level of evidence as per the CHS

guidelines and "level B" evidence as per the AAN/AHS guidelines. While the mechanism of action of beta-blockers is not fully understood, it remains surprising that nadolol is effective when one considers that it is hydrophilic and does not cross the BBB easily. Its hydrophilicity may be beneficial, however, in that nadolol causes fewer CNS side effects than the lipophilic beta-blockers such as propranolol and metoprolol, including less depression and insomnia [44, 45]. Unlike the beta-blockers above, nadolol is not metabolized by the liver and is excreted unchanged in the kidney. It is moderately protein bound (28%). It has a half-life of 14–24 h which is much longer than propranolol and metoprolol, allowing for daily dosing rather than BID, which simplifies its use and increases its compliance [46, 47]. Nadolol has variable pharmacokinetics and needs to be titrated slowly. Nadolol is superior to placebo for migraine prophylaxis [27••]. At lower doses, nadolol appears equally as effective as propranolol in migraine prophylaxis; however, when comparing 160 mg nadolol daily with 80 mg bid propranolol, the former is superior while having a favorable side effect profile [48]. Otherwise, there are no direct head-to-head studies comparing nadolol with other effective prophylactic migraine medications.

Side effects

Beta-blocker side effects generally correlate with the degree of alpha- and beta-receptor selectivity, but also depend on intrinsic sympathomimetic activity (ISA), lipid solubility, and vasodilatory properties related to nitric oxide generation.

The major cardiac side effects of beta-blockers relate to significant negative chronotropy, ultimately leading to congestive heart failure at toxic levels. Beta-blockers should not be administered as new therapy to patients with CHF unless heart failure is well compensated. Despite these concerns, only a minority of patients with stable heart failure appear to deteriorate after initiation of beta-blocker therapy [49]. Although beta-blockers are associated with other symptoms in patients with congestive heart failure including dizziness due to hypotension and bradycardia, the absolute increase of these side effects appears to be small and does not necessitate withdrawal of drug therapy [50]. With regard to negative chronotropic effects—slowing of the resting heart rate and development of sinus bradycardia—beta-blockers are relatively contraindicated in patients over the age of 64 and those with compromised renal function [51•]. They may additionally cause slowing of atrioventricular (AV) node conduction leading to heart block, particularly if used together in other medications that can cause AV node delay such as calcium channel antagonists. All four beta-blockers mentioned above however are without intrinsic sympathetic activity (ISA—ability to stimulate beta-adrenergic receptors and to oppose the stimulating effects of catecholamines in a competitive way) which may cause less impairment of AV conduction [52].

Beta-blockers are also contraindicated in patients with increased airway resistance such as asthma and chronic obstructive pulmonary disease since they impair bronchodilatation in a dose-dependent manner [53]. This is less likely to occur with selective beta-1 blockers (metoprolol from the above list) [54]. Therapeutic doses of selective beta-1 blockers are generally well tolerated,

although some patients who are using inhaled beta-agonists may require an increased dose of the inhaled drug [55].

Non-selective beta-blockers can cause a reduction in cardiac output while simultaneously blocking beta-2 receptor–mediated vasodilation of skeletal muscle vessels; in so doing, beta-blockers can augment vascular insufficiency in symptomatic peripheral artery disease. Studies have shown that non-selective beta-blockers can cause a host of symptoms including cold extremities, absent pulses, cyanosis, and impending gangrene in patients with existing peripheral vascular disease [56]. Beta-blockers with beta-1 selectivity (such as metoprolol) do not affect the peripheral vessels to the same degree as the non-selective drugs. A meta-analysis of published studies in patients with mild to moderate peripheral artery disease found no exacerbation of symptoms with beta-blockers however, so this concern may be overstated, particularly in patients with mild to moderate disease treated with a beta-1-selective agents [57, 58]. Selective beta-1 blockers can be used in patients with severe disease; they should however be used cautiously [59].

Despite widespread assertions that beta-blockers cause "depression," a large review by the Journal of American Medical Association looking at 45 years of trials showed that this does not appear to be true [60]. Similarly, the effects on sexual function appears to be minimal and likely secondary to anxiety provoked by the beta-blockers rather than a direct physiological effect. One study found that in patients who developed erectile dysfunction while using beta-blockers, sildenafil and placebo were equally effective in treating their symptom, suggesting the underlying cause for erectile dysfunction was not the pharmacological effects of beta-blockers. Similarly, the effects on fatigue appear to be minimal [58, 61]. Therefore, there appears to be no good evidence to support withholding beta-blockers for psychiatric, constitutional, or sexual side effects.

Beta-blockers cause minimal weight gain (an average of about 1.2 kg largely within the first month) [62].

Epinephrine, acting via the beta-adrenergic receptors, has important effects on increasing glucose production. Beta-blockers therefore have traditionally thought to exacerbate hypoglycemia and cause symptoms including anxiety, sweating, and fatigue [63]. It does appear however that beta-blockers cause minimal hypoglycemia, even in diabetic patients, and this should not be a reason to avoid them [64]. Even so, beta-1-selective blockers to cause less hypoglycemia than non-selective beta-blockers [65]. In patients who are insulin-dependent however, beta-blockers can potentially be hazardous as they can mask the symptoms normally experienced during hypoglycemia [66].

Combination therapies

When used alone, there is about 50% chance of beta-blockers causing significant improvement (50% reduction) in migraine frequency. Combining beta-blockers with other prophylactic medications with a different mechanism of action can improve the response in patients' refractory to monotherapy [67]. There is some evidence to support this approach.

In two open-label studies combining beta-blockers with sodium valproate and topiramate respectively, both showed increased efficacy compared with monotherapy. In patients whose migraines remained refractory to beta-blockers or

sodium valproate alone, over half (56%) had significant improvements when the other medication was added. The side effect frequency of combined use was 15% in patients who were side effect free on monotherapy [68]. Of note, the mean dose of beta-blockers used (nadolol 59 mg daily, propranolol 73 mg daily) was on the low side and one would expect a better outcome if these were used at a higher dose without necessarily causing more side effects (as discussed in a previous section). Another study evaluated patients whose migraines were refractory to monotherapy with beta-blockers or topiramate; when these medications were then combined, the benefits were even greater than when beta-blockers were combined with sodium valproate. Sixty-two percent had a greater than 50% reduction in the number of monthly headache days [69]. Side effect frequency was similar to that seen when beta-blockers were used with sodium valproate. A more recent study which was a double-blinded, placebo-controlled, randomized clinical trial however has shown no additional benefit in combination therapy of beta-blockers and topiramate [70]. Other trials have shown some benefit when beta-blockers are combined with cyproheptadine and when combined with both nortriptyline and flunarizine [71–73].

Individual choice

There is a host of options when using beta-blockers for the prevention of migraine. Opting for one beta-blocker over another comes down to individual patient factors and prescriber comfort. Propranolol is the oldest beta-blocker used for migraine prophylaxis and the medication with the most evidence. In patients with no other complicating comorbidities, this is often the first choice of medications. While there is some evidence supporting the combination of propranolol with other prophylactic medications such as sodium valproate, topiramate, and amitriptyline, on balance, this evidence is not adequate to make a formal recommendation. Metoprolol has a high level of evidence and due its beta-1 selectivity may have a better side effect profile; it should certainly be considered a first-line agent in patients with obstructive pulmonary disease, severe peripheral vascular disease, and diabetes or in patients who are prone to hyperkalemia. Of the beta-blockers used for migraine prophylaxis, timolol is the least protein-bound making it an option when used in conjunction with other protein-bound medications; it also has low pharmacokinetic variability and should be considered in patients who require more rapid titration. Nadolol has long half-life and so ideal if there are concerns regarding compliance since it can be taken once daily only; in addition, it is not hepatically cleared unlike the other beta-blockers in this category and would therefore be suitable in patients with compromised hepatic function. It has some evidence (open-label) of efficacy when used in combination with other prophylactic migraine medications including valproic acid and topiramate. Of note, pindolol is the only B-blocker that is category B in pregnancy and could be considered as an alternative to memantine in patients who require migraine prophylaxis and where potential pregnancy is a concern.

This review discussed the use of beta-blockers in the prophylactic treatment of migraine headaches. The evidence reviewed were from publications addressing episodic migraine headaches. Although there is some good evidence for the use of other classes of medication for prophylactic treatment of chronic daily

headaches, including chronic migraine, such as anti-epileptic drugs and tricyclic antidepressants, there is no widespread evidence for the prophylactic use of beta-blockers in these [10••, 74]. Only one small study could be found from 1980 suggesting these were likely effective [75]. Often, patients with chronic daily headaches have comorbidities such as mood and sleep disorders and for this reason, other medications are often considered instead [76]. The authors' experience in clinical practice has been mixed with regard to beta-blockers being more effective for patients with episodic versus chronic migraine, with no discernable clinical differences seen between these two groups.

Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no conflict of interest.

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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Demonstrates significant risk of symptomatic bradyarrhythmias in older patients. This is important since many patients within this age group (over 64) are currently on beta-blockers for migraine prophylaxis and this risk factor is often not considered.

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