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# Expert Opinion

## Beta-Blockers for Migraine

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Sometimes the observations by one astute clinician of one patient lead to new treatments. In 1966, Rabin et al[1] in a study of propranolol to prevent angina, noted that a 59-year-old man reported that his migraines and angina improved on propranolol but the migraines returned after a crossover to placebo medication. Since then, propranolol has become a first-line agent for migraine prevention with increasing caveats, some real, others questionable.

### CLINICAL HISTORY

A 38-year-old woman has had migraine without aura of moderate to severe intensity for 15 years. For the last 2 years, the headaches have been occurring about 1-2 times per week with an inconsistent response to triptans. She is otherwise healthy except for a history of moderate depression 3 years previously when she got divorced. She occasionally feels "down." She walks for exercise and does some weight training. Her examination is normal except for a sitting blood pressure of 146/98 with a pulse of 76; height 5′3″, weight 110 pounds. Several repeated blood pressures are similarly elevated. There is no prior history of hypertension. Screening blood tests are normal.

Would propranolol be a good choice for prevention of her migraines and treatment of her hypertension? Are other beta-blockers effective for migraine prevention? What titration schedule do you recommend? What are the lower limits of blood pressure and pulse at which you will initiate treatment with a beta-blocker for migraine prevention? Does propranolol have an increased risk of stroke when used for the treatment of hypertension? Is propranolol contraindicated in migraine with prolonged aura? Are there other contraindications for beta-blocker use? Is propranolol use associated with weight gain? Depression? Is propranolol still a first-line treatment for migraine prevention?

### EXPERT OPINION

This patient is experiencing 4-8 headaches a month, a frequency well above the threshold of 2 to 3 attacks per month beyond which preventive headache treatment is encouraged. Many physicians might recommend treatment with a beta-adrenergic blocker for this patient. Traditional reasons for preferring beta-blockers in this case might include the fact that 2 beta-blockers, propranolol and timolol, are Food and Drug Administration-approved for migraine prophylaxis, a status that reflects the level of evidence supporting their efficacy in migraine treatment. They also are among a handful of drugs considered by treatment guidelines to be first-line choices for prophylaxis.[2]

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Additionally, this patient has stage 1 hypertension, making it attractive to choose a possible "two-fer" drug that might benefit both hypertension and headache. Finally, beta-blockers are inexpensive and widely perceived as safe, despite well-known "nuisance" side effects such as exercise intolerance and fatigue.

This patient does not have one of the few conditions historically considered contraindications to the use of beta-blockers, such as asthma, congestive heart failure (CHF), or aura. Her history of depression might give some physicians pause because of case reports suggesting a link between beta-blocker treatment and the onset or exacerbation of depression.[3,4] Others, however, might conclude that the depression was moderate, situational, and has resolved. Who would not feel "down" having 1-2 headaches a week?

Because new information has emerged regarding the long-term risks and benefits of beta-blockers, it is worth re-examining the evidence, or lack of evidence, that underlies many commonly held beliefs and assumptions about beta-blockers before deciding whether they are a reasonable treatment choice for our case patient.

**Assumption No. 1: "Beta-blockers are a first-line treatment for hypertension."—**Current treatment guidelines do include beta-blockers among the first-line choices for treatment of hypertension, but this has recently come under considerable fire.[5-7] Their original use in hypertension was based on the belief that they might lower the risk of hypertensive complications such as heart attack and stroke. This assumption was not based on direct evidence from controlled trials; rather, it was an extrapolation of the confirmed benefit of beta-blockers in lowering the risk of these events in patients who had *already* suffered a cardiovascular event. A recent meta-analysis concluded that in patients with primary hypertension, beta-blockers in fact are not as effective as other antihypertensives in preventing the secondary complications of hypertension, including stroke.[8] Migraine is an established risk factor for stroke, so this particular disadvantage of beta-blockers, if it withstands scrutiny, might warrant reconsideration of their favored status in migraineurs with hypertension or other stroke risk factors. Additionally, there is at least some evidence to suggest that beta-blockers may actually *increase* the risk of ischemic stroke in some patients who have migraine with aura, as discussed below.

**Assumption No. 2: "Beta-blockers only cause reversible, nuisance side effects like fatigue, but have few or no serious side effects."—**Evidence is emerging that beta-blocker use may be associated with some important health risks, including diabetes, weight gain, and ischemic stroke in patients who have migraine with aura.

*Diabetes.*—It is widely recognized that beta-blockers should be avoided in patients with diabetes, because adrenergic blockade may impede recognition of sympathetically mediated symptoms of hypoglycemia. Emerging evidence suggests, though, that beta-blocker therapy also may have unfavorable effects on glucose metabolism, and perhaps increase the risk of type II diabetes.[9] A recent meta-analysis examined the risk of new-onset diabetes associated with various antihypertensive medications. New onset diabetes was least likely to occur in subjects treated with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, followed by calcium channel blockers and placebo. It was most likely to occur in subjects treated with beta-blockers or diuretics.[10] The association of diuretic and beta-blocker use with diabetes is also supported by the results of another trial.[11] Risks may differ depending upon which beta-blocker is used.[12,13] Until this issue is settled, a prudent approach is to avoid the use of beta-blockers in patients who have risk factors for diabetes such as elevated body mass index or a family history of diabetes. Our case patient has a body mass index of 19.5 (normal weight).

*Weight Gain.*—An association has been suggested between the use of beta-blockers and weight gain. Most patients view weight gain as a highly undesirable side effect of migraine treatment; excess weight may also worsen the clinical course of migraine.[14,15] A systematic review of 8 randomized controlled trials of patients receiving beta-blockers for hypertension found that body weight was higher in the beta-blocker than the control group at 6 months, with a median weight increase of 1.2 kg. Weight gain seemed to occur during the early part of treatment and then plateau.[16] One open, prospective study assessed weight gain at 6 months in migraine

patients using various prophylactic medications. Three of 15 patients treated with atenolol gained a mean of 1.7 kg, and one of 13 patients treated with propranolol gained 6 kg. The authors suggested that the weight gain, at least with atenolol, was "modest."[17] The authors of another review of migraine drugs and weight gain concluded that "it is not clear whether there is any difference in associated weight gain" between different types of beta-blockers.[18]

*Prolonged Aura or Stroke.*—Case reports have suggested that beta-blocker treatment may precipitate or prolong migraine aura, or even cause ischemic stroke.[19-22] The single clinical trial that sheds light on these concerns was conducted to compare metoprolol with placebo for the treatment of classic migraine (which would now be termed "migraine with aura"). Detailed, prospective information was obtained about aura symptoms and frequency, including scotomata, hemianopsia, scintillations, fortifications, paresthesias, paresis, ataxia, and speech disturbances. Metoprolol was effective in decreasing headache frequency and pain compared with placebo, but subjects in the metoprolol group had a statistically significant increase in the percentage of attacks with pre-headache scintillations, paresthesias, and speech disturbances, although there were no differences between the 2 groups on any other studied aura characteristics.[23]

The study authors did not consider the increased frequency in some aura symptoms to be of concern. In fact, they commented that their data did not support the hypothesis that beta-blockers constrict cranial vessels, as "if this is so, it is likely that aura symptoms would be prolonged and aura without headache (migraine equivalents) would occur more frequently during beta-blockade. Our data do not support this."[23] Despite this, worry lingers about the possible dangers of beta-blockers in patients who have migraine with aura. For this reason, many headache experts report that they prefer to avoid beta-blockers in patients with aura, and warn against their use in this setting.[24-25] This cautious attitude is probably best summarized by Bardwell, who comments that "Given the action of beta-blockers on cerebral vascular autoregulation and given the appearance of several case reports linking the initiation of propranolol treatment with stroke in patients with migraines, we feel a strong case can be made against the indiscriminate use of propranolol for prophylaxis in migraine . . . the same prudence should extend to the use of propranolol as to the use of ergotamines and oral contraceptive pills in cases of complicated migraine."[22]

**Assumption No. 3: "Beta-blockers might cause or exacerbate depression."—**An association between the use of beta-blockers and major depression has been suggested, based on case reports and clinical observation, but has never been validated in well-conducted clinical trials.[26,27] A meta-analysis of 15 trials with over 35,000 subjects did not show evidence of an increase in depressive symptoms in subjects treated with beta-blockers. The pooled incidence of depression in those trials was 6/1000.[28,29] Most of the trials examined in the meta-analysis were carried out for conditions other than migraine; an additional criticism is that adverse event information data collection in clinical trials is generally poor. It is possible that patients with migraine may be particularly susceptible to drug-induced depression, as migraineurs are already at higher than average risk of depression and other affective disorders.[30-33] However, no high quality evidence exists to support or refute a connection between beta-blocker use and depression in the general population of patients or any subgroup. Despite this, the assumption that beta-blockers cause depression has proved to be remarkably enduring. One author has referred to the persistent belief in the connection as a "myth without evidence."[34]

**Assumption No. 4: "Beta-blockers are absolutely contraindicated in patients with asthma, chronic obstructive pulmonary disease (COPD), or CHF."—**Randomized clinical trials show that cardioselective beta-blockers prolong life in patients with CHF, and they are now *indicated* for that condition in all but the most seriously compromised patients.[35] Similarly, cardioselective beta-blockers do not appear to increase disease exacerbations or worsen airway function in patients with COPD.[36] Cardioselective beta-blockers also appear to have a reasonable short-term safety profile in patients who have reversible airway disease such as asthma, although the long-term safety remains to be established.[37] The beta-blockers most commonly used to treat migraine are

not cardioselective, so it still is prudent to be cautious in their use to treat headache in these patients. It is, however, equally important to be aware that beta-blocker use may be far less dangerous in these conditions than previously thought.[38]

## APPLYING THE EVIDENCE TO OUR PATIENT

What is the bottom line for this patient and others like her? Many longstanding beliefs about the harms, benefits, and contraindications of beta-adrenergic blocker therapy have been flatly contradicted or called into serious question over the past decade. This case thus illustrates the maxim that "half of what you'll learn in medical school will be shown to be either dead wrong or out of date within 5 years of your graduation; the trouble is that nobody can tell you which half . . ."[39]

Several possible complications of beta-blockers arguably should not weigh heavily in the decision about this patient's treatment. Her body mass index is well within the normal range, so there is little need to worry about a possible risk of beta-blocker-induced diabetes or weight gain. Similarly, she does not have a chronic respiratory condition or heart failure. She may be depressed, and it would be prudent to evaluate this possibility carefully. However, evidence is not compelling to suggest that depression, if present, is a strong contraindication to the use of beta-blockers if they are otherwise an appropriate treatment choice.

In addition to headache, this patient's most pressing medical concern is hypertension. There is now considerable controversy about whether beta-blockers are an appropriate first-line choice for treatment of hypertension. In view of this, the patient and her physician will need to decide whether they still have a preference for a single drug to treat both conditions, or whether they wish to treat both conditions separately. In making this decision, several drawbacks of treating 2 conditions with a single drug should be considered. The first is that it may prove difficult to find a single dose that optimally treats both problems. This increases the likelihood that treatment of one condition, or possibly both, will be suboptimal. Another disadvantage is that use of a single drug may lead to confusion about who is responsible for managing the patient's hypertension over time. If a headache specialist initiates the beta-blocker, counseling about other blood pressure control measures may not occur, and the patient or other physicians caring for her may assume that the headache specialist is also treating hypertension. If the patient lapses from headache care, needed follow-up of hypertension may not occur, particularly if she does not have a primary care physician.

**Table.—Typical Titration Schedules for Selected Beta-Blockers Used to Treat Migraine†**

| Drug | Typical starting dose | Typical dose range | Titration schedule | Comments |
|---|---|---|---|---|
| Atenolol | 50 mg once daily | 50-200 mg/day | For all drugs, evaluate efficacy using a headache diary. Dose can be increased at 8-12-week intervals if desired; it is reasonable to schedule office visits at these intervals to check blood pressure and pulse. Symptomatic hypotension, systolic blood pressure less than 80 mmHg, or resting pulse less than 50 beats per minute suggest the dose should be reduced or the drug stopped. | |
| Metoprolol | 50 mg twice daily | 100-200 mg/day | | Generally given in divided doses; long-acting formulation may be given once daily |
| Propranolol | 40 mg twice daily | 80-240 mg/day | | Generally given in divided doses; long-acting formulation may be given once daily |
| Timolol | 20 mg once daily | 20-30 mg/day | | |
| Nadolol | 40 mg once daily | 80-240 mg/day | | |

†Typical dose ranges based on information contained in: Ramadan NM, Silberstein SD, Freitag FG, Gilbert TT, Frishberg BM. Evidence-based guidelines for migraine headache in the primary care setting: Pharmacological management for prevention of migraine. 2000. Accessed http://www.aan.com/professionals/practice/pdfs/gl0090.pdf.

Despite this, if the physician and patient are aware of these potential problems and take steps to avoid them, a beta-blocker is a reasonable treatment choice for this patient. Other drugs with evidence of efficacy for both migraine and hypertension include verapamil, lisinopril, and candesartan. However, the evidence for these drugs is not as impressive as that for several of the beta-blockers, especially propranolol.[40-43] The Table lists common dose ranges and titration schedules for several beta-blockers frequently used to treat migraine. In considering the use of beta-blocker therapy in patients who are not hypertensive, most physicians avoid their use in patients with pre-existing orthostatic symptoms or low blood pressure and pulse. In the absence of evidence about "how low is too low," a reasonable clinical practice is to adjust the beta-blocker dose based on the patient's symptoms, blood pressure, and pulse. Most physicians aim to avoid systolic blood pressures below 80 mmHg and a resting pulse lower than 60 beats per minute. There is not always a clear correlation between dose and efficacy, or dose and side effects. Thus, trial and error may be necessary to determine the effective and tolerated dose for each patient.

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