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Medication Overuse in Children and Adolescents

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Abstract

Medication overuse is not uncommon among children and adolescents with primary headache disorders. In adults, medication overuse is associated with increased headache frequency and reduced effectiveness of acute and preventive medications. These issues may also exist in children. While withdrawal of overused medications is generally recommended, it may not result in improved headache frequency in all patients. This review summarizes what is known about predicting response to medication withdrawal. Strategies for managing children and adolescents with medication overuse are also offered.

Keywords

medication overuse headache; rebound headache; withdrawal headache; pediatric headache

Introduction

Medication overuse in patients with primary headache disorders is problematic on several fronts:

1. *Potential to lead to increased headache frequency*: In adults, frequent use of acute headache medications is associated with transformation from episodic migraine to chronic migraine[1]. There is concern this may also be the case in children[2]. In adolescents with chronic daily headache, medication overuse is associated with still having chronic daily headache even eight years later[3]. The pathophysiology

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Conflict of Interest
Dr. Peter J. Goadsby is on the boards of Allergan, Colucid, MAP pharmaceuticals, Merck, Sharpe and Dohme, eNeura, Autonomic Technologies Inc, Boston Scientific, Eli-Lilly, Medtronic, Linde gases, Electrocore, Arteaus, AlderBio and BristolMyerSquibb. He has consulted for Pfizer, Nevrocorp, Zogenix, Impax, Zosano and Dr. Reddy, and has been compensated for expert legal testimony. He has grant support from MAP, MSD, Allergan, and Amgen. He has received honoraria for speaking from Pfizer and Allergan, and payment for editorial work from Journal Watch Neurology and for developing educational materials for the American Headache Society.

underlying how medication overuse can lead to increased headache frequency is not definitively known, but may involve central sensitization[4].

2. *Potential to make preventive medications less effective*: Medication overuse has been associated with lower efficacy of migraine preventive medication[5], and withdrawal may bring about a return of preventive efficacy[6]. This too may be secondary to central sensitization that reverses upon medication withdrawal.

3. *Potential for dependence and central side effects*: Barbiturates and opioids have the potential for tolerance and dependence. Their central side effects include sedation and mental fogginess, which are particularly problematic in children as they can impact school performance.

4. *Potential for opioids to reduce triptan effectiveness*: It is reasonably clear that use of an opioid in the month prior to triptan use, specifically where studied rizatriptan, reduced response rates in patients with moderate or severe headache at baseline. Interestingly placebo responses were not different[7].

The frequency of use that constitutes medication overuse depends on the type of medication. Barbiturate use even four days a month is associated with progression to chronic migraine in adults[1]. Opioid, ergotamine, and triptan overuse are defined as use on ten or more days per month in the preceding three months, while for non-specific analgesics the definition is use on at least 15 days per month in the preceding three months[8]. These frequency cut-offs are largely based on expert opinion, although where studied[1], a ten day rule for opioids was born out.

The diagnosis “medication overuse headache” has historically required that there be improvement in headache frequency after medication withdrawal. Therefore the diagnosis could only be made in retrospect. This was practically difficult to apply and therefore in the 2013 International Classification for Headache Disorders, Third Edition[8] (ICHD-III beta), the criteria no longer require that the headache developed or worsened during medication overuse, or that it improved upon withdrawal of medications.

The most recent diagnostic criteria for medication overuse headache are[8]:

A. Headache occurring on ≥15 days per month in a patient with a pre-existing headache disorder.

B. Regular overuse for >3 months of one or more drugs that can be taken for acute and/or symptomatic treatment of headache.

C. Not better accounted for by another ICHD-3 diagnosis.

Nevertheless, the term “medication overuse headache” remains problematic as it implies that the medications are causing the frequent headache. While in some individuals medication overuse can lead to increased headache frequency, and discontinuing the medications can reduce headache frequency, this is not the case in all individuals overusing medications. In some individuals increasing headache frequency is due to worsening of the primary headache disorder, and increased use of acute medications is simply a mirror of clinical progression. In these situations, withdrawing the medications may not result in diminished

headache frequency since the medications are not causative. Lack of improvement after medication withdrawal has been seen in both adults and children with medication overuse[9–11]. Moreover, only about a third of people who overuse medications develop frequent headache, implying there may be an innate genetic susceptibility to medication overuse headache that is not present in everyone[12, 13]. To avoid implying causation, in this paper the term “medication overuse” will be used to refer simply to the mathematical overuse of acute medications—e.g. use of triptans on more than ten days per month.

How common is medication overuse in the pediatric population?

Among U.S. adolescents, the prevalence rate of chronic migraine is 0.79% when those with medication overuse are excluded, and 1.75% when they are included[14]. Given that in the current ICHD-III (beta) criteria chronic migraine is diagnosed even in the presence of medication overuse, this suggests that over half of U.S. adolescents with chronic migraine also overuse acute headache medications. The proportion of pediatric patients with medication overuse varies from 21–60% of those with chronic primary headache disorders[9, 11, 14–17]. When we examined medication overuse data as published[16], it appears to be more common among girls with chronic daily headache than boys (48% vs. 28%, p=0.002). Medication overuse may be less common in children and adolescents with New Daily Persistent Headache (NDPH) compared to other headache disorders, particularly chronic migraine. In one study, 8.7% of those with NDPH had medication overuse compared to 33.3% of those with chronic migraine and 18.2% of those with chronic tensiontype headache[18]. Of the forty pediatric patients in that study with medication overuse, the majority (n=31, 77.5%) had chronic migraine (previously transformed migraine).[18]

What types of medications are being overused in the pediatric population?

In adults, there has been a temporal trend in which types of acute headache medications are being overused. Between 1990 and 2005, the proportion of patients with ergotamine overuse fell while the proportion with triptan overuse rose, likely reflecting the increased use of triptans over that period[19]. Overuse of non-specific analgesics is overall most common in adults[20], and this appears to be the case in children as well. In a small study of forty-two pediatric chronic daily headache patients with medication overuse, more than half were overusing NSAIDs, about a quarter acetaminophen, and only 12% were overusing prescription medications[16]. More data are needed to clarify which types of medications children and adolescents are overusing. The information is important prognostically as in adults certain medication classes seem more likely to lead to progression from episodic migraine to chronic migraine. Barbiturate containing compounds seem most likely to lead to progression (OR 2.1, 95% CI 1.3–3.1), with opioids being also clearly problematic (OR 1.98, 95% CI 1.4–2.2). Triptans appear to be associated with progression, however the 95% confidence interval overlapped the null (OR 1.25, 95% CI 0.9–1.7). Overall NSAIDs were not associated with progression (OR 0.85, 95% CI 0.6–1.2), and in fact NSAID use less than ten days per month appeared to be protective[1].

How does medication overuse influence headache prognosis?

Not every patient with medication overuse improves after withdrawal of the overused medications[9–11]. Hence the medication overuse itself is not necessarily driving the headache frequency in all patients. It remains possible that medication overuse produced a changed in the central nervous system in susceptible individuals, nonetheless, it is important to counsel patients that while a reduction in acute medication intake is prudent, it may not be sufficient for induce symptomatic improvement. For example, in one pediatric study, discontinuing the overused medication(s) led to improvement in headache frequency in only about 40% of pediatric patients with medication overuse[9].

This observation suggests it would be helpful to have a way to predict among all headache patients who are mathematically overusing acute medications, in which ones the medication use is playing a causative role. This would be particularly useful in children as their headache frequency would improve after withdrawal of overused medication and they would not need to be exposed to more aggressive interventions.

Similarly it would be helpful to know in advance which patients have a primary headache disorder that is problematic in and of itself, and the overused acute medications are simply “along for the ride” and not causative. These patients should be targeted early for more aggressive and comprehensive interventions. However, at this time there is no clinical way to distinguish among those pediatric patients with medication overuse those who will respond to withdrawal of acute medications and those who will not. Gene expression patterns do appear to differ and could potentially be used in the future as a biomarker to predict response to treatment[9].

In adults, those patients with medication overuse who improved after drug withdrawal demonstrated a decrease in gray matter volume in the midbrain (periaqueductal gray matter and nucleus cuneiformis), whereas those who did not improve did not have such a reduction[10]. More importantly for predicting treatment response, decreased gray matter volume at baseline in orbitofrontal cortex was correlated with decreased likelihood of improvement after withdrawal[10]. In addition, impairment in orbitofrontal task performance on neuropsychological evaluation is associated with poor prognosis among adult migraine patients with medication overuse[21]. In the future, perhaps assessing a child or adolescent’s genomic expression pattern, orbitofrontal cortex structure (with imaging) and function (with neuropsychological testing) could be used to predict which ones will respond to withdrawal from overused acute medications.

How should medication overuse in children and adolescents be treated?

Certainly this is an area of much needed research. Published evidence in the pediatric population is quite limited.

Strategies to address medication overuse

A course of naproxen sodium—In a small randomized trial of adults with chronic migraine, 60% of whom were overusing triptans at baseline, a per protocol analysis of

naproxen sodium 500 mg used daily as a preventive for a month (plus additional use as needed acutely), reduced total acute medication use[22]. It also led to a significant decrease in migraine headache days, mean 16.4(SD 1.9) days at baseline compared to 6.2(SD 4.0) at one month. It is worth noting however that the drop-out rate in the naproxen group was high. Nonetheless, the observed headache benefit did continue in months two and three when the naproxen sodium was used as needed up to 14 days per month. Disability from migraine, as measured by MIDAS score, was also significantly reduced by this strategy (mean 81 at baseline to 16 at 3-months, $p<0.05$). Those randomized to use combined sumatriptan-naproxen daily for a month also had a reduction in migraine days in the first month, but this effect did not continue into the subsequent months with as needed use.

For children and adolescents with chronic migraine and medication overuse, a similar strategy of daily naproxen for a month followed by as needed use could be used in an effort to reduce headache days while simultaneously aiming to reduce overuse of other acute medications. Supporting this practice is a small placebo-controlled trial suggesting naproxen sodium may be useful for episodic migrain prevention in adolescents[23], and multiple trials of naproxen as a migraine preventive in adults[24–28].

Greater occipital nerve injection—When naproxen is contra-indicated or insufficient, an injection of a mixture of local anesthetic and local corticosteroid in the region around the greater occipital nerve is another treatment option. In an open-label study these injections appear to be beneficial in 53% of children and adolescents with chronic primary headache disorders[15]. Importantly, the odds of benefit are not reduced in the setting of medication overuse (OR 1.1, 95% CI 0.3–4.5)[15]. Similarly in an open-label adult study of greater occipital nerve injections for chronic primary headache disorders the presence of medication overuse did not predict poor treatment response[29]. The mean latency of onset to benefit in the pediatric study was 4.7 (SD 2.3) days. Thus if the child's headache disorder begins to improve in the days following the injection, they may be able to begin to decrease overuse of acute medications without further intervention. Given the benign nature and excellent tolerability of these injections, it is worthwhile considering this treatment before progressing to more aggressive options.

A course of intravenous dihydroergotamine—If these initial measures are not enough, at our center we admit these children for a course of intravenous dihydroergotamine (DHE). We follow a published DHE protocol that has been used in adults with chronic primary headache disorders[30]. If barbiturate or opioid overuse is present, we withdraw these medications on the first day of admission and spend the first several days treating the patient with intravenous fluids, anti-emetics, and NSAIDs as needed for headache and nausea, while providing clonidine regularly for opioid withdrawal or Phenobarbital for barbiturate withdrawal. Conducting the withdrawal in the inpatient setting allows for closer monitoring and the opportunity to provide the child and the family with additional support. Once withdrawal symptoms have passed we begin the DHE. When there is triptan overuse we ask patients to discontinue triptans three days prior to admission. There is some evidence in adults that headache from triptan withdrawal may be shorter and less severe than from other agents[31]. It is also generally prudent to allow the triptan to wash out before starting DHE.

Combination anesthetics or acetaminophen we would also discontinue several days prior to starting DHE.

Treatment approach following withdrawal of overused medications

Opioids and barbiturate containing compounds can be categorically discontinued and their further use discouraged. NSAIDs and triptans are good mainstays for acute headache treatments, along with anti-emetics if needed for nausea. Dopamine receptor antagonists, such as chlorpromazine or prochlorperazine, are useful alternatives, particularly for those with significant nausea or a contra-indication to triptans.

As discussed above, there is evidence that regular naproxen use can act as a migraine preventive and decrease migraine frequency. Acute intermittent use of NSAIDs may also have a disease modifying effect. In adults, NSAID use less than ten days per month appears to be protective against converting from episodic migraine to chronic migraine[1]. Moreover, in a recent adult pilot study naproxen use up to 14 days per month was found to decrease the number of migraine headache days at three months, and to decrease the number of headache attacks as soon as one month into treatment[32]. Given the evidence, it seems unnecessary, and perhaps even counterproductive, to limit significantly the number of days a child uses naproxen, at least from the standpoint of concern for medication overuse headache or conversion of episodic migraine into chronic migraine. Limiting frequency due to renal or gastrointestinal concerns is a different matter.

Triptans have been extensively studied in children and adolescents and there are positive randomized placebo-controlled trials for sumatriptan nasal spray, almotriptan, rizatriptan, and zolmitriptan nasal spray and tablets[33–40]. Almotriptan (Axert) and rizatriptan (Maxalt) are FDA-labeled for treatment of acute migraine in ages 12–17 and 6–17 years, respectively. At our center we generally limit triptan use to two days per week. Combining naproxen with sumatriptan provides greater efficacy, and lower potential of recurrence within the first twenty-four hours, than using either agent alone[41]. This combination of medications has been studied in adolescents and found to be safe and effective[42, 43]. Combining a triptan with naproxen may also decrease the likelihood of developing triptan overuse headache. In animals, repeated exposure to triptans can induce sensitization of trigeminal neurons, an effect that appears to be blocked by co-administration of naproxen[4]. In a pilot study of adults who used combined sumatriptan-naproxen up to fourteen days per month for three months, a frequency that would be thought of as triptan overuse, participants did not develop an increase in headache days. In fact the number of headache days at three months was lower than at baseline, though the difference was not statistically significant[32]. Both using naproxen in isolation, and sumatriptan/naproxen in combination, were associated with decreased use of acute medications over all three months of therapy.

Certainly the overarching goal in managing a child with medication overuse headache is to decrease the number of headache days the child experiences. Optimizing their acute medications is therefore only one piece of the puzzle. The long-term treatment strategy is to find an effective preventive regimen so that acute medications are not as frequently needed. The preventive regimen will likely consist of certain lifestyle modifications, such as regular sleep, as well as migraine preventive medication. While headache frequency is being

brought under control there may be a period of time during which the child can not treat every single headache with a prescription medication. Even if pain is present, limiting acute medication use (other than naproxen) may be necessary for a period in order to avoid medication overuse headache and to allow migraine preventives to have the best possible chance of taking effect. A considerable amount of time and counseling is often needed to explain this to families, which is quite understandable given how difficult this can be. Referrals for support with coping techniques, such as biofeedback or counseling, are sometimes appropriate to help the patient and family get through this transitional stretch.

Conclusions

Medication overuse is relatively common in children and adolescents, particularly among those with chronic migraine. Not every pediatric migraine patient who overuses acute headache medications will respond to medication withdrawal, thus it would be useful to be able to predict who will respond. Similarly, not all acute medications are equally likely to cause the difficulties associated with medication overuse. Based on adult data, barbiturate containing compounds seem to be most problematic in this regard, followed by opioids. Both should be avoided in children. The potential for frequent triptan use to become problematic may be lessened through co-administration of naproxen. It is unclear that NSAIDs in general, and naproxen sodium in specific, can cause medication overuse headache. Naproxen sodium may even be protective and its use could decrease headache frequency. Optimizing preventive therapy is key in helping children and adolescents stop overusing acute medications, and greater occipital nerve injections and IV dihydroergotamine may have roles in providing short-term and medium-term headache control while longer-term preventive therapies take effect.

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• Of importance

•• Of outstanding importance

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