Headache
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ISSN 0017-8748
doi: 10.1111/head.12484
Published by Wiley Periodicals, Inc.

Vox Clamantis

Butalbital and Pediatric Headache: Stay off the Downward Path

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Despite limited evidence from the literature surrounding safety or efficacy, butalbital-containing medicines (BCMs) have maintained their rank as "go-to" prescribed migraine and headache relief drugs in the United States, despite bans on these barbiturates in Germany and other European countries. Providers at the Pediatric Headache Program at Boston Children's Hospital recommend that clinicians prescribe triptan-based medications instead of BCMs, given the known negative side effects of BCMs on the general population, and the uncertain longitudinal trajectory of BCMs on developing brains.

Key words: butalbital, pediatrics, headache, triptan

Abbreviations: BCH Boston Children's Hospital, BCM butalbital-containing medicine, ED emergency department, FDA Food and Drug Administration, NSAID nonsteroidal anti-inflammatory drug, PHP Pediatric Headache Program, RCT randomized-controlled trial

(*Headache* 2015;55:327-330)

Butalbital-containing medicines (BCMs) remain a first choice for symptomatic treatment of migraine and tension-type headache in the United States despite bans on these barbiturates in Germany and other European countries due to reports of associated analgesic overuse headache, tolerance, toxicity, and dependence.[1-3] Discontinuation of high-dose BCMs may result in withdrawal and seizures, especially in vulnerable individuals (eg, pediatric patients).[1] BCMs have been granted Food and Drug Administration (FDA) approval for adults with episodic tension-type headache, following randomized-controlled trials (RCTs) showing modest (27%) efficacy of BCMs compared with placebo.[4] Barbiturates are prescribed frequently for children and adolescents with headache, without supportive RCT trials. We present a brief review of pharmacological treatment of acute headaches and migraines in pediatrics, describe the current prescribing of BCMs at Boston Children's Hospital (BCH), and provide our recommendation to discontinue the use of BCMs for pediatric headache.

Effective pharmacological treatment of headaches and migraines in children and adolescents is highly dependent on individual patient response and often includes varied combinations of abortive, symptomatic, and preventive pharmacological therapies recommended on the basis of severity, duration, and disability.[5] *Nonspecific* acute headache medications

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Accepted for publication October 16, 2014.

Conflict of Interest: None.

Financial Support: None.

and analgesics, including nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, aspirin, and naproxen, are often the first lines of defense for mild to moderate migraines. In Hamalainen et al's double-blind, placebo-controlled trial comparing the single oral doses of acetaminophen, ibuprofen, and placebo in children with migraines, ibuprofen was twice as likely as acetaminophen to terminate the migraine within a 2-hour timeframe.[6] Oral NSAIDs combined with or without analgesics (eg, acetaminophen) and containing caffeine may also be recommended for children with more severe migraine attacks who have responded positively to NSAIDs in the past. Multiple studies have validated NSAIDs as useful for the acute treatment of migraines if able to achieve the maximal permissible dosage at the onset of attack.[5,7] In a recent RCT performed by Cady et al comparing the efficacy of a combination of 85 mg of sumatriptan plus 500 mg of naproxen sodium against 500 mg of naproxen sodium in the daily prevention and acute treatment of migraine, naproxen sodium alone demonstrated a statistically significant reduction in migraine headache days.[8]

Symptomatic treatments, including antiemetics (eg, ondansetron and prochlorperazine), may also alleviate accompanying symptoms of nausea and vomiting and limit escalating severity and pain.[9] While nonspecific acute headache medications may ease the intensity and disability of severe episodes, patients must be wary of medication-overuse headaches (MOH) that induce rather than prevent headache and migraine.[10] In a longitudinal, population-based study, Bigal et al reported that NSAIDs used 5 or fewer days each month may protect against MOH, while 10 or more doses per month actually induces MOH.[11] For children suffering continuous, unremitting headaches lasting 72 hours or more, nasal or intravenous dihydroergotamine has demonstrated effective relief for pediatric patients failing their usual abortive therapies.[12]

Triptans (eg, sumatriptan, zolmitriptan, rizatriptan, almotriptan, and naratriptan) represent *specific* abortive migraine medications in pediatrics, with rizatriptan (Maxalt) and almotriptan (Axert) being the only FDA-approved triptans in pediatrics.[13] In placebo-controlled trials of rizatriptan in children, efficacy appeared quick acting and stable over the course of 2 episodes, with no evidence of tolerance and few adverse events reported.[13] The availability of certain triptans as nasal sprays or orally disintegrating tablets is particularly useful for children experiencing difficulties with swallowing pills. However, in children and adolescents diagnosed with specific migraine variants, including hemiplegic or retinal migraine, triptans are contraindicated due to potential vasoconstrictive effects.[14] One must also note the perception of triptans as considerably more expensive alternatives to other migraine treatments. Loder quotes the wholesale price of a brand name triptan as ranging from $23 to $31, while the cost of a generic sumatriptan tablet is priced as low as $2.55.[15] While treatment cost is an important consideration for families, one cannot overlook the potency of triptans in treating migraines early, effectively, and with the potential to prevent chronic manifestations of headache conditions (that further contribute to the economic burden of migraine).

Unlike triptans, BCMs provide nonspecific treatment for tension-type headache and migraine, acting to sedate and lessen pain temporarily.[16] Several formulations of BCMs are commercially available, with similar formulations labeled with different trade names. Compounding butalbital with acetaminophen and caffeine (eg, Fioricet) or with aspirin and caffeine (eg, Fiorinal) is common.[17] Both drugs can also be compounded with codeine despite an absence of relevant RCTs examining the potential for abuse and dependence.[18] According to recent drug labels and package inserts, adult dosage recommendations for commercially available BCMs limit intake to a maximum of 6 capsules/tablets within 24 hours.[17] Currently, no dosage guidelines, recommendations, or safety measures are in place for prescribing BCMs in pediatrics.

BCMs do *not* treat the underlying mechanisms of migraines, but produce analgesic symptoms that depress the central nervous system and may cause peripheral effects with higher dosing.[1] No evidence suggests safety or efficacy of using BCMs in treating multiple, recurrent headaches. Rather, existing literature reports the dangers of prescribing BCMs in treating headaches, specifically multiple, recurrent

headaches. MOH in connection with BCMs represents an additional concern.[2,3,5,10,18-23] Other adverse effects include altered, dose-dependent sleep cycles, impaired fine motor skills and judgment, and intoxication that is very similar to that caused by alcohol consumption, with symptoms including lethargy, decreased memory faculties, slurred and slowed speech, diminished comprehension, disinhibition, nausea, vomiting, tolerance, and resulting withdrawal.[1,5,19,21] Existing literature demands more rigorous study of the addictive risks of combination agents, including BCMs, though no such prevalence studies have surfaced in pediatric populations.[16,24,25]

Browne et al examine a more serious risk of congenital birth defects in relation to periconceptional BCM use. Butalbital is teratogenic and is associated with severe congenital heart defects, including threefold increased odds of tetralogy of Fallot and fivetime increased odds of pulmonary valve stenosis.[19] This finding is especially relevant to adolescent girls who may or may not be utilizing reliable contraception – an additional consideration for clinicians prescribing BCMs to adolescents. One must revisit studies exemplifying phenobarbital's negative repercussions on young children's cognitive development (language/verbal) as reminders of the devastating, often irreversible consequences of attempting to treat developing brains with poorly researched drugs lacking longitudinal support.[26] With the availability of safer, more effective, and well-researched pharmacological treatments for acute headache relief in children, BCMs are particularly dangerous alternatives that fail to appropriately treat the symptoms of severe headache episodes. With the availability of RCT-supported and FDA-approved specific and nonspecific headache medications, BCM prescriptions should become a historic cautionary tale.

We obtained data on BCM prescriptions for pediatric patients at BCH through an i2b2 platform that anonymously queries medical billing information for patient encounters at BCH. Searching from 2010 to 2013 for hospital-wide BCM prescriptions in relation to headache, we found the number of BCM prescriptions to rise from 122 to 143 cases between 2010 and 2011, with a decline to 117 prescriptions in 2012, and 85 cases in 2013. Evaluating BCH departments most directly involved in headache treatment since 2010 (eg, the Neurology Department, the Pediatric Headache Program [PHP], and the emergency department [ED]), we discovered the majority of BCM prescriptions to originate from the Neurology Department (266 of the 340 cases), followed by the ED (69), and the PHP (5). The majority of patients were female (69%) and between the ages of 10 and 19 years (75.5%). We also captured data on reported side effects of patients prescribed BCMs in the Neurology, ED, and PHP departments since 2010. The most common side effects reported by patients include dizziness (134), shaking (90), drowsiness (80), and confusion (57), followed by overuse (16), abuse (10), withdrawal (3), and agitation (2).

Given that BCMs continue to be prescribed to BCH patients for headaches despite concerning side effects and inconclusive efficacy data regarding actual symptom relief, we recommend that clinicians prescribe triptans in lieu of BCMs for acute pediatric headache and migraine. With unconvincing evidence supporting the efficacy of BCMs in adult headache sufferers and no RCTs or observational studies examining the effects of BCMs on developing brains, providers should seek safer alternatives and avoid the unknown, but likely dangerous path of prescribing BCMs to children and adolescents.

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