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Recognizing Medication Overuse Headache

By Michele Koder, Pharm. D. and Dan Hartung, Pharm. D., both at OSU College of Pharmacy

Population-based studies suggest that the prevalence of medication overuse headache (MOH) or chronic daily headache is 3-5% (1,2). Fifty to 86% of MOH have been attributed to overuse of analgesic and abortive medications (2-5). In a 1996 survey of US family practice physicians, MOH was reported to be the 3rd most common form of headache observed in practice (6).

The International Headache Society (IHS) defines medication overuse headache as a chronic headache (frequency > 15 days per month) after the intake of analgesics or ergots (> 15 times per month for ≥3 months), which disappears after withdrawal of therapy (7). Evidence supporting the existence of MOH is widely published in the medical literature. However, few controlled trials have investigated the epidemiology, risk factors, drug histories and management of patients with MOH.

While the pathogenesis of MOH has not been fully elucidated, suppression of or alterations in the function of endorphins, central opioid receptors, postsynaptic neuronal receptors, nociceptive "on-cells", and serotonin receptors have been implicated (2,3). All available headache and migraine abortive drugs are reported to cause MOH. Major differences in the ability of individual agents to cause MOH do not appear to exist. Some suggest the clinical features of MOH including type, duration and severity of withdrawal differ slightly among drug classes (8-13, 20).

A common presentation is a patient with a history of episodic migraine with or without aura, who complains of increased headache frequency and the development of tension-type headache, that eventually transforms into a daily or near daily headache lasting for prolonged periods (14). Patients may alternate between migraine-type and tension-type headaches. Behavioral and psychiatric comorbidities may be present and are complicating factors. Common clinical features are provided in Table 1.

Table 1- Common Clinical Features of MOH (1,14)

- Daily or near daily headache that varies in severity, type, and location
- Predictable, frequent early morning (2AM to 5AM) headaches
- Low pain threshold upon physical or cognitive exertion
- Additional symptoms such as asthenia, nausea and other GI symptoms, restlessness, anxiety, irritability, mood and cognitive defects. Cold and/or weak extremities, paresthesias, tachycardia, diminished pulse, and hypertension.
- Use of excessive quantities of abortive or analgesic medications (e.g. >15 days per month)
- Development of tolerance to analgesics and withdrawal symptoms upon abrupt discontinuation
- Lack of benefit from prophylactic medications
- Spontaneous improvement in headaches upon slow discontinuation of analgesics

Patients often underestimate their use of analgesics and use multiple types of agents concomitantly. Initially, pain relief provides negative reinforcement, and in some cases changes in mood incurred from barbiturate and caffeine-containing analgesics, may provide additional negative reinforcement, resulting in excessive use (3). Tolerance often ensues and results in increased headache frequency and severity with a decrease in analgesic efficacy. Additionally, concomitant preventive or prophylactic medications (e.g. TCAs, beta-blockers, anticonvulsants) become ineffective during the period of overuse of abortive therapies. Tapering and complete discontinuation of abortive medications is, therefore, the treatment of choice (14). Detoxification is conducted slowly over as many as 8 to 12 weeks and in the most severe cases, may warrant hospitalization (14). A brief discussion of each drug class follows.

Ergot Alkaloids

The efficacy and safety of ergot alkaloids for the treatment of migraine and tension headache are controversial due to limited availability of high quality studies (15,16). Rebound headache associated with overuse of ergot alkaloids was reported as early as the 1940s (15,17-21). Overuse also poses the risk of constant nausea, acrocyanosis, intermittent claudication, and ergotamine toxicity. As a result, the American Academy of Neurology and a European consensus statement recommend limiting the use of ergots to no greater than 1-2 single doses per week and no greater than 6 doses per month (15,16).

Analgesics- Non-Opiate and Opiate

NSAIDs, acetaminophen-codeine, and aspirin-acetaminophen-caffeine combinations have also long been associated with MOH. There is ample data supporting the link between aspirin and acetaminophen, most commonly when in opioid and caffeine combination products and MOH. Opioids, including butorphanol nasal spray, and opioid-combination products frequently cause rebound headache (16). The AMA has cautioned against their routine use in headache management.

The propensity of individual NSAIDs to cause MOH is controversial. A recent study of 103 patients attending a rheumatology clinic for routine monitoring of second-line RA agents (e.g. gold, sulfasalazine), evaluated whether regular use of analgesics for a non-headache indication was associated with the development of chronic daily headache (8). Chronic use of analgesics for indications other than headache or migraine did not result in chronic daily headache or MOH. However, all patients with primary headache disorders (8% of patients with a history of migraine) developed a chronic daily headache with repeated and increasing use of analgesics, including NSAIDs and opioids.

Butalbital-Containing Analgesics

Barbiturate- and caffeine-containing analgesics suppress REM sleep, causing REM rebound, and awakening with severe headache due to withdrawal. Butalbital-containing products can also cause intoxication, tolerance, psychological and physical dependency, and a dangerous withdrawal syndrome that may include seizure, psychosis, circulatory failure and death, in patients using higher doses (23,24). Despite quality evidence supporting their use, data illustrate that butalbital-containing products are among the most commonly overused agents among patients seeking headache treatment (5,20,23). In a study of 200 patients with daily headaches, butalbital-containing products were the most used drugs with 42% averaging 30 tablets per week (range 14-86 tabs/wk) (1). Because evidence to support or refute their efficacy is lacking and their potential for overuse and for inducing MOH is well-documented, the US Headache Consortium recommends that butalbital-containing medications be limited to occasional use and carefully monitored (16). Butalbital-containing products have been banned in several European countries and some experts recommend they also be banned in the US (16,25).

Triptans

Reports of triptan overuse and triptan-associated MOH are rapidly emerging in the literature (6,10,13,26-28). Results from a recent, prospective study, highlight the potential for triptans to cause MOH and prompted investigators to recommend limiting the intake of triptans to a maximum of 10 single doses per month (20). Forty-eight percent, 39%, and 13% of patients were categorized as having overused analgesics, triptans, and ergots respectively for a mean duration of 6.5 years (range, 0.5-25 yr). The mean critical monthly duration until onset of MOH was shortest in patients overusing triptans. Patients overusing triptans were more likely to develop a daily migraine-like headache or an increase in migraine attack frequency, whereas those overusing analgesics and ergots primarily developed daily tension-type headaches.

Drug Use Evaluation

Prescription claims for migraine drugs, triptans, butorphanol nasal spray, and DHE nasal spray, and miscellaneous ergot alkaloids of Oregon Medicaid fee-for-service members from January 1 to December 31, 2002 were reviewed. NSAIDs and opioid analgesics were not included in the analysis because of the inability to specifically determine their indication for use. There were a total of 12,665 claims for 2,801 unique patients. Total amount spent was $2,074,219. The average paid claim for all drugs was $150.59. Sumatriptan (in multiple dosage forms), rizatriptan and zolmitriptan were the most frequently prescribed drugs, accounting for 10,890 (86%) of total claims and $1,840,240 (89%) of total expenditures. Non-triptan agents (e.g. butorphanol nasal spray, DHE nasal spray, and miscellaneous ergot alkaloids) were infrequently prescribed and represented only 4.4% of claims.

Further analysis of triptan claims suggests the following: 1) Between 2-12% of patients within each triptan category were receiving another triptan concomitantly for at least 2 consecutive months, 2) 2,391 of 11,800 (20%) of claims were for quantities > 1x but < 2x the recommended limit and 3) 1,509 of 11,800 (13%) of claims were for quantities > 2x the recommended limit. A significant proportion of patients on triptans is exceeding monthly quantity limits defined by manufacturers' dosing recommendations (Table 2).

Conclusion

MOH is a significant and often unrecognized problem in ambulatory care. A claims analysis suggests that a significant number of OMAP fee-for-service patients are at risk for MOH. There is abundant evidence demonstrating the adverse consequences of overuse of common analgesic and abortive medications for the treatment of tension-type and migraine- headache. Patient education and limiting the quantities of prescribed and OTC medications are critical in preventing MOH. Providers should suspect MOH in patients describing increased headache frequency, daily or near daily headache and other common clinical features in Table 1. A medication diary may be helpful in determining the amount and frequency of headache medications. When MOH is present, slow tapering and withdrawal of all analgesic and abortive medications is often necessary. Once detoxification is complete, re-evaluation of the headache disorder is recommended and if needed, preventive therapy can be initiated. Table 3 lists web-sites containing valuable resources and tools for providers and patients such as headache diaries, headache measurement and evaluation tools, and patient fact sheets.

Table 3 – Provider and Patient Resources

American Academy of Neurology	http://www.aan.com/professionals/patient/hakit/index.cfm
National Headache Foundation	http://www.headaches.org/consumer/educationindex.html
American Headache Society	http://ahsnet.org/resources/patient.php
American Council for Headache Education	http://www.achenet.org/

Table 2 - Triptan Dosing Recommendations (Product labeling)

Generic (Brand)	Initial Dose	Dosage Form	HAs / Mth	Rec'd Limits
Almotriptan (Axert)	6.25-12.5 mg may repeat (MR) in 2hr Max Daily: 25mg	6.25 mg tab 12.5 mg tab (blister pack, 6)	4	12 tabs per 45 days
Eletriptan (Relpax)	20–40 mg MR in 2hr Max Daily: 80mg	20 mg tab 40 mg tab (blister pack, 12)	3	12 tabs per 60 days
Frovatriptan (Frova)	2.5-5 mg MR in 2hr Max Daily: 7.5mg	2.5 mg tab (blister pack, 9)	4	9 tabs per 30 days
Naratriptan (Amerge)	1-2.5 mg MR in 4hr Max Daily: 5mg	1 mg tab 2.5 mg tab (blister pack, 9)	4	9 tabs per 30 days
Rizatriptan (Maxalt Maxalt MLT)	5-10 mg MR in 2hr Max Daily: 30mg	5 mg tab 10 mg tab (blister pack, 6)	4	12 tabs per 45 days
Sumatriptan (Imitrex)	25-100 mg po MR in 2 hr Max Daily: 200mg	25 mg tab 50 mg tab 100 mg tab (blister pack, 9)	4	9 tabs per 30 days
	5-10 mg NS MR in 2 hr Max Daily: 40mg	5 mg, 10 mg NS (box of 6)	4	1 (refill) per 30 days
	3-6 mg SQ MR in 2hr Max Daily: 12mg	6 mg SQ (box 2 syr), kit	4	2 (kit) per 30 days
Zomitriptan (Zomig Zomig ZMT)	1.25-5 mg MR in 2hr Max Daily: 10mg	2.5 mg tab (blister pack, 6) 5 mg tab (blister pack, 3)	3	6 tabs per 30 days

MR = may repeat dose

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Reviewed by Gregory Johnson, M.D., Willamette Falls Immediate Care and Sean H. Karbowicz, Pharm. D., Regence BlueCross BlueShield of Oregon.

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OSU College of Pharmacy
840 SW Gaines Road MC 212
Portland, OR 97201-3098
Managing Editor: Kathy L. Ketchum
Ketchumk@ohsu.edu or 503-494-1589