Reviews/Evaluations

Medication-Overuse Headache

Population-based studies suggest that the prevalence of chronic daily headache is 3-5%(1,2). Drug-induced headaches are the most common cause of chronic daily headache. Fifty to 86% of chronic daily headaches have been attributed to overuse of analgesic and abortive medications (2-5). Yet, medication-overuse headache (MOH), also called drug-induced headache and analgesic-rebound headache, continues to be inadequately addressed in clinical practice. In a 1996 survey of family practice physicians in the US, MOH was reported to be the 3rd most common form of headache observed in practice(6).

The International Headache Society (HIS) defines medication-overuse headache (MOH) as a chronic headache (headache frequency > 15 days per month) after the intake of analgesics or ergots (more than 15 times per month for at least 3 months), which disappears after withdrawal therapy(7). It has been described as "a self-sustaining, rhythmic, headache-medication cycle characterized by daily or near daily headache and irresistible and predictable use of immediate relief medications"(3). Evidence supporting the existence of MOH is widely published in the medical literature. However, few quality, controlled trials have investigated the epidemiology, risk factors, and drug histories of patients with drug-induced headaches.

The pathogenesis of MOH has not been fully elucidated. Some evidence suggests that up-regulation of serotonin receptors and subsequent reduction in serotonin levels, which normalize upon cessation of chronic analgesic use, may play a role(3). The following have also been implicated in the development of MOH:

1. endorphin suppression,
2. central opioid receptor impairment,
3. impaired suppression or downregulation of an already partly suppressed or abnormal antinociceptive system,
4. alterations in density and function of postsynaptic neuronal receptors, and
5. activation of nociceptive "on-cells" in the ventral medulla that facilitate nociceptive reflex responses(2).

All currently available headache and migraine abortive drugs have been reported to cause MOH and major differences in the ability of individual agents to cause MOH do not appear to exist. Some do suggest, however, that the clinical features of MOH including type, duration, and severity of withdrawal may 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 interparoxysmal 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 during this period. Behavioral and psychiatric comorbidities may also be present and are complicating factors. Common clinical features are provided in Table 1. It is common for patients to underestimate their use of analgesics and to 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 positive reinforcement, resulting in excessive use(3). Tolerance, characterized by increasing consumption without regard to potential adverse outcomes, and withdrawal symptoms upon abrupt discontinuation, often ensue and result in increased headache frequency and severity with a decrease in analgesic efficacy. Concomitant preventive medications are relatively ineffective, while the patient is using excessive amounts of abortive agents and complete discontinuation of headache medication is the treatment of choice(14). Detoxification is usually conducted slowly over as many as 8 to 12 weeks and in the most severe cases, may warrant hospitalization(14).

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
- Headaches accompanied by asthenia, nausea and other GI symptoms, restlessness, anxiety, irritability, mood and cognitive defects. Cold and/or weak extremities, parasthesias, tachycardia, diminished pulse, and hypertension may also develop.
- Use of excessive quantities of abortive or analgesic medications (e.g. >15 days per month)
- Development of tolerance to analgesics
- Lack of benefit from prophylactic medications
- Development of withdrawal symptoms upon abrupt discontinuation of analgesics
- Spontaneous improvement in headaches upon slow discontinuation of analgesics

A brief discussion of each analgesic and abortive drug class and MOH follows.

Ergot Alkaloids

The clinical efficacy and safety of ergot alkaloids are controversial due to limited availability of studies utilizing quality methodology(15,16). Evidence supporting efficacy is stronger for DHE Nasal Spray than for oral ergotamine and ergotamine-caffeine combinations(16). Rebound headache associated with overuse of ergot alkaloids has been described as early as the 1940s (15,17-21). The ergot alkaloids have a complex mode of action that involves interaction with a variety of receptors (5-HT, dopamine, and noradrenaline receptors). Several kinds of daily headaches have been described with frequent use of ergots including a constant, diffuse, dull headache; a frequent throbbing headache in the early morning that disappears within 1h after intake of ergotamine; migraine attacks; and withdrawal headache resembling a severe and prolonged migraine attack with gradual return over weeks to the underlying headache pattern if ergotamine is stopped. Overuse also poses the risk of constant nausea, acrocyanosis, intermittent claudication, and ergotamine toxicity. As a result, an evidence-based review by 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

Evidence supporting the efficacy of NSAIDs, combination analgesics, and non-opiate analgesics varies among and within classes(16). NSAIDs, acetaminophen with codeine, and aspirin-acetaminophen-caffeine combination are supported by multiple well-designed randomized clinical trials. These agents, however, have also long

been associated with MOH. While there is ample data supporting the link between aspirin and acetaminophen, most commonly when in butalbital and caffeine combination products, there is debate as to the propensity of individual NSAIDs to cause MOH and this area remains one of controversy. A recent study of 103 patients attending a rheumatology clinic for routine monitoring of second-line agents (e.g gold, sulfasalazine), aimed at determining whether regular use of analgesics for a non-headache indication was associated with the development of chronic daily headache(8). Patients were interviewed for analgesic and headache history. Chronic use of analgesics for indications other than headache or migraine, did not appear to 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. Butorphanol nasal spray, a common opiate analgesic for migraine, has good quality evidence of efficacy, but has been recommended to be limited in its use because of its propensity to cause MOH and dependence(16).

Butalbital-Containing Analgesics

A number of proprietary and generic butalbital-containing products are available, such as Fiorinal (butalbital, aspirin, caffeine), Fioricet (butalbital, acetaminophen, caffeine), and Esgic (butalbital, acetaminophen, caffeine). Barbiturate- and caffeine-containing analgesics suppress REM sleep, causing REM rebound, and awaking with severe headache due to withdrawal. Butalbital-containing products also can cause intoxication, tolerance, and 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). All butalbital-containing products have been approved by the FDA for treatment of tension headache. While proven effective for tension-type headaches, they have not been evaluated for migraine in placebo-controlled trials(20). Although efficacy is contentious, data illustrate that butalbital-containing products are the most commonly overused agents among patients seeking treatment at headache clinics(5,23). In a study of 200 patients with daily headaches, butalbital-containing product was the most overadministered drug with 42% averaging 30 tablets/week (range 14-86 tablets/week)(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 the use of butalbital-containing medication be limited 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- or at least be limited in their use(16,25).

Triptans

Triptans have possibly become the most common treatment of migraine because of their evidence of efficacy and relatively low rate of adverse effects. However, 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). In the study, 98 patients with MOH according to IHS criteria underwent standardized inpatient medication withdrawal. Patient diaries and interview were used to compare the pharmacologic and clinical features of MOH associated with the overuse of acute treatments. Forty-eight percent, 13%, and 39% of patients were categorized as having overused analgesics (NSAIDs, caffeine-combinations, butalbital-combinations, opioids), ergots, and triptans respectively for a mean duration of 6.5 years (range, 0.5-25 yr). The mean critical monthly duration until onset of MOH (MCDO), mean critical monthly intake frequencies (MCMIF), and mean critical monthly dosages (MCMD) were calculated. The MCDO 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. Results are summarized in Table 2.

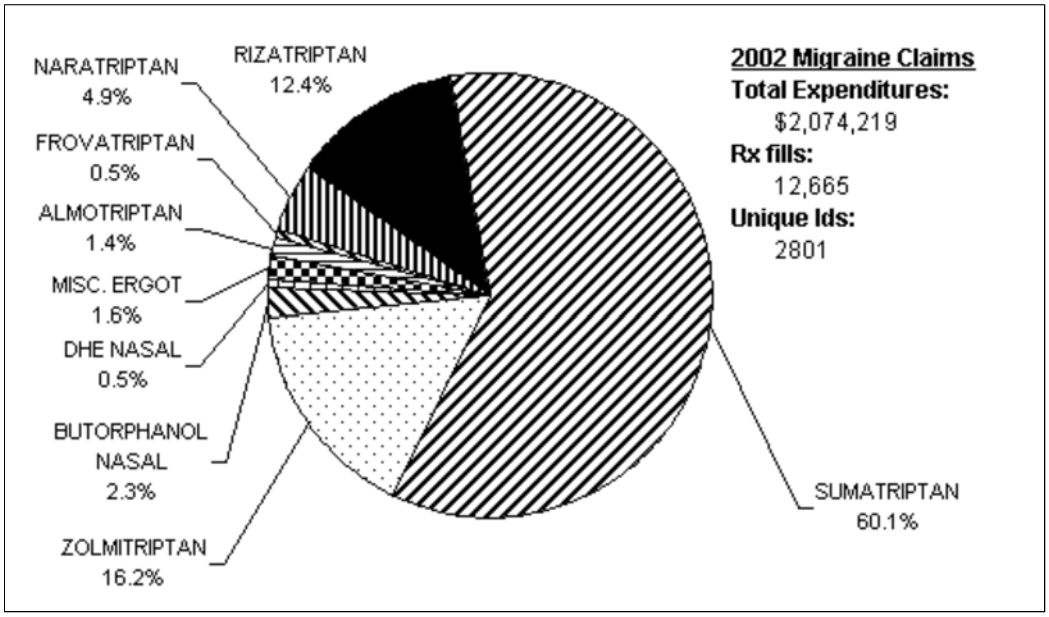
Table 2- Comparison of Clinical Features of MOH by Drug Class (20)

Drug	Patients, n (%)	MCDO, y*	MCMIF, single doses	MCMD, mg
Analgesics	46 (48)	4.8	113.9	7,062-72,550
Triptans	38 (40)	1.7	18.6	46-1612
Ergots	12 (12)	2.7	36.7	53

* Pairwise comparisons: analgesics vs. ergots (NS), analgesics vs. triptans (p=0.001), triptans vs. ergots (NS).

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 1/1/02 - 12/31/02 were reviewed (Figure 1). 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. An average of 8.13 dosage units were dispensed for each Rx (range 2.2 for SQ sumatriptan to 11.8 for po naratriptan). Sumatriptan, (in multiple dosage forms), rizatriptan, and zolmitriptan were the most frequently prescribed drugs, accounting for 10,890 or 86% of total claims and $1,840,240 or 89% of total expenditures. Non-triptan agents (butorphanol nasal spray, DHE nasal spray, and miscellaneous ergot alkaloids) were infrequently prescribed and represented only 4.4% of claims.

Figure 1. - Migraine Claims Analysis: 1/1/02 - 12/31/02



Further analysis of the triptan claims suggests the following:

- The average number of dosage units dispensed per claim (range) were:
  - Almotriptan: 9.5 (2-39)
  - Frovatriptan: 10.1 (2 - 60)
  - Naratriptan: 11.8 (1- 60)

    - Rizatriptan: 10.1 (1-180)
    - Sumatriptan (PO): 11.6 (1-120)
    - Sumatriptan (SQ): 2.2 (1-30)
    - Sumatriptan (NS): 6.6 (1-18)
    - Zolmitriptan: 10 (1-120)
- Naratriptan po had the largest average quantity dispensed per claim (11.8), followed closely by sumatriptan po (11.6).
- Between 2-12% of patients within each triptan category were receiving another triptan concomitantly for at least 2 consecutive months
- 7,900 of 11,800 (67%) claims were for quantities dispensed within recommended dosing ranges.
- 2,391 of 11,800 (20%) of claims were for quantities > 1x but < 2x the recommended limit.
- 1,509 of 11,800 (13%) of claims were for quantities > 2x the recommended limit.

  A significant proportion of patients on triptans are exceeding monthly quantity limits as defined by manufacturers' dosing recommendations and whose safety and efficacy are supported by clinical trials (Table 3). Claims analysis suggests that a significant number of OMAP fee-for-service patients are at risk for MOH (Table 4). 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. There is a lack of study on the pharmacoeconomic impact and overall utilization of healthcare resources, but it is likely to be significant. An area of future analysis would be to investigate the number of patients who are on migraine prophylaxis therapy, particularly those exceeding monthly triptan quantity recommendations.

Table 3: Triptan Dosing Recommendations (Product labeling)

Generic	Brand	Initial Dose	Max Daily Dose	Dosage Form	Max # treated HA's/ Month	Proposed QTY Limits
Almotriptan	Axert	6.25-12.5 mg rpt in 2hr	25 mg	6.25 mg tab 12.5 mg tab (blister pack, 6)	4	12/45d 12/45d
Eletriptan	Relpax	20-40 mg rpt in 2hr	80 mg	20 mg tab 40 mg tab (blister pack, 12)	3	12/30d 12/30d
Frovatriptan	Frova	2.5-5 mg rpt in 2hr	7.5 mg	2.5 mg tab (blister pack, 9)	4	9/30d
Naratriptan	Amerge	1-2.5 mg rpt in 4hr	5 mg	1 mg tab 2.5 mg tab (blister pack, 9)	4	9/30d 9/30d
Rizatriptan	Maxalt Maxalt MLT	5-10 mg rpt in 2hr	30 mg	5 mg tab 10 mg tab (blister pack, 6)	4	12/45d 12/45d
Sumatriptan	Imitrex	25-100 mg po rpt in 2 hr 5-10 mg NS rpt in 2 hr 3-6 mg SQ rpt in 2hr	200 mg 40 mg 12 mg	25 mg tab 50 mg tab 100 mg tab (blister pack, 9) 5 mg, 10 mg NS (box of 6) 6 mg SQ (box 2 syr), kit	4 4 4	9/30d 9/30d 9/30d 6/30d 1 (refill)/30d 1 (kit)/30d

Zomitriptan	Zomig Zomig ZMT	1.25-5 mg rpt in 2hr	10 mg	2.5 mg tab (blister pack, 6) 5 mg tab (blister pack, 3)	3	6/30d 6/30d

Recommendation

- Add quantity limits to triptans to ensure safe and effective dosing, while reducing costs and decreasing the potential for MOH.

Table 4

References

1. Mathew NT, Kurman R, Perez F. Drug-induced refractory headache: clinical features and management. *Headache* 1990;30:634-8.
2. Silberstein SD. Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review): report of the quality standards subcommittee of the American Academy of Neurology. *Neurology* 2000;55(6):754-62.
3. Mathew NT. Transformed migraine, analgesic rebound, and other chronic daily headaches. *Neuro Clinics* 1997;15(1):168-187.
4. Peters GA, Horton BT. Headache: with special reference to the excessive use of ergotamine preparations and withdrawal effects. Proc Staff Meet Mayo Clin 1951;26:153-161.
5. Wenzel RG, Sarvis CA. Do butalbital-containing products have a role in the management of migraine? *Pharmacotherapy* 2002; 22(8):1029-1035.
6. Rapoport A, Stang P, Gutterman DL, et al. Analgesic rebound headache in clinical practice: data from a physician survey. *Headache* 1996;36:14-19.
7. Headache Classification Committee of the International Headache Society. Classification and diagnostic criteria for headache disorders, cranial neuralgia, and facial pain. *Cephalgia* 1998; 8(suppl 7):1-96.
8. Bahra A, Walsh M, Menon, S, et al. Does chronic daily headache arise do novo in association with regular use of analgesics? *Headache* 2003;43:179-190.
9. Prencipe M, Casini AR, Ferretti C, et al. Epidemiology of chronic daily headache in the general population. *Headache* 1999;39:190-196.
10. Capobianco DJ, Cheshire WP, Campbell JK. An overview of the diagnosis and pharmacologic treatment of migraine. *Mayo Clinic Proc* 1996;71:1062-3.
11. Bigal ME, Sheftell FD, Lipton RB, Rapoport AM, Tepper SJ. Evaluation of chronic daily headache: correlation between the International Headache Society and the proposed headache classification for chronic daily headache systems. *Neurology*. 2002;58:A172.
12. Young WB, Hopkins MM. Profile and outcome of chronic migraine patients: a prospective study. *Headache*. 2002;42:436 (Abstract).
13. Katsavara Z, Fritsche G, Muessig HD, et al. Clinical features of withdrawal headache following overuse of triptans and other headache drugs. *Neurology* 2001;57:1694-1698.
14. Moore KL, Noble SL. Drug treatment of migraine: Part I. Acute therapy and drug-rebound headache. *Am Fam Phys* 1997;56(8): 2039-48, 2051-4.

15. Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter: appropriate use of ergotamine tartrate and dihydroergotamine in the treatment of migraine and status migrainosus. *Neurology* 1995; 45: 585-7.
16. The US Headache Consortium. Evidence-based guidelines for migraine headache in the primary care setting: pharmacological management of acute attacks. The American Academy of Neurology; http://www.aan.com/professionals/practice/guidelines.cfm. Accessed on 5/2/03.
17. Friedman AP, Brazil P. Ergotamine tolerance in patients with migraine. *JAMA* 1955;157:881-884.
18. Saper JR, Jones JM. Ergotamine tartrate dependency: features and possible mechanisms. *Neuropharmacology* 1986:9:244-256.
19. Tfelt-Hansen P, Saxena PR, Daholf C, et al. Ergotamine in the acute treatment of migraine- a review and European consensus. *Brain* 2000;123:9-18.
20. Limmroth V, Katsarava Z, Fritsche G, et al. Features of medication overuse headache following overuse of different acute headache drugs. *Neurology* 2002;59:1011-1014.
21. Wolfson WQ, Graham JR. Development of tolerance to ergot alkaloids in a patient with unusually severe migraine. *NEJM* 1949;241:296-298.
22. Bowlder I, Kikan J, Gansslen-Blumberg S, et al. The association between analgesic abuse and headache--coincidental or causal? *Headache* 1988;28:494.
23. Silberstein SD, McCrory DC. Butalbital in the treatment of headache: history, pharmacology, and efficacy. *Headache* 2001;41(10):953-967.
24. Sarrecchia C, Sordillo P, Conte G, Rocchi G. [Barbiturate withdrawal syndrome: a case associated with the abuse of a headache medication]. (abstract) *Annali Italiani di Medicina Interna* 1998;13(4):237-9.
25. Young WB, Siow HC. Should butalbital-containing analgesics be banned? Yes. *Current Pain & Headache Reports* 2002;6(2):151-5.
26. Kaube H, May A, Diener HC, et al. Sumpatriptan misuse in chronic daily headache [abstract]. *BMJ* 1994;308:1573-1574.
27. Limmroth V, Kazarawa S, Fritsche G, et al. Headache after frequent use of new serotonin agonists zolmitriptan and naratriptan [abstract]. *Lancet* 1999;353:378.
28. Gobel H, Heinze A, Dworschak M. Easy therapeutical management of sumatriptan-induced daily headache [abstract]. *Cephalgia* 1994;14:374-37.