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Chronic (transformed) migraine and medication overuse: to withdraw or not?

'...the possibility that drug withdrawal alone may be enough to interrupt daily or near-daily headaches has been raised.'

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Migraine is a prevalent, disabling, undiagnosed and undertreated disease in neurological practice [1]. It is a primary disorder with a clear genetic basis [2,3]. For some uncommon forms of migraine, such as familial hemiplegic migraine, specific pathogenic genes have been identified, and the most common mutation affects a gene on chromosome 19, which codes for a neuronal calcium channel, suggesting that other forms of migraine may also be ion channelopathies [4]. During a migraine attack, neural events result in the dilatation of meningeal blood vessels, which results in pain, further nerve activation and inflammation [5].

Migraine most likely occurs from dysfunction of the brainstem involved in the modulation of craniovascular afferents [2–5]. Brainstem activation may also lead to activation of ascending and descending pathways, with initiation of a perimeningeal vasodilatation and neurogenic inflammation. The pain is understood to be a combination of altered perception (due to peripheral or central sensitization) of stimuli that are usually not painful, as well as the activation of a feed-forward neurovascular dilator mechanism in the first (ophthalmic) division of the trigeminal nerve. Cortical spreading depression is the presumed substrate of migraine aura; spreading depression may also occur in migraine without aura.

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Chronic daily headache refers to a group of patients presenting headache attacks on 15 days or more per month. It represents the most frequent cause of chronic headache seen in tertiary centers, and affects nearly 4% of the general population [6]. Chronic or transformed migraine is a subgroup of chronic daily headache with a migrainous biology [6,7]. These patients may overuse symptomatic medications (SM), such as analgesics, a combination of analgesics, caffeine and barbiturates, opioids, ergotamine derivatives and, more recently, triptans, on a regular basis, which may play a crucial role in the transformation of episodic migraine in chronic migraine [8–10].

Chronic migraineurs overusing SM have been considered refractory to the preventive treatment until their acute attack medications are stopped. The proposed strategies for performing such sudden withdrawal are varied, but there was nearly a consensus on the imperativeness for interrupting the overused medications prior to the preventive treatment initiation until recently [11–15]. However, emerging opinions and studies suggesting that withdrawal is not a prerequisite for successfully achieving a reduction in headache frequency in chronic migraineurs, despite their maintenance of overusing SM profile, have been raising warm debates [16–18]. The possibility that drug withdrawal alone may be enough to

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interrupt daily or near-daily headache is exciting [19]. However, this new concept is countered by the vast literature, which relates the overuse of SM with drug rebound among other pathophysiological mechanisms. It is considered a paradoxical response to the use of acute attack medications, in addition to the influence possibly exerted by various psychological comorbidities. Certain Axis I disorders, such as anxiety and depression, and Axis II disorders, such as borderline personality disorder, may make these patients more prone to drug overuse and poor prognosis [20–22]. In addition, other involved mechanisms do suggest that the overuse of SM may interfere with the intrinsic pain modulatory system by depleting serotonin and, consequently, upregulating its postsynaptic receptors. It may coexist with a defective functioning of the antinociceptive system demonstrated by a persistent and progressive impairment of iron homeostasis in the periaqueductal gray in migraine and chronic migraine patients, along with repeated episodes of peripheral and central pain sensitization of the trigeminal neurovascular pathways [23–27].

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Taken together, this myriad of possible underlying mechanisms makes chronic migraineurs overusing SM difficult to treat regardless of their withdrawal from regularly used acute medications. Relapse is common and more efficient strategies have to be employed in order to achieve better outcomes with this subset of patients [28,29]. Moreover, the debate on whether or not previous drug withdrawal allows preventive treatment to function cannot be considered while completely different populations of chronic migraineurs are placed under the same spotlight. Patients overusing opioids or with clear psychological comorbidities, as those encountered in tertiary center populations in the USA, cannot be compared with those attending Italian, German or Brazilian headache centers where opioid overuse does not seem to occur very frequently [15,19,30–32]. Additionally, there may be interesting pathophysiological differences between chronic migraineurs with daily headache and those with less frequent headache attacks, but still presenting with headaches occuring more than 15 days per month [18]. The few available trials have uncommon characteristics such as a very unusual placebo response rate, which may represent an unblinding issue and impede further conclusions [18].

Therefore, primary studies on drug prophylaxis in chronic migraine patients, despite the persistence of SM overuse, are necessary at this time in order to allow the understanding of optimal strategies for their management, although their conclusions may not be taken as a standard approach until randomized controlled studies can prove that withdrawal is not crucial to allow response to preventive medications. Up to now, the traditional concept that withdrawal of overused symptomatic medications, especially opioids, may interfere with the positive effect of preventive treatment and, therefore, is a desired accomplishment for most of these patients should remain in the minds of those involved with the improvement of chronic migraineurs lives. Additionally, the likelihood that simple interruptions of medication overuse, without the appropriate utilization of preventive therapies combined with behavioral management to maximize outcome, may indeed represent the difference between treatment failure and success. The expectations on the release of randomized controlled studies with these patient populations, along with the clinical practice experience, may further elucidate the future approach for relieving this burden.

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References

1 Stewart WF, Shechter A, Lipton RB. Migraine heterogeneity, disability, pain intensity, and attack frequency and duration. *Neurology* 44(Suppl. 4), S24–S39 (1994).

2 Goadsby PJ. Pathophysiology of migraine. In: *Wolff's Headache and Other Head Pain (7th Edition).* Silberstein SD, Lipton RB, Dalessaio DJ (Eds). Oxford University Press, Oxford, UK 57–72 (2001).

3 May A, Goadsby PJ. The trigeminovascular system in humans: pathophysiology implications for primary headache syndromes of the neural influences on the cerebral circulation. *J. Cereb. Blood Flow Metab.* 19, 115–127 (1999).

4 Goadsby PJ, Lipton RB, Ferrari MD. Migraine – current understanding and treatment. *N. Engl. J. Med.* 346, 257–270 (2002).

5 Welch KMA, Barkley GL, Tepley N *et al.* Central neurogenic mechanisms of migraine. *Neurology* 43, S21–S25 (1993).

6 Silberstein SD, Lipton RB, Sliwinski M. Classification of daily and near-daily headache: a filed study of revised IHS criteria. *Neurology* 47, 871–875 (1996).

7 Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders (2nd Edition). *Cephalalgia* 24(Suppl. 1), 1–160 (2004).

8 Scholz E, Diener HC, Geiselhart S, Wilkinson M. Drug-induced headache – does a critical dose exist? In: *Drug-induced Headache.* Diener HC (Ed.). Springer-Verlag, Berlin, Germany 29–43 (1988).

9 Zwart JA, Dyb G, Hagen K, Svebak S, Holmen J. Analgesic use: a predictor of chronic pain and medication overuse headache. *Neurology* 61, 160–164 (2003).

10 Limmroth V, Katsarava Z, Fritsche G, Przywara S, Diener HC. Features of medication overuse headache following overuse of different acute headache drugs. *Neurology* 59, 1011–1014 (2002).

11 Dodick DW, Freitag F. Evidence-based understanding of medication-overused headache: clinical implications. *Headache* 46(Suppl. 4), S202–S211 (2006).

12 Diener HC, Katsarava Z. Medication overuse headache. *Curr. Med. Res. Opin.* 17, 17–21 (2002).

13 Grazzi L, Andrasic F, D'Amico D, Usai S, Kass S, Bussone G. Disability in chronic migraine patients with medication overuse: treatment effects at 1-year follow up. *Headache* 44, 678–683 (2004).

14 Relja G, Granato A, Bratina A, Antonello RM, Zorzon M. Outcome of medication overuse headache after abrupt in-patient withdrawal. *Cephalalgia* 26, 589–595 (2006).

15 Krymchantowski AV, Moreira PF. Out-patient detoxification in chronic migraine: comparison of strategies. *Cephalalgia* 23, 982–993 (2003).

16 Dodick D. Personal communication. Presented at: *XX Brazilian Headache Congress.* Belo Horizonte, Minas Gerais, Brazil, 14–19 September 2006.

17 Diener HC. Personal communication. Presented at: *49th Annual Scientific Meeting of the American Headache Society. Clinical Crossfire Session.* Chicago, IL, USA, 6–10 June 2007.

18 Diener HC, Bussone G, Van Oene JC, Lahaye M, Schwalen S, Goadsby PJ. On behalf of the TOPMAT-MIG-201(TOP-CHROME) Study Group. Topiramate reduces headache days in chronic migraine: a randomized, double-blind, placebo-controlled study. *Cephalalgia* (2007) (In Press).

19 Rossi P, Di Lorenzo C, Faroni J, Cesarino F, Nappi G. Advice alone vs structured detoxification programmes for medication overuse headache: a prospective, randomized, open-label trial in transformed migraine patients with low medical needs. *Cephalalgia* 26, 1097–1105 (2006).

20 Breslau N, Merikangas K, Bowden CL. Comorbidity of migraine and major affective disorders. *Neurology* 44, S17–S22 (1994).

21 Merikangas K, Stevens DE. Comorbidity of migraine and psychiatric disorders. In: *Neurologic Clinics: Advances in Headache.* Mathew NT (Ed.). Saunders, PA, USA 115–124 (1997).

22 Saper J. Borderline personality disorder and the chronic headache patient: review and management recommendations. *Headache* 42, 663–674 (2002).

23 Mathew NT. Medication misuse headache. *Cephalalgia* 18(Suppl. 21), 34–36 (1998).

24 Srikiatkhachorn A, Puanguiyon MS, Govitrapong P. Plasticity of 5-HT serotonin receptor in patients with analgesic-induced transformed migraine. *Headache* 38, 534–539 (1998).

25 Welch KM, Nagesh V, Aurora S, Gelman N. Periaqueductal gray matter disfunction in migraine: cause or the burden of illness. *Headache* 41, 629–637 (2001).

26 Mao J. Opioid-induce abnormal pain sensitivity: implications in clinical practice. *Pain* 100, 213–217 (2002).

27 Meng ID, Porreca F. Basic science: mechanisms of medication overuse. *Headache Curr.* 1, 47–54 (2004).

28 Guidetti V, Galli F, Fabrizi P *et al.* Headache and psychiatric co-morbidity: clinical aspects and outcome in a 8-year follow-up study. *Cephalalgia* 18, 455–462 (1998).

29 Linehan MM. Combining pharmacotherapy with psychotherapy for substance abusers with borderline personality disorder: strategies for enhancing compliance. *NIDA Res. Monogr.* 150, 129–142 (1995).

30 Katsarava Z, Fritsche G, Muessig M, Diener HC, Limmroth V. Clinical features of withdrawal headache following overuse of triptans and other headache drugs. *Neurology* 57, 1694–1698 (2001).

31 Saper J, Lake AE III, Hamel RL *et al.* Daily scheduled opioids for intractable head pain: long-term observations of a treatment program. *Neurology* 62, 1687–1694 (2004).

32 Lake AE III, Saper J, Hamel RL. Inpatient treatment of intractable headache: outcome for 267 consecutive program completers. *Headache* 46, 893 (2006) (Abstract).

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