Chapter 14
Pathophysiology of Medication Overuse Headache: Current Status and Future Directions

Signe Bruun Munksgaard and Frank Porreca

14.1 Introduction

Migraine is thought to be the world's third most common neurological disorder and is ranked as seventh among the leading causes of disability [1, 2]. Its economic impact is measured in billions of dollars [3, 4], and it accounts for 2.9 % of work time lost due to disability [2]. Notably, these high rankings for the burden of migraine occur in spite of the fact that treatments are available, clearly suggesting that current migraine therapeutics are inadequate [2, 5].

The introduction of triptans represented a significant advance in the therapeutic management of migraine, and triptans as a class are considered the drugs of choice for management of migraine [6–8]. However, the frequent use of triptans can lead to the conversion of episodic migraine into a chronic condition, frequently referred to as medication overuse headache (MOH) [9, 10]. MOH was recognized before the introduction of triptans from patients overusing ergots, opioids, and other analgesics [11–13]. The overuse of analgesics in the treatment of cluster headache or tension-type headache (TTH) [14] can also lead to MOH [15, 16]. Importantly, MOH is more disabling than episodic headache and much more difficult to treat [15–17]. MOH is a chronic headache, affecting patients mainly between 20 and 50 years of age and thus in their most productive years [18–21].

S.B. Munksgaard, MD, PhD (✉)
Department of Neurology, Danish Headache Center, Glostrup Hospital, University of Copenhagen, Glostrup, Denmark
e-mail: signebm@gmail.com

F. Porreca, PhD (✉)
Department of Pharmacology and Anesthesiology, Arizona Health Sciences Center, University of Arizona, Tucson, AZ, USA
e-mail: frankp@u.arizona.edu

© Springer International Publishing Switzerland 2015

M. Ashina, P. Geppetti (eds.), *Pathophysiology of Headaches: From Molecule to Man*, Headache, DOI 10.1007/978-3-319-15621-7_14

The treatments employed in MOH are primarily a combination of information on the disease and further detoxification from the overused drug combined with medical prophylactic treatment and sometimes behavioral therapy. Simple information can be sufficient for MOH patients who do not suffer from comorbidities and who overuse medications that do not cause severe withdrawal symptoms. They are often able to reduce their medication intake and thus experience a reduction in headache frequency to episodic headache [22, 23]. In many patients, especially those with comorbidities or previous relapse to MOH, these treatments are not effective in reducing headache frequency. Current prophylactic migraine treatments arise not from rational, evidence-based approaches, but from serendipity and presumptions of efficacy based on the success of related compounds within a pharmacologic class [18–21]. The limited therapeutic efficacy of currently available prophylactic treatments against chronic migraine and the high relapse rate in MOH underscore a strong medical need for the understanding of basic mechanisms underlying MOH.

14.2 Clinical Description

The possibility that aggressive analgesic therapy can lead to enhanced pain has long been recognized in the clinical management of headache and gave rise to terms such as rebound headache, medication misuse headache, or transformed migraine, later defined as MOH [24]. MOH is characterized by 15 or more headache days/month that result from excessive use of antimigraine drugs or analgesics. The current consensus diagnostic criteria for MOH are summarized in Table 14.1. The general worldwide prevalence of MOH is estimated to be at least 1 % in adults and 0.5 % in adolescents [25–27], and approximately 33 % of individuals reporting chronic daily headache meet the criteria for the overuse of medication [25, 28, 29]. Clinical surveys indicate that only patients predisposed to headache will develop MOH when overusing analgesics [30] and that patients with MOH most commonly have migraine, followed by TTH [14]. The risk of developing MOH increases with lower socioeconomic status and female sex [31–33]; the male/female ratio is 1:3.5 [34]. The prevalence of psychiatric disorders such as obsessive-compulsive disorders, depression, and anxiety is greatly increased in persons with MOH [31, 35–38]. These psychiatric disorders are described as significant risk factors for developing

Table 14.1 The ICHD-3 criteria for medication overuse headache

A. Headache present on 15 or more days/month in a patient with a preexisting headache disorder
B. Regular overuse for more than 3 months of one or more drugs that can be taken for acute and/or symptomatic treatment of headache
1. Ergotamine, triptans, opioids, or combination analgesics on 10 or more days/month
2. Simple analgesics on 15 or more days/month
3. Any combination of acute/symptomatic drugs on 10 or more days/month without overuse of any single class alone
C. Not better accounted for by any other ICHD-3 diagnosis

MOH but also complicate treatment and increase the relapse rate to MOH after withdrawal [31, 35–38]. Other risk factors include stressful life events, sleep disturbances, obesity, increased caffeine consumption, and elevated baseline headache frequency (10 or more per month) [39–42].

Both underlying headache type and overused drug appear to contribute to the pathogenesis of MOH. Most patients with MOH have migraine, and most (>95 %) of migraine sufferers regularly use acute medications that include analgesics, migraine-specific medications (triptans, ergot medications), opioids, or a combination thereof [43]. The choice and frequency of use of acute medications have a major influence on migraine prognosis [44, 45]. Acute medications, particularly opioids, barbiturate-containing combination analgesics, as well as triptans and ergots, potentiate the risk of progression [30, 46–50]. The intensity and frequency of recurrent headaches was increased with opiate use and diminished when opiate administration was terminated [11, 12]. Triptans tend to produce MOH over a shorter dosing regimen than either ergots or analgesics [51]. In a prospective study, it was found that the mean interval between first dose and MOH for triptans was 1.7 years, whereas the mean interval for ergots and analgesics was 2.7 years and 4.8 years, respectively [51]. The duration of withdrawal headache was less severe and shorter in patients overusing triptans (4.1 days) than in patients overusing ergots (6.7 days) or analgesics (9.5 days) [13]. Additionally, the MOH headache pattern reflected both the underlying headache type and the medication overused. Triptans were more likely to produce a daily migraine-like headache or an increase in migraine frequency, whereas simple analgesics and ergots were more likely to produce a TTH-like headache [13, 51]. Studies on subgroups of MOH patients overusing different types of drugs [13, 52–54] show different responses in neuroimaging and cortical potentials.

MOH across different medications appears to share some common neurobiological pathways, including those that modulate motivation, reward, and behavioral control [55]. A large proportion of patients with chronic daily headache with concomitant medication overuse fulfilled the diagnostic criteria for substance dependence [56]. Dependence-like behavior is more frequently observed in patients with chronic headaches without MOH who smoke, who are obese, and who use sleep medications and tranquilizers [31]. Approximately two-thirds of MOH patients were considered to be dependent on acute treatments of headaches, and many of these individuals had migraine as preexisting primary headache, and most of them overused opioid analgesics. The severity of dependence predicted a poorer outcome of treatment for MOH [22, 57–59]. A correlation has been observed between high severity of dependence scale (SDS) score before treatment and a poor outcome of treatment for MOH [58, 57, 60].

14.3 Neurophysiological Mechanisms of MOH

The mechanisms behind the development of MOH are largely unknown, but both human and animal studies indicate drug-induced modifications of peripheral and central pain transmission and modulatory pathways. Cutaneous allodynia, especially when present at extracephalic sites in premonitory phases of migraine, during a migraine attack, and in the post-drome period, is a clinical sign that suggests the

occurrence of central sensitization in humans [61–64]. Individuals with migraine present a greater prevalence of cutaneous allodynia than do those with nonmigraine headaches, and patients with MOH are more likely to develop allodynia than individuals with episodic migraine [15, 63, 65–67]. The mechanisms that trigger a migraine attack are largely unknown but are thought to reflect a disorder of the brain [68, 69]. Evaluating mechanisms that lead to pain in migraine headache is difficult as the pain is intermittent and there is no tissue injury to serve as an obvious trigger [69]. Increasing evidence points ultimately to engagement and sensitization of the trigeminovascular system in the genesis of pain resulting from a migraine episode. Migraine sufferers were found to have increased excitability of the trigeminal nociceptive pathway, both during a migraine episode and during the interictal period [63, 70–72].

Perivascular stimulation of the dura results in pain referred to the head [73, 74]. Activation of trigeminal afferent fibers terminating in the dura can release excitatory mediators accompanied by neurogenic vasodilation of dural blood vessels, further release of pronociceptive mediators, degranulation of mast cells, and extravasation of plasma proteins, thus sensitizing the peripheral terminals of trigeminal nociceptors [74–76]. This cascade of events can also result in enhanced nociceptive transmission into the trigeminal nucleus caudalis and promoting central sensitization of second-order neurons in this brainstem nucleus [71, 72]. Consequently, nociceptive inputs are transmitted to higher brain centers including the thalamus, hypothalamus, and cortical sites, manifesting as migraine pain [62, 71, 72, 77]. Because migraineurs are most vulnerable to develop MOH, and MOH commonly resembles migraine in quality, it is likely that migraine and MOH might share some neural mechanisms. Extrapolation of potential mechanisms of MOH from animal models of migraine-related pain thus seems reasonable.

The application of inflammatory mediators to the dura mater of rodents and the resulting trigeminal sensitization have been used as an animal model of migraine pain [78–80]. Dural inflammation has resulted in electrophysiologic, neurochemical, and behavioral evidence of central sensitization [61, 81, 82]. The development and progression of central sensitization has been shown by the progressive spread of cutaneous allodynia, i.e., enhanced neuronal responses from stimuli applied at cephalic and extracephalic sites [71, 81, 83, 84]. Additionally, dural inflammation was accompanied by enhanced descending facilitation demonstrated by increased discharge of “ON” cells in the rostral ventromedial medulla (RVM). Inactivation of this area with microinjection of local anesthetics abolishes cutaneous allodynia [81]. The generalized spread, and delayed appearance, of cutaneous allodynia implicated a role for central modulation in this preclinical migraine model that is reminiscent of cutaneous allodynia observed in many humans during a migraine attack [61].

Exposure of rats to either opioids or triptans over a period of days produced persistent biochemical changes that appear relevant to promoting a sensitized state of nociceptive transmission [81, 85–88]. During the 7-day period of triptan or opioid infusion, the stimulus required to elicit the orbital and paw withdrawal reflex was shown to decrease gradually, demonstrating cutaneous allodynia that showed a time-dependent reversal toward predrug baseline levels after the infusion was

discontinued. These observations suggested that the pain system can be modulated by acute medication and that it can normalize after detoxification [88]. Following recovery to baseline sensory thresholds, animals with prior triptan treatment have increased sensitivity to provocative triggers including environmental stimuli [88–91]. The persistent hypersensitivity to provocative triggers observed following pretreatment of animals with triptans or opioids was termed "latent sensitization" [88, 92]. Challenge of rats with either opioid or triptan-induced latent sensitization with either bright light stress or a nitric oxide donor was shown to produce a delayed and generalized cutaneous allodynia that is detected in the periorbital region as well as in the hind paw [88, 92]. The delayed and generalized cutaneous allodynia was blocked by inactivation of the RVM with local anesthetics supporting a role of descending pain modulatory systems in promoting central sensitization in this model of MOH, similar to that observed with acute activation of dural nociceptors with inflammatory mediators [80]. Evidence supports a persistent sensitization as these animals previously treated with either triptans or opioids maintain increased sensitivity to human migraine triggers such as stress and nitric oxide donors long after discontinuation of drug administration [88, 92–94].

The mechanisms underlying enhanced sensitivity to innocuous and provocative stimuli are not fully known but may be related to medication-induced adaptations in both primary afferents and central pain transmission pathways. Persistent increased labeling for both CGRP and neuronal NOS (nNOS) in identified dural afferents of the trigeminal ganglia has been observed following pretreatment with either morphine or triptans [90, 92]. Notably, however, the apparent expression of CGRP and nNOS in trigeminal ganglion cells persists long after discontinuation of either opiate or triptan exposure (for at least 2 weeks) and resolution of cutaneous allodynia [88]. These persistent changes in CGRP and nNOS could underlie the sensitization to provocative triggers [90]. Treatment with selective inhibitors of nNOS was demonstrated to be capable of blocking stress-induced cutaneous allodynia [88]. Rats with latent sensitization resulting from either morphine or triptans also showed increased release of CGRP following challenge with provocative triggers [88] consistent with observations during migraine attack in humans [95, 96]; but see [97]. These observations are consistent with provocative studies in migraineurs where nitroglycerin elicits attacks that are indistinguishable from spontaneous migraine that are accompanied by increased blood levels of CGRP [95, 96, 98]. These observations are also consistent with the suggestion that MOH may be associated with a state of central sensitization in afflicted individuals.

Evidence also exists supporting medication-induced changes in cortical excitability. While prophylactic treatments for migraine, such as topiramate and valproate, reduce the frequency of cortical spreading depression (CSD) events [19], sustained exposure to paracetamol has recently been shown to increase the frequency of CSD events induced by cortical potassium chloride as well as c-fos expression in trigeminal nucleus caudalis [99, 100]. Likewise, pretreatment of rats with sumatriptan was shown to significantly decrease the threshold for electrically induced CSD [93]. Topiramate normalized the decreased CSD threshold as well as stress-induced behavioral withdrawal thresholds in sumatriptan-treated rats

compared to saline-treated animals. Additionally, both CSD and environmental stress increased c-fos expression in trigeminal nucleus caudalis (TNC) of sumatriptan- but not saline-treated rats, and these effects were blocked by topiramate. Sumatriptan exposure thus produces long-lasting increased susceptibility to stimuli that could be associated with migraine attack that includes both lowered CSD threshold and enhanced consequences of CSD events (increased activation of TNC) and may represent an underlying biological mechanism of medication overuse headache related to triptans.

Other studies have also implicated medication-induced changes in brain neurotransmitter systems. Exposure to paracetamol and triptans for 15–30 days alters the serotonin system in the rat brain [89, 101–103], and this may also be the case in patients with MOH. In MOH patients, a lower serotonin level than controls and a more rapid uptake in platelets have been reported [104, 105]. Serotonin is important for cortical pain processing and plays a pivotal role in affective disorders that are often found in patients with MOH [31, 35]. A lower endocannabinoid level [23] and a faster degradation of endocannabinoids [106, 107] have been demonstrated in MOH patients with migraine as primary headache. A role of endocannabinoids may be to inhibit transmission from nociceptive afferents [108] suggesting a possible impaired pain inhibition in MOH patients.

14.4 Pain Perception in MOH

Different methods have been used to evaluate pain sensitivity in patients with MOH, generally showing an increase in sensitivity with higher headache frequency [109, 110]. Alterations in pain perception between MOH patients and healthy controls support the presence of a sensitized state in patients with MOH [52, 107, 109, 111, 112]. One study found that patients with MOH are more sensitive to pressure pain than patients with chronic TTH and chronic migraine without medication overuse [109]. Perrotta et al. have demonstrated decreased thresholds for eliciting nociceptive withdrawal reflexes in MOH patients before detoxification compared with healthy volunteers and found that the stimulation needed to elicit these reflexes increased toward baseline after detoxification both after 10 days and after 2 months indicating decreased sensitization after withdrawal [107, 112]. An additional study on pain perception in MOH patients showed that the intensity of pressure pain above the pain threshold continued to decrease during the first year after detoxification [113].

Preclinical evidence suggests that enhanced pain perception of migraineurs could be linked to alterations in descending pain modulatory mechanisms. In rats with opiate- or triptan-induced latent sensitization, inactivation of the RVM with local anesthetics blocks cutaneous allodynia associated with provocative stimuli [88, 90, 92]. An impairment of the diffuse noxious inhibitory controls (i.e., “DNIC”) known in humans as conditioned pain modulation (CPM) has also been noted [114]. The loss of DNIC is consistent with many clinical observations made with patients

with functional pain conditions, including migraine [115, 116], TTH [115, 117], and MOH [112]. Patients with MOH show heightened sensitivity to electrically evoked reflexes, accompanied by increased pain rating and diminished CPM [112]. Studies with rodents showed that persistent morphine exposure reduced the activation threshold of TNC neurons while expanding their receptive fields, indicating the presence of central sensitization [91]. In control animals, activation of these neurons by application of stimuli to their receptive fields in the ophthalmic region was inhibited by placing the tail of control rats in hot water, demonstrating the DNIC response [91]. In contrast, the DNIC response was lost in animals treated with morphine [91]. Importantly, the apparent loss of DNIC in animals treated with morphine could be reinstated by inactivation of the RVM [91]. This suggests that enhanced descending facilitation could present as a loss of inhibition. Distinguishing loss of inhibition from enhanced facilitation has been difficult to dissect in humans. Collectively, however, such studies suggest that an abnormality of pain modulatory circuits results in a net loss of inhibition, possibly due to decreased inhibition or increased facilitation or both, and this loss is likely to be important in the development of MOH.

The possibility of dysfunction of descending pain modulatory pathways as contributing factors to MOH is also supported by imaging studies. In patients with MOH and migraine as the primary headache, changes in both cortical and midbrain pain-related areas have been observed [118–121]. One study using functional magnetic resonance imaging (fMRI) found reduced activity in the right supramarginal gyrus and in the superior and inferior parietal cortex, which normalized 6 months after detoxification [118], implying a reversible change in the pain system caused by the medication overuse. Another study showed increased gray matter volume in the periaqueductal gray (PAG), a structure highly important in the descending pain response, and reduced gray matter volume in several cortical pain-related structures in migraine patients with MOH [121]. In patients with a significant reduction in headache frequency after treatment, the PAG returned to normal [121].

14.5 Future Perspectives

The mechanisms that underlie MOH are just beginning to be uncovered. Future work may begin to explore mechanisms behind MOH with TTH as the underlying headache; TTH is the most common primary headache type and is an important target for future studies. The development of central sensitization in MOH and the differences in MOH patients according to the effect of detoxification could be a target for future studies assessing pain perception. Work from animal models showing increased effectiveness of headache triggers following induction of latent sensitization [94] has yet to determine numerous variables of relevance to patients. It remains unknown whether sensitization is completely reversible, whether the threshold for developing MOH after withdrawal of medication is decreased, and if the critical frequency of medication intake could be reduced. This is supported by

the high relapse rate in MOH patients after treatment. Future clinical strategies of MOH prevention should take these into account. Treatment with onabotulinumtoxinA has proven superior to placebo in reducing headache frequency in a post hoc subgroup analysis on patients with MOH [122]. The mechanisms behind the effect on chronic migraine with and without MOH are still unknown and should be target for further investigation as the use of onabotulinumtoxinA for chronic migraine with MOH is increasing. The development in brain imaging will undoubtedly be valuable for further assessing alterations in pain-processing structures in MOH patients and the possible changes from before to after withdrawal. Research in the pathophysiology behind chronic migraine and TTH without medication overuse will aid the investigation into the relationship and differences between chronic headache with and without medication overuse.

Acknowledgements The authors gratefully acknowledge the assistance and helpful suggestions of Drs. Michael Ossipov, Jennifer Xie (University of Arizona), and Ian Meng (University of New England) in the preparation of the manuscript as well as the support of NIH (NS069572).

References

1. Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M et al (2012) Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 380(9859):2163–2196
2. Steiner TJ, Stovner LJ, Birbeck GL (2013) Migraine: the seventh disabler. Headache J Head Face Pain 53(2):227–229
3. Andlin-Sobocki P, Jonsson B, Wittchen HU, Olesen J (2005) Cost of disorders of the brain in Europe. Eur J Neurol 12(Suppl 1):1–27
4. Goadsby PJ (2009) Pathophysiology of migraine. Neurol Clin 27(2):335–360
5. Burden WHOaLT (2011) Atlas of headache disorders and resources in the world 2011. WHO, Geneva
6. Hoffmann J, Goadsby PJ (2014) Emerging targets in migraine. CNS Drugs 28(1):11–17
7. Dodick DW, Silberstein S, Dahlof CG (2002) Is there a preferred triptan? Headache 42(1):1–7
8. Goadsby PJ, Sprenger T (2010) Current practice and future directions in the prevention and acute management of migraine. Lancet Neurol 9(3):285–298
9. Ghiotto N, Sances G, Galli F, Tassorelli C, Guaschino E, Sandrini G et al (2009) Medication overuse headache and applicability of the ICHD-II diagnostic criteria: 1-year follow-up study (CARE I protocol). Cephalalgia 29(2):233–243
10. Olesen J, Bousser MG, Diener HC, Dodick D, First M, Goadsby PJ et al (2006) New appendix criteria open for a broader concept of chronic migraine. Cephalalgia 26(6):742–746
11. Isler H (1982) Migraine treatment as a cause of chronic migraine. In: Rose FC (ed) Advances in migraine research and therapy. Raven, New York, pp 159–164
12. Schofferman J (1993) Long-term use of opioid analgesics for the treatment of chronic pain of nonmalignant origin. J Pain Symptom Manage 8(5):279–288
13. Katsarava Z, Fritsche G, Muessig M, Diener HC, Limmroth V (2001) Clinical features of withdrawal headache following overuse of triptans and other headache drugs. Neurology 57(9):1694–1698
14. Rapoport A, Stang P, Gutterman DL, Cady R, Markley H, Weeks R et al (1996) Analgesic rebound headache in clinical practice: data from a physician survey. Headache 36(1):14–19

15. Dodick D, Silberstein S (2006) Central sensitization theory of migraine: clinical implications. Headache 46(Suppl 4):S182–S191
16. Dodick DW (2006) Clinical practice. Chronic daily headache. N Engl J Med 354(2):158–165
17. Katsarava Z, Manack A, Yoon M-S, Obermann M, Becker H, Dommes P et al (2011) Chronic migraine: classification and comparisons. Cephalalgia 31(5):520–529
18. Galletti F, Cupini LM, Corbelli I, Calabresi P, Sarchielli P (2009) Pathophysiological basis of migraine prophylaxis. Prog Neurobiol 89(2):176–192
19. Ayata C, Jin H, Kudo C, Dalkara T, Moskowitz MA (2006) Suppression of cortical spreading depression in migraine prophylaxis. Ann Neurol 59(4):652–661
20. Ayata C (2009) Spreading depression: from serendipity to targeted therapy in migraine prophylaxis. Cephalalgia 29(10):1095–1114
21. Dodick DW (2009) Tonabersat for migraine prevention: new life or last gasp? Lancet Neurol 8(8):693–695
22. Grande RB, Aaseth K, Saltyte Benth J, Gulbrandsen P, Russell MB, Lundqvist C (2009) The Severity of Dependence Scale detects people with medication overuse: the Akershus study of chronic headache. J Neurol Neurosurg Psychiatry 80(7):784–789
23. Rossi C, Pini LA, Cupini ML, Calabresi P, Sarchielli P (2008) Endocannabinoids in platelets of chronic migraine patients and medication-overuse headache patients: relation with serotonin levels. Eur J Clin Pharmacol 64(1):1–8
24. Silberstein SD, Liu D (2002) Drug overuse and rebound headache. Curr Pain Headache Rep 6(3):240–247
25. Colas R, Munoz P, Temprano R, Gomez C, Pascual J (2004) Chronic daily headache with analgesic overuse: epidemiology and impact on quality of life. Neurology 62(8): 1338–1342
26. Dyb G, Holmen TL, Zwart JA (2006) Analgesic overuse among adolescents with headache: the Head-HUNT-Youth Study. Neurology 66(2):198–201
27. Zwart JA, Dyb G, Hagen K, Svebak S, Stovner LJ, Holmen J (2004) Analgesic overuse among subjects with headache, neck, and low-back pain. Neurology 62(9):1540–1544
28. Castillo J, Munoz P, Guitera V, Pascual J (1999) Kaplan Award 1998. Epidemiology of chronic daily headache in the general population. Headache 39(3):190–196
29. Chakravarty A (2003) Chronic daily headaches: clinical profile in Indian patients. Cephalalgia 23(5):348–353
30. Williams L, O'Connell K, Tubridy N (2008) Headaches in a rheumatology clinic: when one pain leads to another. Eur J Neurol 15(3):274–277
31. Hagen K, Linde M, Steiner TJ, Stovner LJ, Zwart JA (2012) Risk factors for medication-overuse headache: an 11-year follow-up study. The Nord-Trondelag Health Studies. Pain 153(1):56–61
32. Jonsson P, Linde M, Hensing G, Hedenrud T (2012) Sociodemographic differences in medication use, health-care contacts and sickness absence among individuals with medication-overuse headache. J Headache Pain 13(4):281–290
33. Evers S, Marziniak M (2010) Clinical features, pathophysiology, and treatment of medication-overuse headache. Lancet Neurol 9(4):391–401
34. Diener HC, Silberstein SD (2006) Medication overuse headaches. Lippincott Williams & Wilkins, Philadelphia
35. Atasoy HT, Atasoy N, Unal AE, Emre U, Sumer M (2005) Psychiatric comorbidity in medication overuse headache patients with pre-existing headache type of episodic tension-type headache. Eur J Pain 9(3):285–291
36. da Silva A, Costa EC, Gomes JB, Leite FM, Gomez RS, Vasconcelos LP et al (2010) Chronic headache and comorbidities: a two-phase, population-based. Cross-Sectional Study. Headache 50(8):1306–1312
37. Zebenholzer K, Thamer M, Wober C (2012) Quality of life, depression, and anxiety 6 months after inpatient withdrawal in patients with medication overuse headache an observational study. Clin J Pain 28(4):284–290

38. Lucas C, Lanteri-Minet M, Massiou H, Radat F, Pradalier A, Nachit-Ouinekh F, El HA (2007) Medical and psychological characteristics of patients with chronic daily migrainous features: compared with migraineurs in the general French population. GRIM 3 survey. In: Jensen R, Diener HC, Olesen J (eds) Headache clinics – organization, patients and treatment. Oxford University Press, London
39. Diener HC, Dodick DW, Goadsby PJ, Lipton RB, Olesen J, Silberstein SD (2012) Chronic migraine – classification, characteristics and treatment. Nat Rev Neurol 8(3):162–171
40. Ashina S, Lyngberg A, Jensen R (2010) Headache characteristics and chronification of migraine and tension-type headache: a population-based study. Cephalalgia 30(8):943–954
41. Bigal ME, Lipton RB (2009) The epidemiology, burden, and comorbidities of migraine. Neurol Clin 27(2):321–334
42. Bigal ME, Lipton RB, Holland PR, Goadsby PJ (2007) Obesity, migraine, and chronic migraine: possible mechanisms of interaction. Neurology 68(21):1851–1861
43. Zwart JA, Dyb G, Hagen K, Svebak S, Holmen J (2003) Analgesic use: a predictor of chronic pain and medication overuse headache: the Head-HUNT Study. Neurology 61(2):160–164
44. Bigal ME, Lipton RB (2008) Excessive acute migraine medication use and migraine progression. Neurology 71(22):1821–1828
45. Diamond S, Bigal ME, Silberstein S, Loder E, Reed M, Lipton RB (2007) Patterns of diagnosis and acute and preventive treatment for migraine in the United States: results from the American Migraine Prevalence and Prevention study. Headache 47(3):355–363
46. Bahra A, Walsh M, Menon S, Goadsby PJ (2003) Does chronic daily headache arise de novo in association with regular use of analgesics? Headache 43(3):179–190
47. Bigal ME, Lipton RB (2008) Clinical course in migraine: conceptualizing migraine transformation. Neurology 71(11):848–855
48. Paemeleire K, Bahra A, Evers S, Matharu MS, Goadsby PJ (2006) Medication-overuse headache in patients with cluster headache. Neurology 67(1):109–113
49. Scher AI, Stewart WF, Liberman J, Lipton RB (1998) Prevalence of frequent headache in a population sample. Headache 38(7):497–506
50. Wilkinson SM, Becker WJ, Heine JA (2001) Opiate use to control bowel motility may induce chronic daily headache in patients with migraine. Headache 41(3):303–309
51. Limmroth V, Katsarava Z, Fritsche G, Przywara S, Diener HC (2002) Features of medication overuse headache following overuse of different acute headache drugs. Neurology 59(7): 1011–1014
52. Coppola G, Curra A, Di Lorenzo C, Parisi V, Gorini M, Sava SL et al (2010) Abnormal cortical responses to somatosensory stimulation in medication-overuse headache. BMC Neurol 10:126
53. Fumal A, Laureys S, Di Clemente L, Boly M, Bohotin V, Vandenheede M et al (2006) Orbitofrontal cortex involvement in chronic analgesic-overuse headache evolving from episodic migraine. Brain J Neurol 129(Pt 2):543–550
54. Curra A, Coppola G, Gorini M, Porretta E, Bracaglia M, Di Lorenzo C et al (2011) Drug-induced changes in cortical inhibition in medication overuse headache. Cephalalgia Int J Headache 31(12):1282–1290
55. Calabresi P, Cupini LM (2005) Medication-overuse headache: similarities with drug addiction. Trends Pharmacol Sci 26(2):62–68
56. Fuh JL, Wang SJ, Lu SR, Juang KD (2005) Does medication overuse headache represent a behavior of dependence? Pain 119(1–3):49–55
57. Radat F, Creac'h C, Guegan-Massardier E, Mick G, Guy N, Fabre N et al (2008) Behavioral dependence in patients with medication overuse headache: a cross-sectional study in consulting patients using the DSM-IV criteria. Headache 48(7):1026–1036
58. Lundqvist C, Grande RB, Aaseth K, Russell MB (2012) Dependence scores predict prognosis of medication overuse headache: a prospective cohort from the Akershus study of chronic headache. Pain 153(3):682–686
59. Corbelli I, Caproni S, Eusebi P, Sarchielli P (2012) Drug-dependence behaviour and outcome of medication-overuse headache after treatment. J Headache Pain 13(8):653–660

60. Radat F, Lanteri-Minet M, Nachit-Ouinekh F, Massiou H, Lucas C, Pradalier A et al (2009) The GRIM2005 study of migraine consultation in France. III: psychological features of subjects with migraine. Cephalalgia 29(3):338–350
61. Burstein R (2001) Deconstructing migraine headache into peripheral and central sensitization. Pain 89(2–3):107–110
62. Burstein R, Collins B, Jakubowski M (2004) Defeating migraine pain with triptans: a race against the development of cutaneous allodynia. Ann Neurol 55(1):19–26
63. Burstein R, Cutrer MF, Yarnitsky D (2000) The development of cutaneous allodynia during a migraine attack clinical evidence for the sequential recruitment of spinal and supraspinal nociceptive neurons in migraine. Brain 123(Pt 8):1703–1709
64. Charles A (2013) The evolution of a migraine attack – a review of recent evidence. Headache 53(2):413–419
65. Bigal ME, Ashina S, Burstein R, Reed ML, Buse D, Serrano D et al (2008) Prevalence and characteristics of allodynia in headache sufferers: a population study. Neurology 70(17):1525–1533
66. Lipton RB, Bigal ME (2008) Toward an epidemiology of refractory migraine: current knowledge and issues for future research. Headache 48(6):791–798
67. Bigal ME, Ferrari M, Silberstein SD, Lipton RB, Goadsby PJ (2009) Migraine in the triptan era: lessons from epidemiology, pathophysiology, and clinical science. Headache 49(Suppl 1):S21–S33
68. Akerman S, Holland PR, Goadsby PJ (2011) Diencephalic and brainstem mechanisms in migraine. Nat Rev Neurosci 12(10):570–584
69. Dussor G, Yan J, Xie JY, Ossipov MH, Dodick DW, Porreca F (2014) Targeting TRP channels for novel migraine therapeutics. ACS Chem Neurosci 5(11):1085–1096
70. Moulton EA, Burstein R, Tully S, Hargreaves R, Becerra L, Borsook D (2008) Interictal dysfunction of a brainstem descending modulatory center in migraine patients. PLoS One 3(11):e3799
71. Noseda R, Burstein R (2013) Migraine pathophysiology: anatomy of the trigeminovascular pathway and associated neurological symptoms, cortical spreading depression, sensitization, and modulation of pain. Pain 154(Suppl 1):S44–S53
72. Bernstein C, Burstein R (2012) Sensitization of the trigeminovascular pathway: perspective and implications to migraine pathophysiology. J Clin Neurol 8(2):89–99
73. Wolff HG (1948) Headache and other head pain. Oxford University Press, London
74. Goadsby PJ, Charbit AR, Andreou AP, Akerman S, Holland PR (2009) Neurobiology of migraine. Neuroscience 161(2):327–341
75. Levy D, Burstein R, Strassman AM (2006) Mast cell involvement in the pathophysiology of migraine headache: a hypothesis. Headache 46(Suppl 1):S13–S18
76. Goadsby PJ, Edvinsson L (1993) The trigeminovascular system and migraine: studies characterizing cerebrovascular and neuropeptide changes seen in humans and cats. Ann Neurol 33(1):48–56
77. Noseda R, Jakubowski M, Kainz V, Borsook D, Burstein R (2011) Cortical projections of functionally identified thalamic trigeminovascular neurons: implications for migraine headache and its associated symptoms. J Neurosci 31(40):14204–14217
78. Burstein R, Jakubowski M (2004) Analgesic triptan action in an animal model of intracranial pain: a race against the development of central sensitization. Ann Neurol 55(1):27–36
79. De Felice M, Eyde N, Dodick D, Dussor GO, Ossipov MH, Fields HL et al (2013) Capturing the aversive state of cephalic pain preclinically. Ann Neurol 74(2):257–265
80. Edelmayer RM, Ossipov MH, Porreca F (2012) An experimental model of headache-related pain. In: Luo ZD (ed) Methods in molecular biology. Pain research methods and protocols. Springer, New York, pp 109–120. 851. 2012/02/22 ed
81. Edelmayer RM, Vanderah TW, Majuta L, Zhang ET, Fioravanti B, De Felice M et al (2009) Medullary pain facilitating neurons mediate allodynia in headache-related pain. Ann Neurol 65(2):184–193
82. Oshinsky ML, Gomonchareonsiri S (2007) Episodic dural stimulation in awake rats: a model for recurrent headache. Headache 47(7):1026–1036

83. Burstein R, Yamamura H, Malick A, Strassman AM (1998) Chemical stimulation of the intracranial dura induces enhanced responses to facial stimulation in brain stem trigeminal neurons. J Neurophysiol 79(2):964–982
84. Yamamura H, Malick A, Chamberlin NL, Burstein R (1999) Cardiovascular and neuronal responses to head stimulation reflect central sensitization and cutaneous allodynia in a rat model of migraine. J Neurophysiol 81(2):479–493
85. Woolf CJ (1981) Intrathecal high dose morphine produces hyperalgesia in the rat. Brain Res 209(2):491–495
86. Vanderah TW, Suenaga NM, Ossipov MH, Malan TP Jr, Lai J, Porreca F (2001) Tonic descending facilitation from the rostral ventromedial medulla mediates opioid-induced abnormal pain and antinociceptive tolerance. J Neurosci 21(1):279–286
87. Xie JY, Herman DS, Stiller CO, Gardell LR, Ossipov MH, Lai J et al (2005) Cholecystokinin in the rostral ventromedial medulla mediates opioid-induced hyperalgesia and antinociceptive tolerance. J Neurosci 25(2):409–416
88. De Felice M, Ossipov MH, Wang R, Lai J, Chichorro J, Meng I et al (2010) Triptan-induced latent sensitization: a possible basis for medication overuse headache. Ann Neurol 67(3):325–337
89. Srikiatkhachorn A, Tarasub N, Govitrapong P (2000) Effect of chronic analgesic exposure on the central serotonin system: a possible mechanism of analgesic abuse headache. Headache 40(5):343–350
90. De Felice M, Porreca F (2009) Opiate-induced persistent pronociceptive trigeminal neural adaptations: potential relevance to opiate-induced medication overuse headache. Cephalalgia 29(12):1277–1284
91. Okada-Ogawa A, Porreca F, Meng ID (2009) Sustained morphine-induced sensitization and loss of diffuse noxious inhibitory controls in dura-sensitive medullary dorsal horn neurons. J Neurosci 29(50):15828–15835
92. De Felice M, Ossipov MH, Wang R, Dussor G, Lai J, Meng ID et al (2010) Triptan-induced enhancement of neuronal nitric oxide synthase in trigeminal ganglion dural afferents underlies increased responsiveness to potential migraine triggers. Brain J Neurol 133(Pt 8): 2475–2488
93. Green AL, Gu P, De Felice M, Dodick D, Ossipov MH, Porreca F (2013) Increased susceptibility to cortical spreading depression in an animal model of medication-overuse headache. Cephalalgia Int J Headache 34(8):594–604
94. De Felice M, Ossipov MH, Porreca F (2011) Persistent medication-induced neural adaptations, descending facilitation, and medication overuse headache. Curr Opin Neurol 24(3):193–196
95. Goadsby PJ, Edvinsson L, Ekman R (1990) Vasoactive peptide release in the extracerebral circulation of humans during migraine headache. Ann Neurol 28(2):183–187
96. Juhasz G, Zsombok T, Modos EA, Olajos S, Jakab B, Nemeth J et al (2003) NO-induced migraine attack: strong increase in plasma calcitonin gene-related peptide (CGRP) concentration and negative correlation with platelet serotonin release. Pain 106(3):461–470
97. Tvedskov JF, Lipka K, Ashina M, Iversen HK, Schifter S, Olesen J (2005) No increase of calcitonin gene-related peptide in jugular blood during migraine. Ann Neurol 58(4):561–568
98. Sarchielli P, Alberti A, Codini M, Floridi A, Gallai V (2000) Nitric oxide metabolites, prostaglandins and trigeminal vasoactive peptides in internal jugular vein blood during spontaneous migraine attacks. Cephalalgia 20(10):907–918
99. Ayata C, Moskowitz MA (2006) Cortical spreading depression confounds concentration-dependent pial arteriolar dilation during N-methyl-D-aspartate superfusion. Am J Physiol Heart Circ Physiol 290(5):H1837–H1841
100. Supornsilpchai W, le Grand SM, Srikiatkhachorn A (2010) Cortical hyperexcitability and mechanism of medication-overuse headache. Cephalalgia Int J Headache 30(9):1101–1109

101. Supornsilpchai W, le Grand SM, Srikiatkhachorn A (2010) Involvement of pro-nociceptive 5-HT2A receptor in the pathogenesis of medication-overuse headache. Headache 50(2):185–197
102. Dobson CF, Tohyama Y, Diksic M, Hamel E (2004) Effects of acute or chronic administration of anti-migraine drugs sumatriptan and zolmitriptan on serotonin synthesis in the rat brain. Cephalalgia Int J Headache 24(1):2–11
103. Reuter U, Salomone S, Ickenstein GW, Waeber C (2004) Effects of chronic sumatriptan and zolmitriptan treatment on 5-HT receptor expression and function in rats. Cephalalgia Int J Headache 24(5):398–407
104. Ayzenberg I, Obermann M, Leineweber K, Franke L, Yoon MS, Diener HC et al (2008) Increased activity of serotonin uptake in platelets in medication overuse headache following regular intake of analgesics and triptans. J Headache Pain 9(2):109–112
105. Srikiatkhachorn A, Anthony M (1996) Platelet serotonin in patients with analgesic-induced headache. Cephalalgia Int J Headache 16(6):423–426
106. Cupini LM, Costa C, Sarchielli P, Bari M, Battista N, Eusebi P et al (2008) Degradation of endocannabinoids in chronic migraine and medication overuse headache. Neurobiol Dis 30(2):186–189
107. Perrotta A, Arce-Leal N, Tassorelli C, Gasperi V, Sances G, Blandini F et al (2012) Acute reduction of anandamide-hydrolase (FAAH) activity is coupled with a reduction of nociceptive pathways facilitation in medication-overuse headache subjects after withdrawal treatment. Headache 52(9):1350–1361
108. Akerman S, Holland PR, Goadsby PJ (2007) Cannabinoid (CB1) receptor activation inhibits trigeminovascular neurons. J Pharmacol Exp Ther 320(1):64–71
109. Zappaterra M, Guerzoni S, Cainazzo MM, Ferrari A, Pini LA (2011) Basal cutaneous pain threshold in headache patients. J Headache Pain 12(3):303–310
110. Buchgreitz L, Lyngberg AC, Bendtsen L, Jensen R (2006) Frequency of headache is related to sensitization: a population study. Pain 123(1–2):19–27
111. Ayzenberg I, Obermann M, Nyhuis P, Gastpar M, Limmroth V, Diener HC et al (2006) Central sensitization of the trigeminal and somatic nociceptive systems in medication overuse headache mainly involves cerebral supraspinal structures. Cephalalgia 26(9):1106–1114
112. Perrotta A, Serrao M, Sandrini G, Burstein R, Sances G, Rossi P et al (2010) Sensitisation of spinal cord pain processing in medication overuse headache involves supraspinal pain control. Cephalalgia Int J Headache 30(3):272–284
113. Munksgaard SB, Bendtsen L, Jensen RH (2013) Modulation of central sensitisation by detoxification in MOH: results of a 12-month detoxification study. Cephalalgia Int J Headache 33(7):444–453
114. Yarnitsky D, Granot M, Granovsky Y (2014) Pain modulation profile and pain therapy: between pro- and antinociception. Pain 155(4):663–665
115. Cathcart S, Petkov J, Winefield AH, Lushington K, Rolan P (2010) Central mechanisms of stress-induced headache. Cephalalgia 30(3):285–295
116. de Tommaso M, Difruscolo O, Sardaro M, Libro G, Pecoraro C, Serpino C et al (2007) Effects of remote cutaneous pain on trigeminal laser-evoked potentials in migraine patients. J Headache Pain 8(3):167–174
117. Sandrini G, Tassorelli C, Ghiotto N, Nappi G (2006) Uncommon primary headaches. Curr Opin Neurol 19(3):299–304
118. Grazzi L, Chiapparini L, Ferraro S, Usai S, Andrasik F, Mandelli ML et al (2010) Chronic migraine with medication overuse pre-post withdrawal of symptomatic medication: clinical results and FMRI correlations. Headache 50(6):998–1004
119. Ferraro S, Grazzi L, Mandelli ML, Aquino D, Di Fiore D, Usai S et al (2012) Pain processing in medication overuse headache: a functional magnetic resonance imaging (fMRI) study. Pain Med 13(2):255–262

120. Chiapparini L, Grazzi L, Ferraro S, Mandelli ML, Usai S, Andrasik F et al (2009) Functional-MRI evaluation of pain processing in chronic migraine with medication overuse. Neurol Sci 30(Suppl 1):S71–S74
121. Riederer F, Marti M, Luechinger R, Lanzenberger R, von Meyenburg J, Gantenbein AR et al (2012) Grey matter changes associated with medication-overuse headache: correlations with disease related disability and anxiety. World J Biol Psychiatry 13(7):517–525
122. Silberstein SD, Blumenfeld AM, Cady RK, Turner IM, Lipton RB, Diener HC, Aurora SK, Sirimanne M, DeGryse RE, Turkel CC, Dodick DW (2013) OnabotulinumtoxinA for treatment of chronic migraine: PREEMPT 24-week pooled subgroup analysis of patients who had acute headache medication overuse at baseline. J Neurol Sci 31(1–2):48–56