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EXPERT REVIEWS

Hypnic headache and caffeine

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Hypnic headache (HH) is a rare primary headache disorder primarily affecting patients over the age of 50 years. This headache entity occurs exclusively at night almost always at the same time. Imaging data as well as the strict circadian rhythm of headache attacks suggest a hypothalamic involvement in the underlying pathophysiology of this headache disorder. One interesting clinical feature about HH is its therapeutic response to caffeine as an acute as well as prophylactic agent. This review addresses the efficacy of caffeine in HH as well as in other headache disorders, and attempts to give insight into the analgesic properties of this substance. In addition, it depicts possible problems of caffeine consumption with regard to headache.

Keywords: adenosine • caffeine • caffeine withdrawal • hypnic headache • hypothalamus • medication overuse headache • migraine • postdural puncture headache • REM sleep • tension-type headache

Hypnic headache (HH) is an uncommon primary headache disorder that tends to only affect patients older than 50 years of age. However, single case reports also describe HH also in younger patients and even in children [1]. Patients usually wake up with a holocranial headache on more than 15 nights per month. Usually the headache lasts more than 15 min. As the headache often occurs at the same time at night, this headache entity is also referred to as an 'alarm clock headache'. In addition, HH attacks can also arise from day-time naps. More women than men are affected by this disease. Moderate migraneous features such as nausea or phono- or photo-phobia might accompany the pain, and trigeminal autonomic symptoms such as lacrimation or rhinorrhea are missing in most cases [2]. In contrast to migraineurs, HH patients report that they get out of bed when they awake with headache and perform some motor activity [3]. Some patients take a shower, some eat, some read and some go for a walk. However, HH patients do not present with the kind of restlessness that can be observed in cluster headache patients (**Box 1**).

The underlying pathophysiology of HH is still mysterious. The circadian rhythmicity of headache attacks is the most striking pathognomonic feature in HH, and it is thought to reflect possible hypothalamic involvement. Initially, some authors suggested HH to be a rapid eye movement (REM) sleep disorder, but previously non-REM (NREM) sleep-associated HH attacks have been also described [4,5]. Other authors have suggested that obstructive sleep apnea or nocturnal high blood pressure might cause HH, but these cases should be rather considered as secondary causes. HH can also occur secondary due to intracranial lesions [6–8] or ischemic stroke in the midrostral upper pons [9].

Controlled clinical trials investigating the efficacy of different treatment options are currently unavailable. One typical feature of HH is that caffeine is often helpful to relieve pain as an acute acting agent and also prevents pain due to its prophylactic properties when consumed at night before going to bed.

A significant connection between headache disorders and caffeine is quite well known. Caffeine-containing mixed analgesics are widely used in several headache disorders and are often effective. Chronic caffeine intake can induce withdrawal headache after discontinuation, and overconsumption can also induce a headache itself.

Possible mechanisms of caffeine in pain regulation

Caffeine is probably the most frequently consumed psychoactive compound around the world. For example, regular coffee contains up to 200 mg per serving, brewed tea up to 120 mg and cola up to 70 mg. Caffeine is an antagonist of adenosine A_1, A_{2A} and A_{2B} receptors [10], which are localized at multiple sites such as the spinal cord, the thalamus and other supraspinal sites [11]. Its analgesic properties seem to be mainly based on interaction with these receptors [12]. In higher concentrations, which normally cannot be reached through normal dietary intake, further pharmacological actions can be triggered such as inhibition of phosphodiesterase, Ca^{2+} release and block of $GABA_A$ receptors [10].

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Box 1. Diagnostic criteria of hypnic headache according to the criteria of the International Headache Society classification.

- **A** Dull headache fulfilling criteria B–D
- **B** Develops only during sleep, and awakens patient
- **C** At least two of the following characteristics:
  - Occurs >15 times per month
  - Lasts ≥15 min after waking
  - First occurs after the age of 50 years
- **D** No autonomic symptoms and no more than one of nausea, photophobia or phonophobia
- **E** Not attributed to another disorder

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Intrinsic analgesic effects & interactions of caffeine

Most data on the intrinsic analgesic effects of caffeine result from preclinical data and animal experiments. Antinociceptive effects are generally observed at doses between 35 and 100 mg/kg [13]. Interestingly, some studies even reported hyperalgesia in these low systemic doses [14], potentially based on inhibition of spinal adenosine A_1 receptors as A_1 receptors do not seem to be involved in the antinociceptive effects of caffeine. In contrast, the antinociceptive properties of caffeine result mainly from its interaction with the adenosine A_{2A} and A_{2B} receptors, especially on peripheral action sites. Due to adenosine A_1 receptor antagonism, low doses of caffeine are able to inhibit the analgesic effects of several analgesics such as acetaminophen [14,15], amitriptyline [16–19], carbamazepine and oxcarbazepine [20,21], as well as venlafaxine [18]. These studies raise the question of whether caffeine influences the effectiveness of analgesic drugs.

Adjuvant analgesic effects of caffeine

Moderate doses of caffeine (10–35 mg/kg) lead to an augmentation of the analgesic effect of pain killers such as acetaminophen [22,23] and several nonsteroidal anti-inflammatory drugs [22,24–28]. Several different mechanisms have been proposed to be responsible for these adjuvant analgesic effects of caffeine. One study investigated the inhibitory effects of acetaminophen and caffeine on lipopolysaccharide-induced cyclooxygenase (COX) and prostaglandin E2 synthesis in primary rat microglial cells [29]. Acetaminophen and caffeine led to a dose-dependent inhibition of prostaglandin E2 synthesis as well as an inhibition of COX enzyme activity. Interestingly, caffeine also induced an inhibition of COX-2 protein synthesis. Adjuvant analgesic effects were observed when adding acetylsalicylic acid, salicylic acid and dipyrone. Different authors suggest the central amine system to be involved in the adjuvant analgesic effect of caffeine [29]. Locomotor activity of rats was investigated in hot-plate and formaline tests after systemic administration of caffeine to investigate the mode of action of this compound. In both tests a dose-related antinociception was observed. Anti-inflammatory action was not detected. Application of naloxone did not influence the effect of caffeine, which implies little or no involvement of endogenous opioids at the caffeine site of action. Phentolamine, prazosin and idazoxan enhanced the analgesic effect of caffeine, although each substance augmented different parts of the caffeine effect. The authors concluded that α-adrenergic receptors could be involved in the action of caffeine.

At moderate doses, results regarding the adjuvant effect of caffeine for the analgesic properties of morphine are diverse. Some authors describe an augmentation of opioid effectiveness [30], whereas some authors detected an inhibition [31,32]. Higher doses of caffeine (75–100 mg/kg) lead to an augmentation of opioid effectiveness, despite their own intrinsic properties [31,33].

Possible mechanisms of caffeine in sleep regulation

Caffeine as an antagonist of adenosine is known to have a major influence on sleep from daily experience. Adenosine is a purine nucleoside that is localized in all cells [34]. It is a key signalling molecule for sleep induction [35] and interacts mainly with the cerebral adenosine A_{2A} receptor. The adenosine A_{2A} receptors are present in high concentrations in the striatum, nucleus accumbens and olfactory bulb [36]. Animal experiments have shown that application of adenosine A_{2A} receptor agonists to the subarachnoidal space can induce NREM sleep [37–40]. Huang *et al.* investigated the promotion of wakefulness after caffeine application in mice [35]. Caffeine-induced wakefulness was observed in wild-type mice as well as in adenosine A_1 receptor knockout mice. No effect was observed in adenosine A_{2A} knockout mice, supporting the crucial role of this type of receptor in sleep regulation [41]. The caffeine-induced wakefulness appears, therefore, to strongly depend on its adenosine A_{2A} receptor antagonism.

Caffeine in the treatment of hypnic headache

Until now, approximately 200 HH cases have been reported in the literature. Due to the rareness of this disease, treatment recommendations are mainly based on expert opinion and small case series, as randomized placebo-controlled clinical trials have not yet been carried out. Almost all patients report that drinking a cup of strong black coffee in case of pain is effective in treating acute HH attacks at night. Drinking a cup of coffee before going to sleep is also effective in preventing HH attacks. In our own German HH cohort, 11 out of 14 patients reported caffeine to be an effective treatment option [3], which made it the most effective acute treatment option compared with all other reported treatment attempts. However, the efficacy rates reported in the literature are quite diverse. Many cases seem to have a very good treatment response with caffeine, but in some cases no relevant pain relief was reported. Many patients are afraid that this treatment might lead to the disruption of their natural sleep pattern, especially because many older patients are affected by insomnia anyway. However, caffeine-induced sleep problems are only described in a few patients [42,43]. Caffeine-containing analgesics seem to be effective in HH as well. Typically, patients report that caffeine-containing

analgesics (e.g., paracetamol/acetaminophen and caffeine) lead to substantial pain relief during an acute HH attack, whereas analgesics alone have shown no influence on the headache. In our own German cohort, caffeine-containing analgesics were effective in five out of nine patients [3]. However, mixed analgesics run the risk of the development of medication overuse headache (MOH). As many HH patients suffer from HH attacks almost every day, total doses of combination drugs may easily exceed the crucial amount. In addition, the analgesic compound used has been associated with further side effects (e.g., acetylsalicylic acid associated with: gastrointestinal bleeding), and contraindications other than caffeine treatment alone might apply. Therefore, intake of mixed analgesics should be avoided and intake of caffeine alone is recommended.

Interestingly, most patients discovered caffeine as an effective treatment option on their own before they were diagnosed with HH. Dramatic treatment response to caffeine seems to be a pathognomonic clinical feature of HH that may help clinicians to correctly diagnose this rare headache disorder.

Caffeine should always be considered as a first-line therapy, as it is effective in many patients and is associated with no major side effects and no relevant contraindications.

Other treatment options in hypnic headache

Due to the low prevalence of HH randomized placebo-controlled clinical trials, date on the efficacy of distinct drug treatments are still missing. Therefore, only class IV evidence is available, mainly based on experts' opinion and clinical experience [44]. Similar to caffeine treatment, acute and prophylactic treatment regimens should also be distinguished.

Acute treatment options

Medication is considered as an acute treatment when taken in case of headache, relieving the pain rapidly. Before starting a medication, headache frequency needs to be evaluated. Some treatment options may be effective but may also be accompanied by major side effects when taken every day.

Triptans, especially in combination with caffeine, has been described as effective in some HH patients [42]. In our own German cohort, only four patients tried triptans as an acute medication, and it was effective in all of them [3]. In contrast, the majority of case reports and case studies in the current literature found a rather small efficacy rate of triptans [45–50]. As the duration of the headache is often short, a fast-acting agent (such as nasal spray or an orally disintegrating tablet) might be preferred, even though subcutaneous sumatriptan has not been effective in HH treatment [43]. To avoid side effects, no more than two doses of any triptan should be taken within 24 h. Triptans can induce MOH when taken for more than 10 days per month for >3 months. Migraineurs in particular are prone to develop MOH, and many HH patients have also suffered from migraine headache attacks in their younger years, although the coexistence of HH and an active migraine has been only reported in a few cases. Therefore, intake on more than 10 days a month should be avoided. Triptans are contraindicated in patients with established heart disease, high blood pressure, peripheral vascular disease, impaired liver function, stroke and diabetes, which might exclude a substantial part of HH patients from this treatment option.

Many substances that are used on a regular basis in other headache disorders, especially trigeminal autonomic cephalalgias, have been shown to be ineffective in HH (**Box 2**).

Box 2. Ineffective or not sufficiently effective acute drug treatment in hypnic headache.

- Nonsteroidal anti-inflammatory drugs
- Acetaminophen
- 100% oxygen inhalation
- Opioids
- Indomethacin
- Ergotamine

Prophylactic treatment options

Medication is considered as a prophylactic treatment when taken on a daily basis to prevent the occurrence of headache attacks. Before starting prophylactic medication one should always take the elderly patient population of HH into account. These patients often suffer from different concomitant diseases, often develop side effects of prescribed drugs and have limited medication tolerance. As the majority of HH attacks is of mild-to-moderate intensity and mainly of short duration, patients are often more concerned with prophylactic treatment than symptomatic treatment options [51]. They often complain about the high frequency of headache attacks (in most cases >15 per month), which lead to substantial sleep disturbances.

Numerous case reports and case studies have described the efficacy of lithium in prophylactic treatment of HH [3,46,47,49,52–67]. However, titration to the adequate blood level is difficult and many patients discontinued therapy due to side effects (e.g., tremor, diarrhea, increased thirst and polyuria). In our German cohort, more than half of the patients stopped lithium therapy in this regard [3]. In addition, further drug interactions need to be considered.

Topiramate (dosage 25–100 mg/day) was reported to be effective in some cases as a prophylactic HH treatment [47,63]. In our German cohort, five patients were administered topiramate, two of which reported it to be effective in preventing HH attacks [3].

In patients with unilateral HH disorders, indometacin (dosage 25–150 mg/day) might be a further treatment option. However, the reported treatment outcomes are rather diverse [3,42,46,48,50,51,61,65,67–75]. Gastrointestinal side effects are frequently reported and may lead to premature treatment discontinuation.

Single case reports and smaller case studies indicate the possible prophylactic effects of melatonin (dosage 3–5 mg/day) [48,70], amitriptylin (dosage 10–100 mg/day) [43,45,47–50,56], oxeteron (180 mg/day [54]), botulinum toxin type A [45] and pregabalin (dosage 75–150 mg/day) [70]. Other reported treatment options seem to be ineffective or not sufficiently effective as prophylactic therapeutic options (**Box 3**).

Hypothalamic involvement in hypnic headache

The hypothalamus plays a key role in the regulation of sleep and wakefulness, mainly due to hypothalamic subsections such as the suprachiasmatic nuclei. Besides other important regulation features, it is involved in pain control as it displays extensive afferent and efferent neuronal connections to nociceptive and antinociceptive brainstem nuclei. The strict association between sleep and HH lead to the assumption that hypothalamic changes could be involved in the pathophysiology of HH. This hypothesis is supported by voxel-based morphometry data showing a significant reduction of gray matter within the hypothalamus of affected patients [101]. Some studies suggest that HH could be a REM sleep disorder as some polysomnography studies have reported a high association between the occurrence of HH attacks and REM sleep [43,48,49,60]. More recent studies, however, have doubted this obligate association and show that HH attacks occur just as commonly during NREM sleep stages [4,5,61].

Caffeine in the treatment of other headache disorders & non-headache disorders

Migraine & tension-type headache

Approximately 30 years ago, repeated clinical trials indicated that adding caffeine to analgesics such as aspirin, acetaminophen and ibuprofen reduced the analgesic need by 40% [76–80]. Clinical trials suggest that doses of 65 mg may be useful for analgesic enhancement. Caffeine-containing analgesics more often lead to pain relief in primary headache disorders than the analgesic compound alone [81]. Some studies even suggest an intrinsic analgesic property of caffeine. Ward *et al.* investigated 53 patients with non-migraineous headache [82]. In a double-blind, placebo-controlled multiple crossover design, four different treatments were compared: placebo, acetaminophen, two doses of caffeine, and a combination of caffeine and acetaminophen. The results indicated caffeine-independent analgesic effects. A different study investigated 301 patients with tension-type headache in a randomized, double-blind, parallel, multicenter, single-dose, and placebo- and active-control study design [80]. The following treatment groups were investigated: ibuprofen and caffeine, ibuprofen alone, caffeine alone and placebo. According to previous data, caffeine showed intrinsic analgesic properties, although the effects were not as substantial as the combination of ibuprofen and caffeine.

Box 3. Ineffective or not sufficiently effective prophylactic drug treatment in hypnic headache.

- Flunarizine
- Prednisone
- Benzodiazepines
- Gabapentine
- Verapamil
- β-blockers
- Antidepressants other than tricyclics
- Valproate
- Acetazolamide

Postdural puncture headache

Postdural puncture headache (PDPH) is a well-known headache entity that occasionally follows diagnostic or therapeutic dural punctures. According to International Headache Society criteria, PDPH usually develops less than 7 days after dural puncture [2]. A postural component is mandatory, meaning that the headache worsens within less than 15 min after getting in the upright position and improves within <30 min when laying supine again. Oral or intravenous caffeine seems to be an effective treatment option in PDPH. It has been shown to be effective in postpartum patients [83]. Despite the good response rates after caffeine treatment (75–80%), headache recurrence seems to be a major problem as the headache returns in most cases [84].

Caffeine leading to headache

Caffeine withdrawal

Caffeine withdrawal is commonly recognized as important lifestyle factor causing headache. It has been shown that not only do high intake doses above 600 mg/day cause withdrawal symptoms after discontinuation, but so do moderate or even low doses of 100 mg/day [85]. Headache usually starts after 12–24 h following caffeine intake discontinuation and lasts approximately 1 week. The pain peaks between 24 and 48 h [86]. Caffeine withdrawal might be one factor of the often observed perioperative headache, as many surgeries require patients to fast [17,87]. Hampl *et al.* investigated 40 patients that underwent a minor surgical procedure. Half of the patients were treated with caffeine tablets, the other half only received placebo tablets. In the placebo group 50% of the patients reported headache after surgery; in the caffeine group no one suffered from headache [88]. Similar effects can be seen with intake of caffeinated beverages as well as intravenous application of caffeine [89].

Medication overuse headache

Medication overuse headache (MOH) is a common cause of chronic headache. The prevalence in the general population in Western societies ranges between 1 and 2% [90]. MOH is defined as a chronic headache (≥15 days/month ≥3 months) that occurs after frequent intake of ergot derivatives, triptans, opioids or analgesics as acute treatment medication [2]. Simple analgesics should not be taken for ≥15 days/month, and mixed analgesics containing caffeine pose an even higher risk for inducing MOH compared with single-substance formulations and should therefore not be taken for ≥15 days/month. Caffeine seems to increase the risk of MOH development to a level similar to that of ergot derivatives and opioids [2]. The distinct mechanisms of MOH occurrence are still enigmatic and the role of caffeine in this context remains unclear.

A different study investigated the correlation between chronic headache in children and adolescents and excessive caffeine consumption due to caffeine-containing soft drinks intake [91]. Thirty six subjects (17 girls and 19 boys; mean age: 9.2 years; mean headache duration: 1.8 years; soft drink intake: 1.5 l per day [192.88 mg caffeine]) participated in this study. After gradual withdrawal from caffeine-containing soft drinks, in 33 patients the chronic headache disappeared in 33 patients.

Expert commentary

From our point of view, drinking a cup of coffee in the evening is an effective, safe and cheap treatment option that should be attempted as a first-line therapy in the prophylactic treatment of hypnic headache. However, many patients do not accept this treatment option due to concerns of increased sleeplessness. Interestingly, this side effect has only been described in very few patients and does not seem to be as prevalent as patients and doctors often think [42,71]. Patients should be encouraged to attempt caffeine at least once, as they could genuinely benefit from a strong cup of coffee before going to bed.

Caffeine-containing analgesics are also effective in acute headache treatment in migraine and tension-type headache. However, they imply an increased risk of MOH compared with single-substance analgesics and should, therefore, be avoided in higher dosages and taken sporadically.

High caffeine, especially in the form of coffee, tea and other types of caffeine-containing beverages, can induce withdrawal headache when caffeine intake discontinues. The caffeine effect varies individually (e.g., due to body size) and depends on the degree of tolerance. Therefore, a maximum threshold for caffeine intake cannot be recommended in general.

The mode of action of caffeine with regard to its analgesic properties is still not completely understood. Several associated mechanisms have been identified such as adenosine A_{2A} receptor antagonism, inhibition of prostaglandin E2 synthesis, inhibition of COX enzymes and involvement of the cerebral amine system. However, with regard to HH the therapeutic response to caffeine goes beyond the usual analgesic effects observed in other headache disorders.

Clinical and imaging data suggest hypothalamic involvement in the pathophysiology of HH.

Five-year view

Further neurophysiological and neuroendocrinological studies will illuminate the underlying pathophysiology of HH. Increased knowledge about HH will likely increase the estimated prevalence rates. Multicenter approaches will help to conduct placebo-controlled clinical trials to improve treatment options of HH. More focus will be placed on caffeine-containing beverages in the context of medication overuse headache and withdrawal headache, especially as many children are used to drinking large amounts of these drinks.

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Key issues

- Owing to the rareness of hypnic headache (HH), placebo-controlled therapeutic studies remain unavailable. Therefore, therapeutic recommendations are exclusively based on case reports, smaller case studies and experts' opinions.
- Caffeine appears to be an effective treatment option for HH, with only a few side effects.
- Caffeine can be used as an acute treatment option in case of nocturnal headache, as well as a prophylactic treatment option to avoid occurrence of HH.
- Caffeine use alone and the combination of caffeine with analgesic drugs are also effective in treatment of migraine, tension-type headache and postdural puncture headache.
- Adenosine is the natural agonist at the adenosine A_{2A} receptor, which is mainly responsible for sleep induction and sleep regulation. It is mainly localized in the striatum, nucleus accumbens and olfactory bulb.
- Caffeine is an antagonist of the adenosine A_{2A} receptor and shows adjuvant analgesic effects as well as intrinsic analgesic properties.
- Caffeine withdrawal can lead to strong headaches, which is sometimes even seen in children who drink caffeine-containing beverages on a daily basis.
- Caffeine-containing analgesics used as an acute treatment more often induce medication-overuse headaches than simple analgesics and should, therefore, be avoided in headache therapy.

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