Current Treatment Options in Neurology
DOI 10.1007/s11940-011-0156-3

Headache (JR Couch, Section Editor)

Hypnic Headache: Clinical Course and Treatment

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Keywords Hypnic headache · Treatment · Prophylaxis · Diagnosis · Caffeine · Lithium · Indomethacin · Topiramate · Triptans · Hypothalamus

Opinion statement

Thus far, no data from randomized placebo-controlled clinical trials are available for hypnic headache, so current treatment recommendations are based on single case reports and smaller open case series. In the predominantly elderly patient population affected by this disease, tolerability of the substances used is at least as important as their efficacy. Caffeine is the preferable first-line therapy for both acute treatment (i.e., a cup of strong coffee when awaking with headache) and prophylaxis (a cup of strong coffee before going to bed). Sleep problems should be considered as substantial side effects of this therapy, although they seem to occur far less than expected. For acute treatment, analgesics containing caffeine are also effective, but they may carry the risk of medication-overuse headache. Treatments that *not* effective for acute pain relief include nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, 100% oxygen, and acetaminophen Triptans may be effective in single cases. For prophylaxis, lithium should be tried as a second treatment option if caffeine intake is not effective or tolerated. Lithium has been reported to be effective in many patients, but it was often discontinued because of side effects. Indomethacin may be a viable option for third-line prophylactic therapy.

Introduction

Hypnic headache (HH) is a rare primary headache disorder. It was first described by Raskin in 1988 [1], and only 174 cases have been reported in the literature so far. The core characteristic clinical feature in HH is the strict association of headache attacks with sleep. Additionally, the headache attacks often occur at the same

Published online: 10 November 2011

Table 1. Diagnostic criteria of hypnic headache (ICHD-II 4.5)

1. Dull headache fulfilling criteria 2–4
2. Develops only during sleep, and awakens patient
3. At least two of the following characteristics:
   - occurs>15 times per month
   - lasts≥15 minutes after waking
   - first occurs after age of 50 years
4. No autonomic symptoms and no more than one of nausea, photophobia or phonophobia
5. Not attributed to another disorder

(*Adapted from* The International Classification of Headache Disorders: 2nd edition [2].)

time each night, so HH is sometimes referred to as "alarm clock headache." In 2004 this headache entity was first included in the International Classification of Headache Disorders (ICHD-II) (Table 1) [2].

Epidemiology

Because of the rareness of the disease, prevalence data for HH are not available. The frequency of HH was estimated to be between 0.07% to 0.1% of all treated headache patients in several tertiary headache centers [3–5]. The assumed characteristic clinical picture changed with time as more and more patients were reported in the literature [6, 7•, 8, 9•]. The majority of patients are female (male:female ratio, 1:1.2 to 1:1.7). The age at onset is usually about 60 years, but in some case reports, even children are possibly affected [10, 11].

Clinical characteristics

The headache is described as moderate and localized, mainly bilateral with dull character. The typical duration of an attack is at least 15 min and averages about 80 min, but attacks can last up to 6 h. The frequency per night is averages 1 to 2 attacks, with a mean frequency per month of about 23. Interestingly, most patients display motor behavior when awakening with headache at night, such as reading, watching TV, listening to radio, eating, drinking, walking around, taking a hot shower, or cooling the head, but these symptoms never reach the level of agitation or restlessness that can be observed in cluster headache attacks [6, 7•, 8, 9•]. The natural course of the disease is unknown. Some cases seem to proceed episodically without recurrence and some are episodic with recurrence [5, 6, 8], but the majority display a chronic course.

Pathophysiology

The pathophysiology of HH is still enigmatic. It was previously suggested that HH attacks might be associated with REM sleep, an idea supported by some polysomnographic (PSG) reports [6, 12, 13]. Recent studies have contradicted this early assumption, however, finding that up to 73% of HH attacks arise from NREM sleep stages [8, 14•].

A different hypothesis suggested a crucial role of obstructive sleep apnea in the underlying pathophysiology of HH. Although all PSG studies in HH showed an increased apnea/hypopnea-index (>5), the onset of the recorded HH attacks was not temporally correlated with the observed drop of oxygen saturation [8, 14•]. Presumably, the increased prevalence of obstructive sleep apnea is related to the age of the population rather than to the disease itself [15].

The clinical features of HH, with its chronobiological presentation, lead to the hypothesis of a hypothalamic alteration in HH. The hypothalamus is involved in regulation of the sleep-wake cycle as well as in central pain processing, among other things [16]. Structural imaging of 14 HH patients using voxel-based morphometry (VBM) showed a decrease of gray matter within the posterior hypothalamus [17••]. Changes of trigeminal pain processing in terms of central facilitation and alteration of habituation, which were commonly observed in other primary headache disorders such as migraine, were not detected in HH [18]. Further investigation of HH pathophysiology may offer a better understanding of the disease and may provide new treatment approaches in the future.

Treatment

- Treatment of patients with HH remains a tremendous challenge, as no evidence-guided treatment options exist. Randomized, placebo-controlled clinical trials are urgently needed but will be difficult to perform because of the rareness of this primary headache disorder. International cooperation may make it possible to achieve high enough patient numbers. Further investigation of HH pathophysiology may offer a better understanding of the disease and may provide new treatment approaches in the future.

Diet and lifestyle

- There is currently no information about whether distinct diet and lifestyle changes influence the clinical course of HH.

Pharmacologic treatment

- Data from randomized, placebo-controlled trials are not available because of the rarity of HH, so treatment recommendations are based on case reports or smaller case series and reflect experts' opinion and clinical experience (only Class IV evidence).
- In the mainly elderly patient population, adverse effects of medication are crucial and should always be taken into account before starting treatment. Many patients report no benefit from any therapy or decide to tolerate the pain instead of suffering from medication side effects.
- Acute and prophylactic treatment options should be distinguished. Acute medication is taken when the headache attack occurs at night and awakens the patient. Prophylactic medication is taken on a regular basis every day (e.g., lithium) or before going to sleep (e.g., caffeine) to avoid the nocturnal occurrence of headache attacks (Table 2).
- Some patients with short headache duration and mild to moderate intensity of pain do not require pain treatment. The number of these

Table 2. Potentially most effective pharmacologic treatment options for hypnic headache

Drug	Presumed mode of action
Caffeine	• Competitive antagonism at the adenosine receptor (A_1, A_{2A}, A_{2B}) → vasoconstriction, change of cerebral excitability level
Lithium	• Indirectly increases nocturnal incretion of melatonin • Downregulation of serotonin receptors • Increase of serotonin release
Indomethacin	• Lowering cerebrovascular fluid pressure

patients is probably underestimated, as their HH is often not diagnosed, or they do not seek professional medical attention.

Acute drug treatment

- To be considered effective, acute treatment should terminate an attack of HH as rapidly as possible. As HH occurs in many patients almost every night (sometimes even two or more times per night), the high frequency of headache attacks must be considered before acute drug treatment is prescribed. Almost all reported drugs have few adverse effects if they are taken infrequently, but if they are taken almost daily, the risk of major adverse effects increases. Additionally, daily intake of analgesics by headache patients always raises the possibility of medication-overuse headache (MOH). This complication is especially common in migraine, but patients with HH also may be at risk for aggravation of pain due to frequent administration of acute drug treatment, although MOH has not yet been reported in HH. Many HH patients also suffer from migraine, which probably makes them even more prone to developing MOH.

Caffeine

- Caffeine (at least one cup of strong black coffee when awakening with headache) was reported to be effective in several cases [9•, 19]. Some studies even report it to be the most effective treatment option in HH [9•].
- Most patients are afraid of disrupted sleep pattern after caffeine intake, although this was described in only a few cases [3, 20].
- Caffeine is generally a safe drug treatment, with no relevant contraindications or side effects. Increased heart rate may occur in some patients.
- The efficacy rate is subject to controversy in the literature, which shows many patients with very good treatment response and some with no pain relief at all [3–5, 19, 21–26]. In our own German patient cohort, a cup of coffee led to relevant pain relief in 11 of 14 patients [9•]. Similarly, analgesics containing caffeine (e.g., acetylsalicylic acid+caffeine) also are often effective, as reported in single case reports and small case series [3, 9•]. In our own HH cohort, analgesics containing caffeine were effective in 5 of 9 patients [9•].
- Although some patients seem to be nonresponders, in our opinion caffeine should be considered first-line acute therapy, as it is safe and of course inexpensive. Interestingly, many patients detected the efficacy of caffeine by themselves before their HH was diagnosed. The phenomenon of headache relief by caffeine may sometimes even facilitate the correct diagnosis, as it is a characteristic feature of this unique headache disorder. Patients should avoid caffeine-containing analgesics, which increase the risk of MOH and also may produce more adverse effects from the analgesic compound, which is presumably unnecessary for treatment response.

Triptans

Triptans, particularly in combination with caffeine [3], seem to be effective in some HH patients. In our own German cohort, four patients took triptans (two rizatriptan, one sumatriptan, one zolmitriptan), which were effective in all of them [9•]. However, in most reported cases the efficacy of triptans seems to be rather small [21–23, 27–29]. Subcutaneous sumatriptan is not effective [4].

Although efficacy has not been proven decisively, it seems to be appropriate for patients to try triptans at least once for acute therapy if they have severe HH attacks that do not respond to caffeine. However, it is important to inform patients about possible adverse events if recommendations about dosage and frequency are not followed.

Standard dosage The currently available triptans are naratriptan, almotriptan (6.25 mg/12.5 mg tablet), frovatriptan (2.5 mg tablet), sumatriptan (50 mg/100 mg tablet, nasal spray, subcutaneous application), rizatriptan (5 mg/10 mg, tablet or orally disintegrating tablet), eletriptan (20 mg/40 mg tablet), and zolmitriptan (2.5 mg/5 mg tablet or disintegrating tablet). No more than two doses of any triptan should be applied within 24 h. There should be at least 2 h between doses. Different triptan types should not be mixed up. Intake more than 10 days a month has been shown to cause MOH (at least in migraineurs) and should be avoided.

Contraindications Patients with established heart disease should not take triptans. Additionally, high blood pressure, high cholesterol, angina, peripheral vascular disease, impaired liver function, stroke, and diabetes should be ruled out before intake. Triptans should not be used in combination with ergotamines or monoamine oxidase inhibitors (MAOIs).

Main side effects Used in the correct dose and frequency, triptans have very few adverse effects. Common triptan-associated side effects include nausea, dizziness, and sleepiness. In rare cases, pain or pressure sensation in the chest or throat may occur.

Other drugs

- The high impact of the disease on each patient's life explains why many drugs and other treatments have been tested for acute treatment of HH, including nonsteroidal anti-inflammatory drugs [4, 9•, 22, 23, 29], acetaminophen [9•, 11, 27, 28, 30], oxygen inhalation 100% [4, 9•, 29, 31], metamizole [9•], opioids [9•], indomethacin [27, 28], nimesulide [22, 27, 28, 32], and ergotamine [30]. These drugs have shown efficacy in treating migraine or trigeminal autonomic cephalalgias such as cluster headache, but most of them have provided no relevant benefit in HH therapy.

Prophylactic drug treatment

Lithium carbonate

Lithium was the first drug reported to be efficient in the prophylaxis of HH, and it is the drug most commonly used for this purpose [1, 5, 7•, 8, 9•, 19, 22, 27, 28, 30, 31, 33–41].

In our opinion, lithium seems to be a quite effective prophylactic treatment, but considering its side effects, we consider it to be a second treatment option for patients who do not respond to prophylactic caffeine therapy (Fig. 1).

Standard dosage	Lithium should be initiated with a starting dose of 150 mg/d. Depending on tolerability and the individual serum level, it can be titrated up to 600 mg/d. The dose should be adapted to plasma levels, with a therapeutic range of 0.5 to 1.0 mmol/L. It should be taken in the evening for better efficacy.
Contraindications	Lithium is contraindicated in medical conditions such as heart failure, kidney failure, psoriasis, salt depletion, cardiovascular disease, heart disease, electrolyte disturbance, and hypothyroidism. Renal and thyroid function must be evaluated before initiation of therapy and periodically during treatment to avoid toxicity.
Main side effects	Many patients discontinue therapy because of poor tolerability, especially because this patient population is mainly elderly. In the German cohort, lithium therapy was discontinued by 6 of 11 treated patients owing to side effects [9•]. The main side effects of lithium are tremor, diarrhea, increased thirst, and polyuria.
Main drug interactions	Lithium may interact with diuretics, NSAIDs and angiotensin-converting enzyme (ACE) inhibitors. Additionally, many other drug interactions have also been observed and must be checked individually before starting lithium treatment.
Special points	Interestingly, a transient HH was reported after medication was discontinued in one patient who was treated with lithium because of a bipolar disorder [42•].
Cost	Although lithium itself is rather cheap, this therapy involves many secondary costs owing to the need for blood tests.

Caffeine

- Drinking at least one cup of strong coffee before sleeping seems to be another highly effective prophylactic treatment option in HH [3–5, 19, 21–26]. In our German cohort, eight patients tried caffeine as

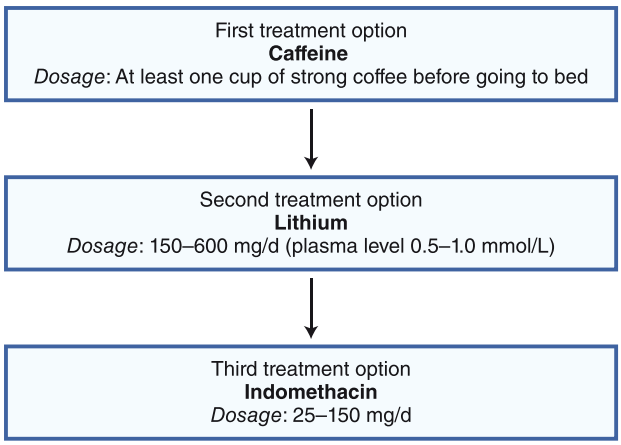

Figure 1. Proposed treatment algorithm for prophylactic therapy in hypnic headache.

prophylactic treatment; four reported it to be beneficial, and two of them reported complete disappearance of HH attacks. Interestingly, pain suppression was observed almost immediately after starting therapy [9•].

- From our point of view, drinking a cup of coffee in the evening is a very efficient, safe, and cheap treatment option which should be tried as first-line therapy (Fig. 1), but many patients are reluctant to try this option because they are afraid of increased sleeplessness. Interestingly, this side effect was described in very few patients, and it seems less important than patients and often doctors think it will be [3, 20]. Patients should be encouraged to at least try a cup of strong coffee before going to bed, to see if they benefit.

Topiramate

Some case reports have shown good efficacy of topiramate in treatment of HH. Autunno et al. [37] reported that HH in a 63-year-old patient responded to a low dose of topiramate (25 mg at bedtime). Guido and Specchio [27] reported successful treatment of a 67-year-old woman using 100 mg/d of topiramate. In our own cohort, topiramate was taken by five patients (with a dosage increasing from 25 to 100 mg/d) and was reported beneficial in two patients. However, complete suppression of HH attacks was achieved in only one patient, at a dose of 75 mg/d [9•].

Because of the high frequency of side effects and the small therapeutic benefit observed so far, topiramate cannot be recommended as first-line prophylactic therapy in HH.

Standard dosage Usually therapy is initiated with 25 mg per day at night. Some patients may start with 12.5 mg to avoid early side effects. The initial dosage should be increased only slowly every 2 weeks up to 100 mg daily, which should be administered as two daily doses (50 mg bid).

Contraindications Topiramate should not be prescribed for patients with a known history of depression or other psychiatric disorder, or for patients with nephrolithiasis.

Main drug interactions Carbamazepine may increase the elimination of topiramate. Topiramate increases plasma levels of phenytoin, but at the low doses used for HH therapy, this effect may be rather small.

Main side effects Many patients report paresthesias (numbness and tingling). After the start of therapy, mild to moderate weight loss may occur. Major side effects of topiramate are cognitive deficits such as short-term memory loss and word-finding difficulty; these often lead to discontinuation of therapy. Depression and blurred vision also may occur.

Indomethacin

Indomethacin has been reported to be effective, especially in HH patients presenting with unilateral headache attacks [21]. The efficacy of this drug in some patients suggests a common underlying pathophysiology with paroxysmal hemicrania and hemicrania continua, in which indomethacin response is an almost pathognomonic feature.

Indomethacin treatment of more than 20 patients with HH has been reported in the literature, and the clinical outcome seems to be mixed [3, 9•, 20–22, 24–26, 29, 35, 39, 41, 43–46]. About half of the patients respond to therapy, but the effect was small or not detectable at all in the other half. In our own cohort, indomethacin was effective in one of three patients, whose HH stopped completely after initiation of indomethacin therapy at a dose only 25 mg at night. The other two patients had to stop treatment because of gastrointestinal side effects [9•].

Although indomethacin may be effective in at least some patients, it cannot be recommended as first-line therapy because of its high rate of discontinuation, mainly due to gastrointestinal side effects.

Standard dosage Effective doses range from 25 mg to 150 mg per day.

Contraindications Indomethacin intake is contraindicated in patients with peptic ulcers or a history of ulcer disease.

Main side effects Many patients discontinue the use of indomethacin because of unbearable gastrointestinal side effects. Another major side effect that sometimes limits therapy is new onset of daytime headache.

Melatonin

The therapeutic effects of melatonin reported in the literature have been small [21, 26]. In our own German cohort, melatonin was beneficial in one of three patients, who reported only a moderate effect. One patient stopped melatonin treatment because of aggravation of headache symptoms [9•].

The daily dose of melatonin is 3 to 5 mg. Such low doses of melatonin have no significant side effects.

Although the circadian rhythmicity of HH attacks strongly suggests an involvement of the melatonin metabolism in its pathophysiology, evidence of beneficial therapeutic effect is lacking in most patients. Therefore, melatonin cannot be recommended as first-line therapy in HH, but because its tolerability is quite good, it might be worth trying if other treatment options fail.

Amitriptyline

The efficacy of tricyclic antidepressants in HH therapy is still questionable [4, 19, 21, 23, 27–29, 35, 47, 48]. In a large review including 71 patients, Evers and Goadsby reported that amitriptyline therapy was effective in only 1 of 18 patients [6]. In our own cohort, it was used by five patients, three of whom responded to therapy [9•]. The observed therapeutic effect was only moderate, and none of the patients achieved complete pain suppression. Most patients discontinued amitriptyline therapy because of adverse effects.

Because of insufficient data, an evidence-based assessment of the efficacy of amitriptyline is quite difficult. Therefore, it cannot be recommended as first-line prophylactic therapy at this time.

Standard dosage The daily dose of amitriptyline is 10 to 100 mg/d, which should be taken once daily at bedtime. It is preferable to initiate therapy with a low starting dose (10–25 mg) to avoid side effects and early discontinuation of therapy.

Contraindications	Amitriptyline is contraindicated in patients with severe cardiac arrhythmias. ECG should be performed before starting therapy and for further monitoring.
Main side effects	The most frequent side effects are dry mouth, drowsiness, obstipation, and weight gain. Cardiac arrhythmias and personality changes may also occur.

Oxetorone

One recent French case series showed beneficial effects of oxetorone in HH treatment of eight patients [7]. Oxetorone is a serotonin antagonist with additional potential antihistaminergic properties; its efficacy has been demonstrated in migraine treatment. However, this drug is available only in France, so its value for HH therapy in general is small.

Standard dosage	The usual dose is 60 mg three times a day.
Main side effects	Good tolerability was described in the literature. Sometimes patients report sedation and dryness of the mouth.

Botulinum toxin type A

Botulinum toxin type A (BTX-A, Botox®) has been extensively investigated as a prophylactic agent for idiopathic and symptomatic headache disorders, but its efficacy for the treatment of HH has been reported only anecdotally, in a single case report in a peer-reviewed journal [23].

The reported patient received a total of 75 MU (2.5 MU Botox® injections per side into two frontal sites, into the corrugator muscle, and into two sites of the splenius capitis muscle, and 5 MU Botox® injections bilaterally into two sites of the semispinalis muscle and three sites of the trapezius muscle). The initial interval between injections was 3 months. After the first injection, pain intensity significantly decreased, but headache frequency did not change. After the second injection, headache frequency decreased, and after 1 year of treatment, the patient was pain-free. The headache recurred after 3 months, but intervals of re-injection could be extended up to 5 months.

BTX-A injections should not be used in patients using anticoagulation drugs (e.g., warfarin).

Side effects of BTX-A therapy are generally minor and temporary. They include primarily paralysis of the wrong muscle and allergic reaction at the site of injection. Additionally, bruising at the injection site due to the mode of administration may last about 7 to 10 days.

As BTX-A was applied in only one patient, its efficacy has not been determined. A placebo effect cannot be ruled out. Therefore, BTX-A cannot be recommended as initial therapy for HH at this time.

Pregabalin

Pregabalin showed efficacy in one 78-year-old woman suffering from HH for 6 years. After failing to respond to therapy with indomethacin and melatonin, she was started on pregabalin. The initial dose was titrated up to 150 mg at bedtime over 4 weeks. Within 14 days after reaching this dose, the headache completely disappeared. Interestingly, HH recurred within 6 months after the dose of pregabalin was reduced to 75 mg. After increasing the dose to 150 mg again, the headache vanished right away and did not reappear with continued treatment (follow-up, 14 months) [26].

	As pregabalin has been used in only one patient, its efficacy remains anecdotal. Therefore, pregabalin cannot be considered a first-line or second-line therapy for HH at this time. It may be considered if other treatments fail or patients present with additional neuropathic pain.
Standard dosage	Therapy is usually started with 75 mg/d or even smaller doses. The dose can be increased, dependent on tolerability and efficacy, up to 300 mg per day (150 mg bid).
Main drug interactions	There are no relevant pharmacologic interactions described in the literature.
Main side effects	Very common side effects are dizziness and drowsiness. In some patients, diplopia, increased appetite, and extremely vivid dreams may occur.

Other drugs

- Many other drugs have been tested as prophylactic treatment for HH therapy. Substances were chosen that had already shown good efficacy in other headache disorders such as migraine or trigeminal autonomic cephalalgias, but most of these agents failed to show any relevant influence on the course of HH and therefore should not be prescribed on a regular basis for this purpose. Among these drugs that appear to have no relevant prophylactic effect in HH (or have shown only some anecdotal effects) are flunarizine [4, 8, 19, 22, 27, 28, 33, 37, 49, 50], prednisone [3, 5, 22, 31, 32, 37], benzodiazepines [28, 31], gabapentin [22, 26, 35], verapamil [4, 21, 22, 28], β-blockers [3, 27–29, 31], antidepressants other than tricyclics [23, 29, 31, 35, 46], valproate [27–29], and acetazolamide [45].

Disclosure

Conflicts of Interest: H-C Diener: Consulting fees or honoraria, support for travel, and fees for participation in review activities from Addex Pharma, Allergan, Almirall, AstraZeneca, Bayer Vital, Berlin Chemie, Coherex, CoLucid, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Gruenenthal, Janssen-Cilag, Lilly, LaRoche, 3M Medica, Medtronic, Minster, MSD, Novartis, Johnson & Johnson, Pierre Fabre, Pfizer, Schaper and Brümmer, Sanofi Aventis, and Weber & Weber; M Oberman: none; D Holle: none.

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