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Headache, drugs and sleep

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Abstract

Background: Headache and sleep mechanisms share multiple levels of physiological interaction. Pharmacological treatment of headache syndromes may be associated with a broad range of sleep disturbances, either as a direct result of the pharmacology of the drug used, or by unmasking physiological alterations in sleep propensity seen as part of the headache symptom complex.

Purpose: This review summarises known sleep and circadian effects of various drugs commonly used in the management of headache disorders, with particular attention paid to abnormal sleep function emerging as a result of treatment.

Method: Literature searches were performed using MEDLINE, PubMed, and the Cochrane database using search terms and strings relating to generic drug names of commonly used compounds in the treatment of headache and their effect on sleep in humans with review of additional pre-clinical evidence where theoretically appropriate.

Conclusions: Medications used to treat headache disorders may have a considerable impact on sleep physiology. However, greater attention is needed to characterise the direction of the changes of these effects on sleep, particularly to avoid exacerbating detrimental sleep complaints, but also to potentially capitalise on homeostatically useful properties of sleep which may reduce the individual burden of headache disorders on patients.

Keywords

Sleep, drugs, headache, migraine, cluster headache, REM, NREM, somnolence, insomnia, melatonin, circadian, restless legs syndrome, polysomnography

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Introduction

Headache and sleep share neurophysiological and anatomical substrates, which are likely to be homeostatically linked to some extent at a systems level. From a headache perspective, a disturbance in sleep (too much, too little, inappropriate timing or inappropriate sleep behaviour) can be a symptom, trigger or treatment of headache; and headache can be a symptom of sleep disturbances and side effect of sleep- or wake-modulating treatments. The intricate complexity of this relationship has not been fully elucidated, but is being actively explored, with progress towards an improved understanding being made (1).

When considering sleep and headache drug effects, this relationship must be acknowledged, and rightly assumed to be bidirectional. However, this assumption further fuels the complexity of investigating this relationship, as reporting sleep effects (often, although not always deemed to be adverse events) in headache treatment, and headache (always deemed to be an adverse event) in sleep treatments may not just be straight forward, drug-related phenomena; it may represent unmasking of a more fundamental physiological process by alleviating a symptom (such as attenuating the pain of a migraine attack), or causing a perturbation of homeostasis.

The best example of this comes from Goadsby and colleagues, who used pooled data from seven

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placebo-controlled trials of triptan use in acute migraine, to demonstrate higher rates of somnolence in responders than non-responders, with similar rates of somnolence in those who responded to either active treatment or placebo, which demonstrated that it must be due, at least to a significant part, to headache relief and unmasking of somnolence as a symptom of the syndrome of a migraine attack, rather than just a side effect of treatment (2).

The labour intensity, cost and duration of accurately assessing sleep physiology make studies examining this relationship as a primary end point exceptionally rare (and hence this is an area lacking in systematic evidence), with studies including it as a secondary outcome seldom going beyond binning adverse events into broad central nervous system (CNS)-related adverse events, which include 'sleep disturbance' (whereby fatigue, tiredness, insomnia, parasomnia and somnolence are incorrectly considered to be one and the same thing). Bearing these complexities in mind, this review attempts to explore known and theoretical physiological effects of various drugs used in the treatment of headache on sleep.

Acute headache medications

Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs such as aspirin, ibuprofen and naproxen are mainstay agents in the acute treatment of headache attacks, as well as indomethacin's use as a preventive drug in specific trigeminal autonomic cephalalgias, and interestingly also its use in some cases of hypnic headache (3). Their common mechanism of action is non-selective inhibition of two isoforms of cyclooxygenase (COX), the key enzyme involved in the arachidonic acid inflammatory cascade. However, concurrent action of indomethacin at other targets is likely to explain the exquisite sensitivity of hemicrania continua and paroxysmal hemicrania to it (4). COX inhibition attenuates the production of a range of prostaglandins. Despite being the most abundant prostaglandin in the CNS both of humans and experimental animals, Prostaglandin D_2 (PGD_2) was previously thought to be biologically inactive (5). However, it was found to be potently hypnogenic after microinjection into the brains of rats (6), and later rhesus monkeys (7), where it greatly enhanced the amount of both non-rapid eye moment (NREM) and rapid eye movement (REM) sleep, which was physiologically identical to normal sleep. This occurred in both a dose- and time-dependent manner (8), whereby prolonged sleep deprivation was also shown to raise endogenously circulating levels of PGD_2. Furthermore, circadian rhythmicity of the concentration of this molecule has also been convincingly demonstrated, with peaks coinciding with nocturnal sleep (9,10). NSAID use might therefore be expected to disrupt sleep based solely on its effects on PGD_2, before even considering the fact that NSAIDs as a class dampen the amplitude of the nocturnal rise in endogenous melatonin, and also attenuate the circadian core body temperature nadir, which usually occurs approximately two to three hours before spontaneous awakening (11). However, despite these three class effects, polysomnographic studies of NSAID use in healthy volunteers have shown minimal adverse or positive effects on sleep (12–14), although the trend, if any, would appear to be toward a very mild reduction in sleep efficiency (15). Improvement of sleep quality in patients with painful conditions, including dysmenorrhoea (16) and arthritic pathologies (17), has been largely attributed to an improvement in pain rather than a primary effect on sleep. Similarly, indomethacin may offer a unique sleep effect, and anecdotal reports suggests that high doses of it may have a hypnotic effect, although whether this is due to an unmasking event by treating the head pain in indomethacin-sensitive headaches remains to be proven. In addition, there are reports of indomethacin worsening sleep-disordered breathing (18), so caution should be paid to this when prescribing the drug in patients at risk of, or with pre-existing, obstructive sleep apnoea.

Triptans and ergot alkaloids

The triptans, and the ergot alkaloids ergotamine and dihydroergotamine, exert their specific headache therapeutic actions via agonist effects at central and peripheral receptors of the serotonergic neurotransmitter system, especially 5-HT_1, and most potently the 5-$HT_{1B/1D}$ receptor subclass, with ergotamine and dihydroergotamine also acting as agonists at 5-HT_2, alpha adrenergic and dopamine receptors. Drug-related somnolence is occasionally reported as an adverse event in placebo-controlled trials of triptans used as an abortive medication in migraine and cluster headache. Somnolence within 24 hours of oral sumatriptan use appears to be dose dependent from pooled data of randomised placebo-controlled trials, with no difference in somnolence rates between active drug and placebo at 25 mg (5% vs 5%), but a greater difference in trials where 300 mg has been used (5% vs 1%) (19). Interestingly, the rate of somnolence between active treatment and placebo does not appear to be different when intranasal (20) and subcutaneous (21) routes of delivery of sumatriptan have been used in migraine, which might reflect early evolution of somnolence as a symptom of the wider migraine attack. A slightly greater rate of somnolence has also been reported in placebo-controlled trials of zolmitriptan, both oral

and intranasal preparations, in cluster headache (22). However, none of these trials has been reanalysed in the same way as described in the introduction, whereby somnolence rates were examined in responders and non-responders (2). There appears to be a greater incidence of general CNS-related side effects (including somnolence) reported with the use of strongly lipophilic, brain penetrant triptans with active metabolites such as eletriptan, zolmitriptan and rizatriptan, with slightly lower reported rates of side effects attributed to less lipophilic and non-penetrant triptans such as sumatriptan, almotriptan and naratriptan (23). Controversy exists over whether these effects are the result of a direct action of the drug on the serotonergic system per se (which in the case of somnolence might seem less likely, given that although the effects of serotonin on sleep and wakefulness are mixed, the most compelling evidence is that it is largely a wake-promoting neurotransmitter (24)), or a more general unmasking phenomenon.

As endogenous melatonin is derived from serotonin, there may be some theoretical merit in suggesting that drugs with a serotonergic effect may modulate the secretion of melatonin by the pineal gland, which might impact on sleep regulatory processes, either by alteration of the amplitude of melatonin secretion (and hence affecting the circadian drive to initiate sleep), or by modulating sleep continuity. This would be more likely to occur with uptake inhibitors rather than specific agonists, such as the triptans. There are currently no clinical or preclinical studies which report on this specifically with regard to the triptans, ergotamine or dihydroergotamine.

Preclinical evidence exists to suggest that alterations at 5-HT_1 receptor subtypes may modulate sleep, which is something to bear in mind when considering the potential effects triptans and other serotonergic drugs may have on sleep. 5-HT_{1B} receptor knock-out mice have increased amounts of REM (25) and micropipette administration of the selective agonist CP-94253 in normal mice resulted in a reduction of REM sleep (26), whereas its administration systemically increased wakefulness, and reduced both REM and slow wave sleep (24). Conversely, the 5-HT_{1B} antagonist GR-125939 was shown to increase REM sleep (24).

Preventive headache medications

Serotonin antagonists

The potential effects on sleep mediated by the 5-HT_2 receptors are more intriguing than those of the 5-HT_1 subclass. The drugs methysergide, pizotifen and cyproheptadine, all of which are used in prophylactic migraine treatment, are strong non-selective antagonists at 5-HT_2 receptors, as well as agonists and antagonists at other 5-HT receptor subtypes, in addition to having broader anti-cholinergic, -histaminergic and -dopaminergic effects, all of which may impact upon sleep physiology. This makes their potential effects on sleep, and indeed melatonin physiology, complex and difficult to predict. An early study in healthy individuals showed only minor effects of methysergide on sleep architecture (27), which may reflect its broad effects across multiple systems. It did not, however, report on specific effects (positive or negative) on breathing during sleep, and this should theoretically be considered, particularly as methysergide has been experimentally shown to abolish hypoglossal atonia seen during carbichol-induced, REM-like sleep (28), without affecting REM sleep generation in animal models (29). Methysergide and pizotifen also have differential effects on the circadian secretion profiles of both growth hormone and prolactin, with methysergide attenuating the nocturnal surge in prolactin and increasing the amplitude of growth hormone secretion, whereas pizotifen has no effect (30). No studies have examined their effects on melatonin physiology.

Broadly, preclinical evidence would suggest that 5-HT_2-specific agonists (especially at 5-HT_{2A} and 5-HT_{2C} receptors) increase wakefulness and reduce sleep (31), which may theoretically be borne out clinically as insomnia; and indeed, 5-HT_{2A} specific antagonists in particular cause robust increases in slow wave sleep, either with a positive effect on sleep, or a tendency towards hypersomnolence. Antidepressants with 5-HT_{2A} antagonist effects (such as trazodone and mirtazapine) are generally useful slow wave-boosting sedative drugs, particularly in patients with depression and co-existent insomnia, and specific silent 5-HT_{2A} antagonists (and inverse agonists) have been explored as hypnotics, or in the case of ritanserin, also as a potential migraine prophylactic, albeit one lacking any substantial evidence (32).

Beta-blockers

While lipophilic beta-blockers such as propranolol appear to be associated with more adverse sleep effects, and indeed general CNS effects, than hydrophilic drugs (e.g. atenolol) (33), high β_2 and/or 5-HT receptor affinities might be mechanistically more important in mediating this effect (34). Reported side effects include tiredness, insomnia and vivid dreams, which may manifest as frank nightmares in some (35). In fact, one meta-analysis of study data suggests that beta-blockers are the drug most likely to be associated with nightmares reported as an adverse event, usually in the magnitude of less than 10% (36). Melatonin synthesis is also mediated by the extrinsic cranial sympathetic system,

and the pineal gland is innervated by the superior cervical chain (37). Beta-blockers will therefore lower the amplitude of endogenous, circadian melatonin secretion, leading to a reduced circadian signal to initiate sleep, which may have a functional effect causing sleep disruption, and may indeed increase the likelihood of fragmentation, particularly during REM sleep. Two studies assessed the effect of beta blockade on sleep in normal individuals with polysomnography (PSG) (38,39), and concluded that propranolol increased the number of remembered awakenings and dreams, whereas atenolol did not, compared to placebo. One study alluded to a reduction in REM sleep (38), but the other found no change (39). An increase in dreaming with either no change or a reduction in REM sleep could be explained by beta-blockers, particularly propranolol, reducing the arousal threshold during REM, leading to greater fragmentation and awakenings, and hence the likelihood of dream recall. REM density itself may also be affected by the reduction in endogenous melatonin levels, and indeed there are reports of beta-blockers worsening REM behavioural disorder (RBD) (40,41). A single report also exists of beta-blockers worsening restless legs syndrome (RLS), which is a major cause of sleep initiation insomnia (42). Supplementary exogenous melatonin administration can improve the insomnia associated with beta blockade experienced by some cardiac patients, and hence might be considered in this situation in headache disorders (43).

Antidepressants

Antidepressant drugs can both improve and disturb sleep (44), and data on the direction of this effect are confounded by the patient groups in which the studies have been performed. In general, REM sleep onset is delayed, its percentage within total sleep time is reduced, and fragmentation of sleep increases (45). This is most likely due to enhanced levels of the excitatory neurotransmitters serotonin and noradrenaline (45). Depression as a disorder has unique physiological manifestations on sleep architecture which make generalisations about the effect of antidepressants on sleep in other non-depressed patient groups and healthy volunteers very difficult to predict (46).

The tricyclic antidepressants (TCAs) are the main class of antidepressants used in headache treatment, with amitriptyline being the most studied. They have multiple receptor effects which may explain their effects on sleep. These include antagonism at H_1 receptors, and also α_1 and 5-HT_2 blockade, all of which may contribute to an overall sedating effect. Class-specific polysomnographic effects (with the exception of trimipramine) include, in general, a reduction in sleep latency, increase in REM onset latency, decrease in REM (REM effects are most noticeable after a few days of treatment, and reduce slightly with chronic use) and increase in total sleep time (45). There is also a notable effect of REM rebound after TCA withdrawal. It is worth noting that this effect is greater in depressed patients than in healthy controls, or for example in chronic pain conditions such as fibromyalgia (44). Morning drowsiness and reduced alertness is common with TCAs. Most studies of amitriptyline do not show any difference in sleep continuity from baseline after a few days of treatment, but one study showed a reduced number of awakenings after chronic use in depressed patients (44). A disease-specific effect of TCAs on sleep has not been examined in migraine or tension-type headache. In contrast to stronger REM-suppressing TCAs such as clomipramine and imipramine, TCAs with more use in headache disorders such as amitriptyline, nortriptyline, and dosulepin improve, rather than disrupt, sleep in the first few days of use in healthy volunteers (45). It is said anecdotally in headache neurology that nortriptyline may cause less sedation than amitriptyline, although there is no empirical evidence to substantiate this, and a head-to-head trial in this respect may prove enlightening.

Selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine and the serotonin/noradrenaline reuptake inhibitor venlafaxine have a dose-related and consistent reduction in REM sleep, in addition to an increased latency to the first REM episode (45). There is some suggestion of efficacy of these drugs as migraine preventives, particularly in patients with co-existent depression (47,48). Neither TCAs nor SSRIs have any appreciable effect on slow wave sleep, although comparison studies assessing delta or slow wave power are lacking (45).

As mentioned above, trazodone, a serotonin antagonist and reuptake inhibitor (SARI), is known to enhance slow wave sleep, and has some evidence to suggest efficacy as a preventive in episodic migraine in children (49), which is interesting given that naps are effective treatment for childhood migraine attacks. However, its active metabolite meta-chlorophenylpiperazine, has also been implicated as a delayed migraine trigger (50), so its sleep and headache interaction is likely to be bidirectional and complex.

With the exception of bupropion (dopaminergic effects), all antidepressants have the propensity to worsen or precipitate the symptoms of RLS (51,52), which has a co-association with migraine (53,54). They may also worsen or induce the associated periodic limb movement disorder (PLMD) (52), which can lead to a great reduction in sleep efficiency from recurrent cortical arousals associated with periodic limb

movements during sleep. Therefore use of antidepressant drugs as headache preventives should be avoided in patients with co-existing RLS or known PLMD. Reports that SSRIs such as fluoxetine may also worsen bruxism should also be noted, as this may exacerbate temporomandibular joint-related headache (55). There are also reports of a reduction of atonia in REM sleep, which might manifest as or worsen RBD, with use of most antidepressants, particularly the TCAs, fluoxetine, venlafaxine and mirtazapine (52).

While reduced dream recall is the usual finding in antidepressant drug use, nightmares are infrequently reported as adverse events, more so with TCAs than SSRIs, and it is hard to reconcile what role underlying psychopathology has to play given the clinical populations reporting these effects in clinical trials (56). The phenomenon of excessive dreaming on withdrawal of antidepressants is noted, and thought to possibly be due to an anticholinergic effect (45).

Anticonvulsants

The anticonvulsants topiramate, carbamazepine, sodium valproate, lamotrigine, gabapentin and pregabalin are used as preventive medications in the treatment of primary headache disorders. Their effects on sleep have been most extensively studied in patients with epilepsy (57–59). Topiramate has the most convincing evidence as a headache preventive, and its mechanism of action includes glutamatergic blockade, augmentation of gamma-aminobutyric acid (GABA) ergic activity at $GABA_A$ receptors, and antagonism of both voltage-gated sodium channels and carbonic anhydrase. Given its multiple targets, it is difficult to predict what effect it would have on sleep. One study examined PSG variables in patients initiated on topiramate for untreated partial seizures, and found no difference in the sleep architecture or daytime sleepiness as measured by the multiple sleep latency test (MSLT) compared to baseline or control subjects in patients established on 200 mg total daily dose (60). Only two of 14 patients, who were considered sleepy at baseline, reported sleepiness after initiation of topiramate (60). Only one placebo-controlled trial of topiramate in migraine (61) has systematically reported on sleep disturbances (the other two reporting only fatigue as an adverse event (62,63)), and found little difference in the rate of insomnia with treatment compared to placebo (10% vs 10%), but it did suggest a higher rate of somnolence compared to placebo (8% vs 2%). Anecdotally, somnolence is thought to be most likely to occur at treatment initiation. It is also worth noting that topiramate has been successfully used in the treatment of sleep-related eating disorder (64), thought to be an NREM arousal parasomnia, and may also be effective in the treatment of cluster headache (65), attacks of which may manifest at similar times as the NREM arousal parasomnias do across the nocturnal sleep period.

Subjective data would suggest that carbamazepine use is also associated with a greater degree of somnolence. Studies examining objective PSG data in drug-naïve healthy volunteers, compared to baseline, taking a range of doses, consistently show a reduction in sleep latency and arousals, and an increase in visually, but not necessarily quantitatively scored, slow wave sleep (66–68), changes which were also seen in one head-to-head trial comparing it to levetiracetam in patients with epilepsy (69).

Sodium valproate is traditionally associated with sedation as a side effect, and there is one study comparing a range of doses of sodium valproate with placebo in healthy volunteers, which demonstrated no significant effects on sleep scoring parameters, but again did not examine the sleep electroencephalogram (EEG) quantitatively (70). There is also preclinical evidence which suggests that sodium valproate might delay or advance circadian rhythms of clock gene expressions in vitro (compared with lithium, which phase-lengthens the circadian period) (71).

Similar levels of somnolence to other anticonvulsants are reported in trials of lamotrigine for a variety of disorders. However, insomnia has also been reported to be a less common adverse event. One study examined the effect of lamotrigine on the sleep EEG of patients with epilepsy commenced on the drug as monotherapy, which demonstrated no change in either PSG or MSLT parameters from their drug-free baseline (72). A further study of patients with drug-refractory epilepsy reported that lamotrigine may increase REM, and reduce slow wave sleep (72), which is a finding replicated by at least one other study (73,74). This may explain the higher rates of insomnia occasionally reported with use of this anticonvulsant.

Gabapentin and pregabalin both have high affinities to the $\alpha 2\delta$ subunit of N-type voltage-gated calcium channels, which results in a reduced synaptic release of both glutamate and noradrenaline. They also demonstrate N-methyl-D-aspartate (NMDA) receptor antagonism. Both drugs notably enhance slow wave sleep, as well as reducing latency to REM (75,76), subjectively enhancing sleep quality by reducing the number of nocturnal awakenings, and also reducing the frequency and amplitude of periodic limb movements. As such, they are a recognised treatment for both RLS and PLMD (77).

Melatonin

Melatonin is one of the most studied endogenous peptides mediating sleep and its diurnal propensity, and is

conveniently the only compound available as a treatment in its own right, with some evidence to suggest efficacy in primary headache disorders, particularly in cluster headache (78,79). It is secreted by the pineal gland in a robust circadian rhythm, which in health is entrained to the solar cycle (37). Secretion requires stimulation via β_1 adrenergic pathways, which synapse in the superior cervical ganglion. The effects of various medications on this, especially beta-blockers and NSAIDs, are discussed above (37). It has a dual use as both a hypnotic, particularly in age-related insomnia (80), and also as a chronobiotic in circadian rhythm sleep disorders, as it has a clear phase response curve, which allows timed administration of melatonin to phase advance or delay intrinsic circadian rhythms with a less robust, but clinically useful, effect than timed bright light exposure, which assumes an intact retinohypothalamic pathway (81–83). However, administration of exogenous melatonin for its hypnotic effect is also circadian-phase dependent (84), and more likely to be effective during the biological day where the homeostatic drive to sleep is lower, and is hence useful in shift workers, as well as being more likely to convey better hypnotic effect in individuals with low nocturnal levels of endogenous melatonin secretion. In this scenario, reports of attenuated nocturnal melatonin secretion in patients with both migraine (85) and cluster headache (86) might mean that such patients do derive a beneficial hypnotic as well as antinociceptive benefit from use of melatonin. Several studies report that the hypnotic effect is not dose dependent, and that melatonin has only modest effects on sleep latency and maintenance (87). Of interest, headache is the most frequently reported adverse event in trials of melatonin as a hypnotic (87). Exogenous melatonin does not appear to alter NREM or REM architecture (but may modestly reduce slow wave power) to any great extent (87), but increases sleep efficiency, and may affect core body temperature such that it may have an effect on REM density, which may partly explain its efficacy in treatment of REM behavioural disorder (88). The phase-shifting properties of melatonin might convey analgesic effects in sleep-related headache disorders, but this is untested. Newer dual melatonin agonists, such as the novel antidepressants ramelteon and agomelatine, have to date not been tried in headache disorders, and are perhaps worthy of further exploration.

Miscellaneous

The myriad of biological mechanisms which corticosteroids influence make the exact effects of this class of medications on sleep unpredictable. However, one of the most notable and often disabling side effects of high doses of prednisolone (such as those given at the onset of a cluster headache bout) is insomnia. In one of the largest studies of the use of high-dose prednisolone versus placebo for optic neuritis, 70% of patients complained of insomnia compared to 50% placebo (89). In terms of the physiological effects on sleep, it seems corticosteroids reduce REM sleep and increase nocturnal awakenings and increase wake after sleep onset times (90,91). Broader suppression of inflammatory processes which generate hypnotic substances such prostaglandins and interleukins may be partially responsible for this effect.

Lithium is used in the treatment of cluster headache, and has also been reported to be effective in a few cases of hypnic headache (92). Physiologically, it seems to enhance slow wave sleep and reduce REM sleep (93), but also of interest might be its chronotherapeutic effect, especially in the context of these two disorders. Lithium inhibits glycogen synthase kinase-3, a known modulator of the translational transcriptional feedback loop, best characterised within the neurons of the suprachiasmatic nucleus (SCN), which drive circadian rhythmicity, so it may have an effect on both the SCN itself as well as other peripheral oscillators within the CNS. This overall effect is phase lengthening, but may also involve enhancement of the amplitude of the circadian signal (94,95). Adversely, lithium has also been implicated in worsening RLS (96).

Studies examining the direct effects of calcium channel antagonists such as verapamil and flunarizine on human sleep are lacking, despite sleep disturbances being listed as uncommon adverse events in drug labelling. Both agents have the propensity to cause drowsiness, particularly during initiation. Troublesome fatigue, which is common at higher doses of verapamil, may be confused for somnolence, even when reported in clinical trials. Insomnia has been reported with use of both drugs, and vivid dreaming with verapamil (97). Given the crucial function of calcium signalling in the regulation of many of the sleep-wake circuits, it would be wise to expect that these drugs may affect sleep regulatory processes to some degree, and is therefore worthy of further attention, especially in high doses of verapamil used in cluster headache. A recent study showed some quantitative EEG changes in sleep spindle generation with flunarizine, suggesting it has some modifying effects on NREM sleep, although the functional significance of this, particularly with regards to headache disorders, remains unknown (98). It is, however, intriguing that flunarizine is potentially a more useful preventive agent in paediatric migraine, which appears to be more susceptible to modulation by sleep than adult migraine. Verapamil is said not to affect the synthesis of melatonin, but does accelerate its excretion in humans, which may have some impact

on sleep, and may also be relevant in terms of concurrent dosing of both drugs in cluster headache. Preclinical evidence exists to suggest that calcium channel blockers of both L-type (verapamil) and N-type (flunarazine) potentiate and prolong the effects of both benzodiazepine and z-drug hypnotics, with L-type calcium channel blockers showing the greatest effect, and therefore caution might be exercised in prescribing hypnotics in headache patients taking calcium channel blockers as preventive medications (99). Few studies have examined the effects of angiotensin-converting enzyme inhibitors such as lisinopril (bar the well-known side effect of nocturnal cough, which may be very disruptive to sleep) or indeed angiotensin II blockers such as candesartan on sleep.

The xanthine-derivative stimulant caffeine, when used in combination with NSAIDs, can convey a superior effect as an acute treatment of migraine in combination rather than alone (100,101). Caffeine is also analgesic in itself (98), and higher doses of it are useful in the treatment of low cerebrospinal fluid (CSF) pressure headaches. Anecdotal reports also exist that caffeinated energy drinks may be useful at the onset of a cluster headache attacks, and it is well described that caffeine before bed might reduce the likelihood of hypnic headache attacks occurring, as well as offering an acute treatment for the attacks arising during the night (102). This might in part be due to the slow wave sleep-boosting effect caffeine uniquely has in the second NREM-REM or sleep cycle of the night (103). Case series suggest that unlike cluster headache attacks, hypnic headache attacks are more likely to occur several hours after sleep onset (102), which is temporally much more in keeping with state transitions or arousals occurring in the second NREM-REM sleep cycle than in the first.

A drug receiving headache-specific attention of late is sodium oxybate, used primarily in narcolepsy with cataplexy, particularly in patients in whom anticataplectic medications have failed, but is also gaining popularity in the treatment of fibromyalgia (104). This compound, the sodium salt of gammahydroxybutyrate, has an anticataplectic effect in narcolepsy with cataplexy and probably a net daytime stimulating effect of unknown mechanism, which may be due to improved nocturnal sleep. It may modulate dopaminergic, GABAergic, serotonergic and glutamatergic systems, with the most robust effect described being modulation at the $GABA_B$ receptor. It results in a consolidated boost of slow wave sleep in the first NREM-REM sleep cycle of the night, a reduction in stage 1 (light) sleep and REM latency in healthy controls (105,106). It may be these slow wave consolidating effects of the drug, together with an arousal boost during wakefulness, which may have been responsible for reducing the likelihood of attacks of cluster headache occurring in an open-label study of a small number of patients with the chronic form of the disorder (107).

Novel hypnotics

The neuropeptide orexin is inherently linked to arousal and regulation of state transitions, particularly those involving REM. Dual orexin-receptor antagonists have been developed as novel hypnotics (108) and are in development for primary headache disorders, based on preclinical work described elsewhere in this edition of *Cephalalgia* (1). In general, they are reported to reduce sleep latency and sleep after wake onset, increase total sleep time, but not significantly alter slow wave sleep in situational models of insomnia in healthy volunteers (109). At higher doses, however, they recapitulate the phenomenon of sleep-onset REM-periods characteristic of the sleep disorder narcolepsy (109). Interestingly, headache was reported to be the main adverse event in one trial of a dual orexin-receptor antagonist in healthy volunteers (109).

Future directions

The development of novel headache treatments targeting specific receptors may give rise to new understanding of both the mechanisms of sleep regulation, and the interaction between the systems governing sleep and wakefulness and those generating head pain. Close attention should therefore be paid to these symptoms and adverse events in placebo-controlled phase I studies, and where possible an ideal combination of both subjective reporting of sleep effects and objective measures, such as PSG and multiple sleep latency testing should be systematically recorded in subjects. Molecules antagonising specific targets such as orexin receptors, calcitonin gene-related peptide (CGRP) receptors, the 5-$HT1_F$ receptor (lasmiditan), and the transient receptor potential (TRP) channels may offer us much insight into this relationship, as may non-pharmacological interventions such as the use of botulinum toxin and targeted neurostimulation techniques, as is already being learnt from sleep studies in cluster headache patients undergoing deep brain stimulation. Broader approaches may also be employed which sensitively subdivide CNS-related adverse events in clinical trials into more appropriate categories such as treatment-emergent insomnia or somnolence, which combined with personalised medicine approaches offered by large-scale pharmacogenetic association studies may also offer additional insights into the relationship between headache, its treatment and sleep.

Furthermore, the development of drugs with a primary purpose in sleep medicine may prove beneficial in certain headache disorders. This might include weaker stimulants, novel melatonin agonists, potential orexin agonists (being discussed as a potential treatment for narcolepsy) and repurposing of old or shelved hypnotic drugs with clear slow wave-boosting effects such as the $GABA_A$ agonist gaboxadol, or the 5-HT_{2A}-specific antagonists.

It is likely that a combination of a better understanding of the link between sleep and headache both at a preclinical and a human physiological level, coupled with close observation in a translational medicine setting, will offer much towards unravelling this close association.

Clinical implications

- Headache treatments may unmask sleep disturbances, which are physiologically part of the headache attack or underlying headache syndrome, or may cause independent sleep effects.
- Attention should be paid to known effects of headache treatments on sleep, and caution used in their prescription, so as to either avoid worsening pre-existing sleep complaints, or to capitalise on potential sleep effects of medications in a constructive way.
- Consideration needs to be given to specific central nervous system (CNS)-related adverse events involving a disruption in sleep (for instance insomnia, somnolence or daytime sleepiness) when reporting clinical trials.

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Conflict of interest

None declared.

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