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# Hypnotics with novel modes of action

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## Abstract:

Insomnia and more generally lack of sleep are on the rise. Traditionally treated by classical hypnotics, such as benzodiazepines and Z drugs, which both act on the $GABA_A$ receptor, and other modalities, including non-drug therapies, such as cognitive behavioural therapy, there is a range of new hypnotics which are being developed or have recently received market approval. Suvorexant and the likes target the orexin / hypocretin system: they should have less side effects in terms of drug-drug interactions with e.g. alcohol, less memory impairment and dependence potential compared to classical hypnotics.

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## Introduction:

Insomnia is a common sleep disorder characterized by difficulty in initiating/maintaining sleep, or abnormalities in the quality/quantity of sleep, despite adequate time/opportunity for sleeping. Sleep is essential for survival and normal functioning; lack of sleep is detrimental, affecting well-being, metabolism and mental capacities. This is particularly the case in aging, where sleep quality and duration tend to decrease dramatically. It is estimated that 30-50 % of the aged population (> 65) suffer from insomnia, which has negative consequences on cognitive functions, attention, balance and day-time functioning (see (1)). However, the problem of insomnia is not limited to the elderly. A number of neuropsychiatric conditions are characterised by poor sleep: depression, anxiety, PTSD, Alzheimer's diseases, FTD and others. Finally, in our "modern" hyper-stimulated way of life, with TV, media, night life, night shifts, globalisation, jet lag, computers and other devices, a good deal of the young and adult population also suffers from sleep deprivation / fractionation and eventually from insomnia with all its negative consequences.

Traditionally, insomnia has been treated with barbiturates, benzodiazepines (e.g. triazolam, temazepam, estazolam, flurazepam, quazepam), and more recently with Z drugs (e.g. zolpidem, zaleplon, zopiclone and variations thereof) which all act on the same target, the $GABA_A$ receptor, but on different receptor subunits (see e.g. (2)). Histamine receptor antagonists (doxepin, diphenhydramine, doxylamine), or drugs acting on the melatonin system (melatonin, ramelteon, tasimelteon, piromelatine) are used or being investigated. Also used off-label are antidepressants, antipsychotics and serotonin receptor antagonists (e.g. trazodone, mirtazapine, amitriptyline, quetiapine), other GABA drugs (Tiagabine), and plant extracts (valerian). Yet, the most effective way to treat insomnia is cognitive behavioural therapy (CBTi); however, access to and compliance with CBTi are limited, since it takes time for the treatment to become effective (3). Some of the recent approaches for new hypnotics have had a bumpy road and lost momentum (e.g. 5-$HT_{2A/2C}$ receptor antagonists or histamine receptor inverse agonists). The only new active and successful field of research is that of orexin, a major modulator of sleep wake cycle and arousal (4-6) with a number of drugs on the market or at preregistration stage (suvorexant, lemborexant, seltorexant, daridorexant) based on very extensive phase III studies. Until recently, the whole hypnotic field was plagued by an abundance of low powered and only short term studies (see (7)).

## Hypocretin/ Orexin:

The hypnotic landscape, dominated by variations on Z drugs (with different formulations and PK features and/or combinations), changed in 1998 with the discovery of orexins (aka hypocretins), two neuropeptides and their 2 receptors and their role in sleep wake regulation (8-13). By 1999/2001, it was established that orexin neurons, which are exclusively located in the lateral hypothalamus (LH), are absent, and no orexin detected in the CSF, in patients

suffering from type I narcolepsy (narcolepsy with cataplexy) (14-18). In contrast to humans, narcoleptic dogs have a non-functional mutated orexin 2 receptor ($OX_2R$) which is responsible for the disease (19). In rodents, the same clinical phenotype can be reached by either knocking out the peptide or both orexin receptors, or by destroying the LH orexin-producing cells (20-22). Non-detectable levels of orexin have become the diagnostic biomarker for type I narcolepsy (23), a disease which is probably due to an autoimmune defect (24).

By 2007, the first phase II clinical trials in insomnia were reported with Almorexant, a dual orexin receptor antagonist (DORA) by Actelion (25). Almorexant went to phase III, but co-development by GSK and Actelion was stopped. Actelion, now Idorsia, has another DORA in phase III, Daridorexant or ACT-541468 (26) for insomnia and sleep apnoea (NCT03545191; NCT03575104). In 2012/2013, Merck submitted the DORA Suvorexant (27, 28), to regulatory authorities in Japan and the USA, following the largest and longest ever phase II/III trials in primary insomnia (see (29-35)). Suvorexant was accepted in Japan, but the FDA requested further studies with lower doses, as it considers that a good night of sleep lasts 7-8 hours, but not longer. The FDA rejected the 30 and 40 mg doses based on their next morning side effects, primarily somnolence (36). Only a few months later, the FDA accepted the resubmitted, lower doses suvorexant dossier (37). The Australian TGA did the same in 2015/16. Suvorexant (Belsomra®) has to be taken when in bed, 30 minutes before the intended sleep time, and the patient should have at least 7 hours of sleep ahead (37). It is recommended not to drive the morning following treatment (38). Suvorexant has a long half-life, both in terms of PK and receptor occupancy (39), hence these restrictions. The FDA has also unilaterally reduced the starting doses of a number of hypnotics in the last few years, for next morning somnolence and impaired attention, reduced balance and driving abilities (40). In April 2019, more restrictions were applied by the FDA to the use of eszopiclone, zaleplon and the different formulations of zolpidem (41).

Although the double orexin receptor KO in mice leads to narcolepsy with cataplexy, there is little evidence that DORAs will induce cataplexy/sleep paralysis in control animals or humans under baseline conditions. Suvorexant, is contra-indicated in patients suffering from Narcolepsy type I (with cataplexy), as it induced cataplexy-like events in narcoleptic dogs. One needs to keep in mind that canine narcolepsy relates to a null mutation of the $OX_2R$ receptor, which has never been observed in humans (human narcolepsy is due to the absence of orexin producing cells in the lateral hypothalamus and by extension to the absence orexin in the CSF). In the extended phase II/III trials with Suvorexant, sleep paralysis has been observed in a few limited occasions. As far as we can tell, $OX_2R$ receptor antagonists have no such side effects. We have demonstrated that blocking the $OX_2R$ is sufficient to induce sleep which appears physiological (i.e. a proportional increase in REM and NREM sleep), whereas blocking both receptors leads to increased REM sleep only, without effects on deep sleep (42-45). This pattern has been observed in rodents and verified in the clinic

(30, 46). Another DORA (SB-649868), which has a strong $OX_1R$ blocking component, affected only REM, reduced latency to REM and in phase II trial produced sleep-onset REM, which is common in narcolepsy (47). Merck had another DORA in development, filorexant, with a similar profile to suvorexant and which in the clinic produced similar effects on sleep (48, 49). Furthermore, REM sleep may be an issue in some neuropsychiatric disorders (50). Contrary to BZDs and Z drugs, OXR antagonists do not suppress REM sleep. If anything, DORAs strongly promote REM sleep, whereas 2SORAs promote a proportional increase in both NREM and REM sleep. Based on such findings, J&J / Minerva, decided to develop $OX_2R$ selective antagonists: seltorexant (JNJ-42847922, MIN-202) is in late stage development, with positive data in phase in insomnia and adjunctive therapy in depression (44, 46, 51, 52) (NCT03375203, NCT03321526, NCT03227224, NCT02464046).

Most recently, Esai/Purdue, announced two positive phase III trials (Sunrise 1 and 2) with the DORA lemborexant (53-56) (NCT02952820, NCT02783729), but the complete clinical data have not yet been published. Lemborexant is also in phase II for irregular sleep-wake rhythm disorder associated with dementia in Alzheimer's disease (NCT03001557) and obstructive sleep apnoea as is daridorexant.

Altogether, the orexin approach looks very promising. Orexin receptor antagonists do not suffer from drug-drug interactions like the $GABA_A$ targeting molecules, especially with alcohol (57, 58). There is no evidence for cognitive impairment or addiction potential; on the contrary, orexin receptor antagonism appears a viable approach to treat drug dependence, and appears otherwise safe (59-63). The fact that DORAs exclusively stimulate REM sleep could be an advantage in disorders where REM sleep is primarily affected, e.g. Alzheimer's disease (64-67): suvorexant's recent phase III data in AD patients looks highly promising (68). Similarly, orexin receptor antagonists have other clear advantages over benzodiazepines or Z drugs: no general dampening on brain activity, no cognitive impairment (69). Animals or patients treated with orexin receptor antagonists appear to be able to wake up upon adequate stimulation (25, 70, 71), contrary to most other hypnotics. For the time being, it is unclear whether selective $OX_2R$ antagonists and DORAs have different effects on sleep architecture in humans (45, 46, 72, 73); this will be defined in the clinic, based on polysomnography rather than subjective patient-reported data.

## Other approaches:

There are at least 180 known drug discovery and development programmes in big Pharma, Biotech or academic centres dedicated to insomnia over the last 3 decades, in many cases with unknown targets.

Melatonin: the melatonin system appears an obvious target when considering sleep disorders and insomnia. Melatonin is available over the counter in the US and other countries

and is widely used by shift workers or to treat jet lag. Whether melatonin in its various forms (74) or low molecular weight melatonin receptor agonists (ramelteon, tasimelteon) are effective hypnotics is not supported by robust clinical data (7, 75), although some of these molecules have been approved in the US and/or Europe. They are primarily recommended to improve sleep onset. Combination drugs also acting as melatonin receptor agonists are being developed for insomnia (see below) or depression (agomelatine) with variable success.

Serotonin (5-HT): there have been numerous attempts over the last 35 years with 5-$HT_2$ receptor antagonists or inverse agonists (e.g volinanserin) or combinations of 5-$HT_{1A}$ (piromelatine) or 5-$HT_{2C}$ (agomelatine) activity with melatonin agonism for the treatment of insomnia or depression with sleep disorders. In preclinical models, 5-$HT_2$ receptor antagonists improved slow wave sleep. However, the 5-$HT_{2A}$ approach alone (e.g. volinanserin, eplivanserin, pruvanserin, pimavanserin) did not result in breakthrough for the treatment of insomnia and we are still waiting for the other drugs to show positive effects in adequately powered clinical trials (e.g. lumateperone, piromelatine).

Histamine: Some of the antidepressants that are prescribed off-label for insomnia have anti-histamine activity (e.g. doxepin, mirtazapine) with limited effects on sleep maintenance. Although more or less selective $H_1$R inverse agonists have been in the development, most of them seem to be abandoned (LY2624803, ACP125, esmirtazapine) (76) and the European guideline does not recommend histamine antagonists for insomnia.

Melanin Concentrating Hormone (MCH): MCH looks like an interesting target, as it affects both REM and NREM sleep (77). The MCH system is expressed in brain regions compatible with sleep wake regulation including the LH, but no activity in the clinic has been reported so far with MCH modulators.

Various Calcium Channel modulators have been tested in insomnia with variable success, i.e. no breakthrough. The same can be said for $alpha_2$ adrenoceptor modulators e.g. dexmedetomidine and medetomidine; the former is principally used as a sedative in adult intensive care unit patients (78), the latter in animal health. Also, the cannabinoid system has been targeted, e.g. $CB_1$ receptor modulators (e.g. oleamide, which also modulates 5-$HT_7$ receptors or endogenous cannabinoid synthesis modulators) have been investigated. Nabilone, a $CB_1$ receptor agonist, is apparently still in development for insomnia in non-malignant pain patients. 5-$HT_7$ receptor modulators/antagonists were in early preclinical development, due to the location of the receptor in the suprachiasmatic nucleus, with no or little clinical translation.

Propofol and other barbiturates were developed over the several past decades with different formulations, but such approaches are at best life cycle management and barbiturates are not recommended for the treatment of insomnia.

## Conclusion:

Recent breakthroughs in insomnia treatment relate primarily to the orexin system, specifically orexin receptor antagonists, with drugs either on the market or at preregistration stage, that treat insomnia without the side effects of common hypnotics/ sedatives (general dampening, drug-drug interactions especially with alcohol, cognitive impairment, somnolence, negative effects on balance). Targeting the melatonin system in insomnia looked promising, but the clinical data with ramelteon and other melatonin receptor agonists are rather weak, although latency to sleep may be reduced slightly. Along the same lines, preclinical studies in rodents with numerous 5-$HT_2$ receptor antagonists suggested markedly improved slow wave sleep, which however did not translate into the clinic. Histamine appeared to be another interesting target, especially histamine 1 receptors, but drug development has been stopped in a number of cases. Obviously, some off-label use of antidepressants with a histaminergic component is frequent, although variable, in Europe, America and the rest of the world, but then these drugs are not receptor subtype selective. Finally, MCH looked like a very promising target, but so far little has translated into the clinic, acknowledging that the target is relatively new and drug development is a very long process. It should be kept in mind that a healthy life is buoyed by good sleep hygiene, which is not well supported by our "modern" 24/7 way of life with its constant intrusions of the next generation technology.

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