

Drugs affecting sleep and wakefulness: a review

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ABSTRACT

It was in the second half of the twentieth century that Sleep Medicine was recognized as an immensely respected field of clinical research. As a result, past few decades have seen this field making some giant strides towards a better understanding of the neurochemical mechanisms that regulate the state of sleep and wakefulness. This involves a complex interplay of neuronal systems, neurotransmitters and some special nuclei located in the brain. Major wakefulness promoting nuclei being the orexinergic neurons in the lateral hypothalamic region and the tuberomammillary nucleus (TMN) while the sleep-promoting nucleus being ventrolateral preoptic nucleus (VLPO). Sleep-related complaints are one of the common complaints encountered by the physicians and the psychiatrists. As, long-standing sleep disturbances can have far-reaching implications on an individual's physical, mental and social wellbeing, the importance of drugs affecting sleep and wakefulness could not be stressed upon anymore. Broadly, the sleep disorders are classified as insomnia, hypersomnia, and parasomnia and the presently available drugs work either by acting on the sleep-promoting GABAergic system like benzodiazepines, barbiturates etc. or by interacting with wakefulness promoting system like histaminergic system, 5-hydroxytryptaminergic system, orexinergic system etc. There are drugs which interact with other mechanisms which modulate arousal, like melatonin receptor agonists which promote sleep and adenosine receptor antagonists which promote wakefulness. This review article tries to have an overview of the available drugs for use in pathological states of sleep and wakefulness with a special emphasis on the commonly prescribed drugs and the recently approved one's.

Keywords: Circadian rhythm, Insomnia, Orexinergic system, Sleep, Wakefulness

INTRODUCTION

Sleep happens to play a pivotal role in the normal, healthy day to day activities of human beings. It is during this period that the human brain and the body work in sync to provide the necessary rest and recuperation required by an individual to be at the best of his abilities the next day and perform the task that he intends to do.

According to Stahl's textbook of essential psychopharmacology, sleep is considered to be "vital sign" related to psychiatry and is considered equally important and in the same league by psychopharmacologists as pain,

while evaluating the psychiatric health of an individual.¹ The evidence is there supporting the fact that inappropriate sleep may not only affect an individual's mental and physical balance but can even go up to an extent that the person may depart from putting up a civilized behavior in the society and exhibiting appropriate moral principles.²

According to a study in the United States, about 60 million people suffer from long-standing problems related to sleep or wakefulness.³ Though a definite number could not be found in this regard for India, one does not expect these numbers to be very different.⁴

The International Classification of Sleep Disorders-3 (ICSD-3) broadly defines sleep-related disorders in 7 categories (Table 1).⁵

Table 1: ICSD-3 major diagnostic sections.

| |
|---------------------------------------|
| Insomnia |
| Sleep-related breathing disorders |
| Central disorders of hypersomnolence |
| Circadian rhythm sleep-wake disorders |
| Parasomnias |
| Sleep-related movement disorders |
| Other sleep disorders |

Drugs used in sleep and wakefulness disorders manipulate complex interplay of neurons and neurotransmitters thus controlling sleep and arousal states at the desired time of the day.⁶ Though, sleep medicine has made rapid strides in its field in the past few decades an ideal drug which does not extend its effect the next day and has a no potential for abuse is yet to be found.⁶

BIOLOGY OF SLEEP AND WAKEFULNESS

The phenomena of wakefulness are operated by a coordinated interplay of namely five neurotransmitters. They are Histamine, Dopamine, Norepinephrine, Serotonin, and Acetylcholine. These neurotransmitters together form the ascending reticular activating system to maintain the state of arousal. When the very system gets obstructed or impaired due to any reason, it leads to sleepiness.¹

In addition to the circadian inputs contributing to the sleep cycle over a period of 24 hours the body's sleep drive which tries to maintain the normal homeostasis, is also at play.

During the course of the day because of adding up of fatigue the sleep drive increases and starts decreasing during the night while taking rest or sleeping and goes away by next morning. A newly discovered neurotransmitter adenosine has been found to be associated with this drive and is believed to increase in concentration during the day and decrease by the night.^{1,7}

The neurotransmitter histamine is released from the tuberomammillary nucleus (TMN) which acts on the cortex to maintain the state of arousal and on the ventrolateral preoptic nucleus (VLPO), inhibiting the initiation of sleep.

As the day advances, the wakefulness-promoting effect of the circadian inputs starts coming down and finally touches a point when the VLPO nucleus is stimulated leading to sleep/wake switch to be turned off. This leads to release of γ -aminobutyric acid (GABA) which inhibits TMN, thus leading to diminished wakefulness.¹

HOW DO THESE DRUGS ACT IN SLEEP AND WAKEFULNESS?

The conditions leading to excessive daytime sleep (EDS) happen due to the so-called sleep /wake switch being "off" during daytime, drugs promoting wakefulness during the whole duration of the day induce histamine release by the TMN neurons and make the person stay awake.

Conditions leading to wakefulness at night can be treated by administering drugs potentiating GABA, thus promoting sleep. Another mechanism by which they act is by blocking histamine release. The third type of condition occurs because of an anomaly in the body's circadian rhythm. Here it may present either as 'phase delayed' where the sleep-wake switch gets turned on later than the normal expected time during a 24 hour period or as 'phase advanced' with sleep-wake switch getting turned on earlier than normal during a period of 24 hours. While the former situation is seen commonly in depression patients and administering such people with a dose of evening melatonin and exposing them to morning light can bring their circadian clock to normal, the latter condition is most commonly observed in elderly populations thus exposing them to light in the evening and administering melatonin in the morning can turn their circadian rhythm back to normal.¹

PHARMACOTHERAPY FOR INSOMNIA

Diagnostic and Statistical Manual - 5 (DSM-5) defines insomnia as "any dissatisfaction with quality or quantity of sleep which leads to the distress of significant nature or impaired social or workplace performance."⁸

Insomnia is divided mainly into two types. Primary insomnia, which happens to be a condition with a decline in quality of sleep characterized by difficulty in initiating sleep, waking up many times from sleep at night and facing difficulty falling asleep again. This could not be attributed to any co-morbid condition of the patient. Whereas secondary insomnia is a very common condition and is a result of other medical or psychiatric condition like heart diseases, restless leg syndrome or consumption of certain items like alcohol, caffeine, anti-depressants etc.⁹

While prescribing drugs for a patient of insomnia prime importance is given to the quality and the duration of sleep. Though the above two factors are also influenced by some non-pharmacological therapies like relaxation and biofeedback, the pharmacotherapy has to consider the pattern of symptoms, the goals of treatment, patients past response to treatment if any, patients other accompanying conditions, possible adverse effects and of course the cost of the treatment to name a few.¹⁰

Medications approved by FDA for insomnia belong to 3 classes:

- Benzodiazepine Receptor Agonists

- Agonists for melatonin receptors
- Antagonists for H₁ histamine receptors

Though each medication comes with its own share of adverse effects, there was an umbrella warning issued by the FDA covering all these drugs in the year 2007. First, was that all these medications prescribed for insomnia had the propensity towards a rare but possible anaphylaxis reaction of severe degree. They also instructed that patients who go on to develop such reactions should never be re-challenged by giving these medications again. The second concern that the FDA raised was regarding some changes in behavior in patients taking these medications.¹¹

Benzodiazepine Receptor Agonists (BZRA's)

These BZRA's are absorbed very fast from the stomach thus preferred for sleep onset. These drugs act by attaching to GABA_A receptor with varying affinities. While agents of benzodiazepine group show an almost same preference for subunits of α type 1,2,3,5 the non-benzodiazepines prefer the $\alpha 1$ subunit over the others. As the BZRA's modulate the GABA receptor complex allosterically, attachment of these compounds to their target site on the GABA receptor leads to an influx of chloride ions in the cell and thus the inhibitory effect.⁸

Benzodiazepines

- Triazolam - A short-acting benzodiazepine
- Estazolam and Temazepam - Intermediate-acting benzodiazepine
- Quazepam and Flurazepam - Long-acting benzodiazepine

Out of the above drugs, Temazepam happens to be the benzodiazepine which is most frequently advised for insomnia. The choice of these benzodiazepine depends on the desired time of onset and the desired period for which the action of the drug is required. These drugs also have a tendency to fall prey to the phenomena of tolerance thus limiting their use for long duration.⁸ These drugs have also been reported to cause impairment of memory, increased excitement, impulsivity and teratogenicity.¹²

Non-benzodiazepines

These drugs are also known as the "Z" drug. They came into the picture during 1990's. Drugs available for use are zaleplon, zolpidem and eszopiclone.^{8,11}

Zolpidem

The first so-called z drug to break into the scene, zolpidem is an imidazole pyrimidine class drug.¹³ It is the only drug amongst the three which is available not only as immediate release and extended release formulations but also as oral spray and mouth dissolving formulations. An interesting observation with zolpidem was that it did not affect the retrograde part of an individual's memory unlike

benzodiazepines but the anterograde memory was seen to be affected.^{14,15} It was seen that co-administration with drugs like imipramine, ketoconazole etc. led to increased exposure to zolpidem as these drugs inhibit the CYP3A4 enzyme which metabolizes zolpidem.⁸

The recommended dose for zolpidem was 5mg - 10mg. The very fact that female sex metabolizes zolpidem slower than males led to FDA directing the drug companies to decrease the dose for women to 5mg from 10mg and to 6.25mg from 12.5mg for extended-release tablets. Also, the FDA in 2013 notified that some data had shown the levels of zolpidem to be higher in the blood of certain individuals in general. This could result in the residual effects the very next morning, which could culminate in accidents. So they recommended the starting dose to be brought down to 5mg and 6.25mg for immediate release and delayed release tablets subsequently even in case of males.⁸

For people complaining about waking up in the middle of the night and then having difficulty falling asleep again, orally dissolvable formulations in the strength of 3.5mg for males and 1.75mg for females, elderly people and people on concomitant CNS depressant drugs was suggested.¹¹

Zaleplon

A pyrazolopyrimidine class drug, the group of non-benzodiazepines.¹³ The second such drug of the group nonbenzodiazepines for insomnia it has a rapid but shorter period of action thus making it useful for patients with a complaint of getting up in the middle of the night.⁸ This drug was found to have a lesser degree of residual sedation in comparison to zolpidem.¹⁶

It is metabolized by aldehyde oxidase enzyme and concomitant administration of inhibitors or inducers of CYP3A4 do alter the levels of zaleplon in the plasma but not to an extent which needs dose modification. The normal dose range for these drugs is 10mg-20mg with 5mg for elderly and hepatic impairment patients. The drug absorption is delayed with fatty meals and most commonly seen adverse effects of the drug are a headache and dizziness. No serious situation arises on sudden discontinuation of the drug, though return of insomnia episodes can happen.⁸

Eszopiclone

An s-enantiomer of zopiclone, it belongs to class cyclopyrrolone, received approval for treating insomnia on a long-term basis.^{1,13} This drug has a long half-life should be used when a person has at least about 7 hours of sleep time in hand.⁸

Adverse effects most commonly seen in patients with eszopiclone were unpleasant taste in mouth, headache, and dizziness but no signs of any rebound of insomnia were seen on discontinuation of the drug.^{17,18} Maximum dose

approved is 3mg for adults and 2mg in case of patients on concomitant drugs which are CYP3A4 inhibitors and in elderly patients.⁸ Like other members of its group this drug also undergoes rapid absorption in the gastrointestinal tract and its absorption too is delayed by a fatty meal. It is metabolized by CYP3A4 mainly thus dose needs to be modified accordingly when given with inducers or inhibitors of CYP3A4.⁸

Following FDA warning in 2014 regarding impairment of driving abilities the day following drug intake the recommended dose for starters was set at 1mg at night.⁸

Melatonin agonists

Drugs acting via other mechanism to moderate arousal state.¹⁹

Ramelteon

Approved for people having difficulty falling asleep.^{8,11} It acts as an agonist for MT1 and MT2 receptor. These receptors are present in SCN and also known as circadian system's master keeper.¹¹ It has no affinity towards GABA receptors thus bypassing any possibility of abuse of the drug.²⁰ Body's homeostatic drive decides the sleep required by the body and the circadian system facilitates the sleep by coordinating with the day's photoperiod. The arousal driven by the circadian inputs declines at the bedtime, this is the time of body's melatonin release. Agonistic activity at MT1 receptor decreases circadian input towards arousal and facilitates sleep. Same melatonin acts at MT2 receptors and strengthens the rhythmicity of circadian cycle. The dose available is 8mg once in a day.¹¹

Most common adverse effects available with ramelteon are dizziness and nausea.⁸ It undergoes high extent of first-pass metabolism and absorption is delayed with food. As the drug has a half-life of about 1.3 hours, it is not suitable for patients who have the problem of getting up in the middle of sleep but it does help in inducing natural sleep in people having difficulty in falling asleep.^{1,8} Dose needs to be decreased while co-administering with CYP3A4, CYP2C9 inhibitors like ketoconazole, fluconazole etc. and it needs to be increased when using with CYP3A4 inducers like rifampicin. Most importantly, it should not be combined with fluvoxamine, a CYP1A2 inhibitor.⁸

Ramelteon is considered safe in patients if used carefully with hepatic impairment of mild to moderate degree but is not suggested in people with severe derangement of liver functions.^{8,11}

Tasimelteon

Received approval in 2014 by FDA for non 24-hour sleep-wake conditions. About a year later it received approval by European Medicines Agency (EMA) for treatment of above-mentioned condition in case of totally blind

patients. The drug undergoes metabolism by CYP1A1, CYP1A2, CYP2C9, and CYP2D6.²¹

In general deranged lipid profile, alcohol abuse and severe liver and renal compromise are some conditions where melatonin agonists are not indicated.²¹

Tri-Cyclic Antidepressants (TCA)

Doxepin

It has affinity for H₁ receptors and causes sedation at extremely low doses in comparison to the dose used for depression. It was approved for use by the FDA in 2010 in people having a problem in maintaining sleep. Histamine is a wakefulness-promoting neurochemical so drugs like doxepin which act at histamine H₁ receptors as antagonists at low doses promote sleep. These drugs are supposed to be given half an hour before the time of going to bed at night. Starting from 3mg dose can be titrated up to 6mg in patients with normal liver functions and maximum 3mg in geriatric patients and patients with impaired liver function.^{8,11}

At doses higher than that prescribed for insomnia, other variety of receptors may get activated and negate the sedating effects of H₁ antagonist action of doxepin. No residual effects are seen with this drug at doses prescribed for insomnia. Food delays absorption of the drug especially fatty food thus it is directed that the drug should not be consumed within 3 hours of food intake. CYP2C19 and CYP2D6 are responsible for the drugs, metabolism. The drug should be avoided in patients with urine retention of severe degree and pre-existing narrow-angle glaucoma, also doxepin should not be given with MAO inhibitors concomitantly.^{8,11}

Orexin receptor antagonists

Suvorexant

An antagonist of the orexin receptors it is the most recent addition to the family of drugs approved for prescription in case of insomnia, in 2014.²² It is approved for treating insomnia of both types, be it related to the inability of falling asleep or difficulty in maintaining sleep.²² Suvorexant acts as an antagonist for this wakeful state maintained by orexinergic neurons and induces sleep. Since it does not involve GABA receptors, there are no chances of adverse effects like a hallucination, dependence etc.²²

Suvorexant's absorption happens to be inversely related to its dosage as an 80mg leads to a lesser bioavailability in comparison to 10mg. It is advised better to take empty stomach as food prolongs the absorption. CYP3A4 is responsible for a major share of the drug metabolism apart from CYP2C19 which metabolizes a small portion of the drug.²²

Animal studies showed that suvorexant increases REM sleep.²² With regard to human trials as of now, 3 trials (randomized, placebo-controlled, double-blinded) have been done to evaluate the safety and efficacy of suvorexant and all the trials showed improvement in the sleep patterns of the test groups in comparison to the placebo group.²³⁻²⁵ Commonest side effect was found to be somnolence in one of the trials in about 1.6% of people in a group which was receiving the approved starting dose of the drug. The adverse effects were found to be dose-dependent and more in women. No alarming adverse effects were seen, and neither was any significant rebound phenomena reported on withdrawal of the drug.^{23,25} Four drug strengths have been approved by the FDA for suvorexant they come in doses of 5,10,15,20mg with the starting dose being 10mg supposed to be taken half an hour before going to bed. 20mg is the maximum permitted dose of suvorexant. For patients on concomitant CYP3A4 inhibitors, the starting dose was decided to be 5mg and maximum dose to be only up to 10mg.²²

Barbiturates

Though barbiturate use has been approved by FDA for treating insomnia the use is not much encouraged due to the remarkable degree of adverse effects coming with these apart from the possibility of development of dependence and their therapeutic window being narrow.⁸

Off-label treatment of Insomnia

Many drugs are being prescribed for insomnia though they have not been approved for that purpose. The reason being their pharmacological properties which induce sedation. This is mostly seen with the antidepressants and antipsychotics.¹¹ Since these drugs also have some degree of antagonism at serotonergic and histaminergic receptors, it leads to sedation but the problem with using these drugs lies with their long half-lives which may lead to prolonged sedation.¹¹

Trazodone

Inhibits about 50% of 5HT_A receptors at a dose of around 10mg, thus can be used as a hypnotic. For insomnia 25mg or 50mg of trazodone is recommended with maximum up-titration permitted, up to 100mg.²⁶

Mirtazapine

Acts as a sedative by antagonizing H₁ histaminergic receptors. Used for insomnia in a dose of 30mg every night before retiring to bed. One noteworthy point with this drug is that if the dose of the drug is increased the sleep-promoting effect of the drug may go away.⁸

Other TCA's

Apart from doxepin which is approved for treatment in case of insomnia other TCA's like amitriptyline,

imipramine is prescribed for insomnia treatment. But these drugs are not very popular in presence of other safer options and also because they are not considered very safe in the geriatric population.⁸

Atypical antipsychotics

Drugs like quetiapine, risperidone etc. are used for insomnia. The sedation is caused by their antagonistic action on H₁ receptors for histamine and 5HT₂ receptors for serotonin receptors. Again, their use is not very popular in the wake of possible adverse effects like extrapyramidal effects, metabolic syndromes, and availability of safer options.⁸

Finally, some over the counter drugs are also present for use such as antihistamine like diphenhydramine but these have no supporting data and also because resistance to the sedative effects of the drug develops very fast, they are not much preferred. Other such drug is melatonin, which comes as a nutritional supplement but is used for treating insomnia which happens in people after shift work or in travelers suffering from jet lag.⁸

PHARMACOTHERAPY OF NARCOLEPSY

Narcolepsy is an incurable neurological condition where the sleep and wake cycle of the individual is disturbed, and the person exhibits Excessive Daytime Sleepiness (EDS) with REM type sleep. The ICSD -3 classifies narcolepsy in 2 divisions.²⁷

Narcolepsy Type 1- it is narcolepsy accompanied with cataplexy (cataplexy is a sudden loss of tone in the muscles of the body and is one of the pathognomonic findings of narcolepsy with about 70% people having it).²⁷ In this condition, there is a loss of hypocretinergic neurons by possibly an autoimmune etiology.²⁸

Narcolepsy Type 2- It is also a disorder of central hypersomnolence but without cataplexy. The hypocretin neurons are not damaged here, so the etiology of the condition is not quite clear.²⁸

Clinically diagnosis of narcolepsy is done based on five symptoms. They are:²⁷

1. Excessive daytime sleepiness
2. Cataplexy (except for narcolepsy type 2)
3. Hallucination (Hypnagogic and hypnopompic type)
4. History of interrupted sleep at night
5. Sleep paralysis

Treatment for narcolepsy is more symptomatic.²⁸ The drugs used for narcolepsy and cataplexy are:

Methylphenidate

Approved by FDA for treatment of EDS.²⁷ It is a drug which blocks monoamine reuptake. For example -

Dopamine.²⁸ It is used when modafinil and sodium oxybate could not give the expected result. The short-acting formulation and the sustained release one's both are available for this drug. It has been found to be having lesser side effects like tachycardia, palpitation raised blood pressure and some neurological ones like anxiety. They also have a low risk of abuse.²⁸ Starting dose is 10mg and can go up to 60mg in one day.²⁸

Amphetamines

Another class of drugs approved for EDS. It works by increasing the dopamine and norepinephrine concentration. The dextroamphetamine isomer focusses on the dopamine pathway and thus increases stimulation.²⁸ The starting dose is 5mg and can go up to 60mg per day.

Though at lower doses the drug does not show too serious side effects and resembles methylphenidate in those terms, at higher doses it leads to irritability, insomnia etc. These drugs are contraindicated in patients with a history of cardiovascular disease.²⁸

Modafinil

It is the first-line drug for EDS approved by FDA and EMA. It has been observed that it increases the activity of neurons involved in the promotion of wakefulness by blocking the dopamine transporter which leads to a rise in the concentration of dopamine extracellularly. Studies had revealed that modafinil was efficient in a dose of 200-400mg in a day for controlling EDS. The starting dose was 100mg twice daily and could be increased to 200mg two times daily i.e. its maximum limit that was approved. Overall it did not show any serious side effects, rarely allergic reactions related to skin were seen. It was found to increase enzymes of cytochrome P450 class and thus metabolism of oral contraceptives.²⁸

Modafinil's R enantiomer, Armodafinil has been developed and found effective in controlling EDS and worked for a longer duration than modafinil. The upper limit for the dose was 250mg in a day.²⁸

Sodium oxybate

Approved by FDA it acts on the GABA-B receptor complex as an agonist. It is found to provide better quality sleep and relief from cataplexy too.²⁸

This is the only drug approved by FDA and EMA for both narcolepsy and cataplexy. As the half-life of the drug is about 1 hour, the patient is administered 2.25g of the drug before going to bed and then another 2.25g after about 4 hours of sleep (The patient actually has to wake up and take the drug). This is done for 4 weeks then the dose is titrated up to 6g a day. The dose most suited for the desired action is 9g in a day in two divided doses and it takes 1-2 months to show maximum benefits.²⁸

Adverse effects seen mainly were headache, nausea and neurological symptoms like anxiety, confusion etc. Risk of abuse was seen to be minimal with the drug.²⁸

Mazindol

It is a drug which can be obtained only following the approval of National Drug Agency in France. This drug acts by inhibiting dopamine and norepinephrine reuptake and also has a minor action in promoting the release of dopamine. Dose used for narcolepsy starts from 1mg a day to a maximum of 4mg in a day. Rare incidences of valvular heart disease, pulmonary hypertension have been reported with this drug, otherwise, common adverse effects seen are dry mouth, constipation.²²

Antidepressants

The first class of drugs used for cataplexy in narcolepsy type 1 was TCA's. They work by inhibiting MAO reuptake.²² Drugs like Clomipramine in a starting dose of 10mg a day is the most commonly used drug in this class. This dose usually goes up to 25mg a day. In certain conditions, it can go even up to 100mg a day but the flip side of these drugs is a greater degree of side effects in comparison to SSRI's and SNRI's.²²

Venlafaxine, an SNRI is very commonly used in cataplexy. Dose ranges from 37.5mg a day to 300mg a day. No serious side effects are observed and complaints of nausea, dry mouth and dizziness have been noted.²²

Similarly, SSRI's like Fluoxetine, Citalopram are also used for cataplexy.²²

Pitolisant

Approved for use in European Union on March 31st 2016, pitolisant is an H₃ receptor inverse agonist for narcolepsy with cataplexy or without it. It received orphan drug status from FDA in 2010.²⁹ It has not been approved by CDSCO till date. Starting dose recommended was 4.5mg per day and could be up-titrated up to 30mg in one day.²⁹ It undergoes rapid absorption after oral administration and is metabolized mainly by CYP3A4 and CYP2D6. With a half-life of around 12 hours, it is excreted mainly in urine.²⁹

In case of mild liver impairment no adjustment in the dose is required but in case of severe impairment of liver function, it is contraindicated. Pitolisant has high affinity towards H₃ receptors in comparison to other receptors.²⁹

In phase III trials it was found to be efficient in controlling EDS with cataplexy or without it but was found to be inferior to modafinil in this regard.²⁹

In the trials, pitolisant was found to be effective in decreasing EDS. It also brought down daytime sleepiness episodes in the patients with narcolepsy. In another study,

it also showed a decrease in number of cataplexy episodes in treatment-resistant patients. It was a relatively safe drug with no severe adverse effects reported in patients during the trials. The commonest adverse events reported were headache, insomnia etc. No drug abuse potential or withdrawal effects were seen with the drug.²⁹

Narcolepsy Type 2

For treatment of EDS same drugs are used with same guidelines for narcolepsy type 1.

DRUGS FOR FUTURE

With the discovery of orexin peptide and development of drugs like suvorexant, newer avenues are being explored for treating insomnia so one may expect few more drugs breaking into the scene in future which will have some better qualities than its predecessors. Similarly, in the pharmacotherapy of narcolepsy hypocretin replacement therapy is being explored further and hypocretin therapy related to genes has shown promise. Also, given the immune-mediated destruction being the possible reason for orexin deficiency immunotherapy is also being explored in this regard. Other than these new stimulant drugs like (JZP-110) a derivative of phenylalanine with a dopaminergic combined with noradrenergic activity is also being tried. So one hopes that a better and smarter option emerges in the coming years.²⁸

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