# The Efficacy and Safety Difference Between Daridorexant and Suvorexant

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**Abstract.** The prevalence of insomnia is rising in today's culture under the influence of many factors. However, experts have long been concerned about the negative consequences and effects of hypnotic medicines. Currently, more and more researchers are focusing on the effects of drugs that target orexin receptors on sleep. Both daridorexant and Suvorexant are two effective dual orexin receptor antagonists in treating insomnia. According to the data collected from Google Scholar, JSTOR, NCBI, and PMC, the comparison of the effectiveness and the abuse potential between daridorexant and suvorexant is concluded. Suvorexant already is a common medicine for patients. The best dose for suvorexant is 30/40mg. Suvorexant has some unserious side-effects like nasopharyngitis. Daridorexant is a relatively new drugs that just enter the market in 2022. It has more function than Suvorexant like improving day-time function and sleep structure. The best dose for daridorexant is 50 mg. Daridorexant has unserious side-effects like fatigue and somnolence.

**Keywords:** Insomnia; Dridorexant; suvorexant; efficacy; security.

## 1. Introduction

According to a 1994-1995 study in the United States, 23% of the population suffered from insomnia [1]. In the fast-paced life of today, it is more commonly to have difficulties in falling asleep, and this symptom is defined as insomnia. The prevalence of insomnia among adults is high, estimated to be between 35% and 50%. And The prevalence of chronic insomnia as defined by specific diagnostic criteria is estimated to be 5-15% [1]. Insomnia is more common in women, those of lower socioeconomic status, and those with medical or psychiatric conditions [1, 2]. Prolonged insomnia has a lot of bad influences, such as heart disease, high blood pressure and dementia. In order to deal with this tricky disease, a series of drugs for insomnia have been released one after another.

However, many drugs for insomnia may have side effects. While daridorexant, a new drug for insomnia may have better curation and less side effects, it is slowly making its way into the limelight.

First approved by FDA for the treatment of adult insomnia patients in 2022, daridorexant is an oral dual orexin type 1and type 2 (abbreviated to OX1and OX2) receptor antagonist [3]. The hypothalamic peptides known as orexins include subtype A and B (sometimes referred to as orexins 1 and 2). They are virtually exclusively generated in the brain by unique neurons of the perifornical lateralis hypothalamus; in addition to short intrahypothalamic projections, these neurons transmit long and short axonal projections to a variety of different locations of the brain. A key role for orexins in the regulation of behavioral arousal, sleep, and wakefulness is indicated by the distribution of orexin fibers and receptors in brainstem, limbic, and basal forebrain regions—regions connected to the control of REM sleep and waking [4]. The neuropeptides orexin, also known as hypocretin, that promote wakefulness, are mostly produced by a small subset of the hypothalamus' neurons, and daridorexant inhibits their actions. To accomplish this, daridorexant exactly binds to both orexin receptors and has an equally potent antagonistic effect on OX1R and OX2R [5]. As a result, the medication can reduce "hyperarousal" and enhance irregular sleep.

Among the special qualities of daridorexant are its ability to support healthy, natural sleep, maintain memory and thought, prevent the development of physical dependency or tolerance, and

enhance daytime performance [5]. In two key phase III trials, participants who took daridorexant successfully reduced wake time following the start of sleep and the latency to persistent sleep, daridorexant can improve the daytime function when patients took 50 mg as well [3]. The tolerability of daridorexant is not a problem for patients. A 12 mouths extension study did not find any evidence that prove the existence of tolerability of daridorexant [6]. However, a phase II clinical research revealed side effects such as nasopharyngitis, headaches, inadvertent overdoses, exhaustion, nausea, dizziness, and sleepiness [3]. Besides, the dependency on daridorexant increased with increasing dose. As a new drug that is expected to solve insomnia, how to reduce its side effects needs more clinical trial data to research.

## 2. Methods

### 2.1. Data Sources and Description

In this paper, we searched various academic websites for the information we needed. These academic websites include Google Scholar, JSTOR, NCBI, and PMC. We logged into the sites, looked up the papers and cited the data in the papers. To categorize the data in more detail, we can break it down into the duration of action of various soporific drugs in animals and humans, the effects of the action (e.g., sleep-aiding effects, time interval between dosing and onset of action), and the proportion of side effects, etc. Data from a 2018-2020 phase III clinical trial evaluating the efficacy and safety of ACT-541468 (daridorexant) in the treatment of insomnia disorder were obtained from National Center for Biotechnology Information (NCBI). The clinical trial covers multiple regions, including ten countries in Europe and North America. The number of participants in the clinical trial was 930 who were all at least 18 years old and diagnosed with insomnia. MK-4305 (suvorexant) safety and efficacy study data are also from NCBI, which was studied in 2010-2011, with 1023 volunteers and the same age requirements as the previous study.

### 2.2. Selection and Description of Indicators

This study mainly focused on two hypnotic drugs, daridorexant and suvorexant. Daridorexant was marketed by the FDA in 2022 and the other was approved for marketing by FDA in 2014. The indicators from two clinical trials are following (Table 1).

**Table 1**. Indicators of two hypnotic drugs

| Drug | Daridorexant | Suvorexant |
|---|---|---|
| Responsible Party | Idorsia Pharmaceuticals Ltd. | Merck Sharp & Dohme LLC |
| Intervention/Treatment | Daridorexant 25 mg<br>Daridorexant 50 mg<br>Placebo | Suvorexant High Dose (HD)<br>Suvorexant Low Dose (LD)<br>Placebo |
| Drug Administer | tablet form<br>once a day<br>at night | tablet form<br>once a day<br>at bedtime |

### 2.3. Methods Introduction

As shown in Fig 1, this paper prepares to discuss the potency and side effects of two hypnotic drugs. By means of comparation between daridorexant and suvorexant, this study would draw appropriate conclusions about the two drug and direction of new drug development.

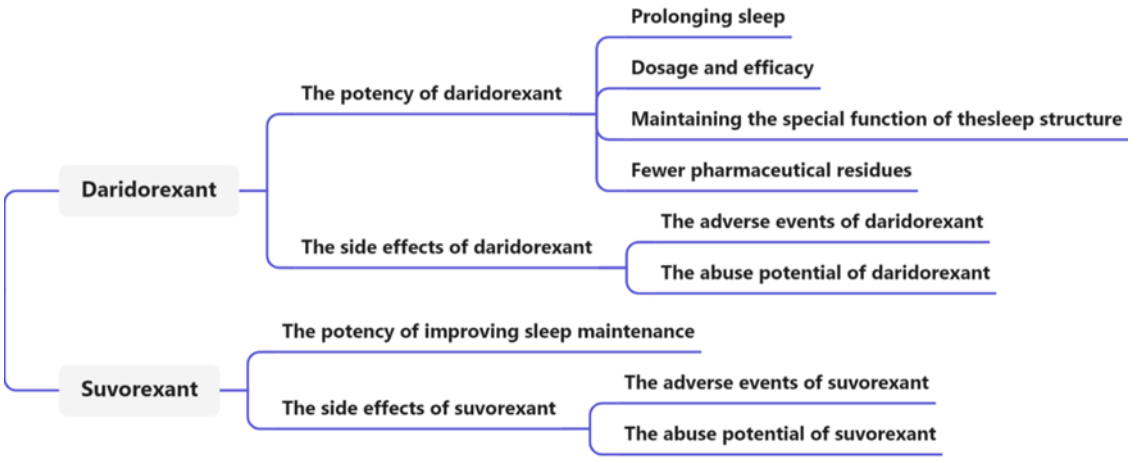


**Fig. 1** The diagram of comparative discussion

## 3. Results and Discussion

### 3.1. The Potency in Prolonging Sleep of Daridorexant

After Treiber did an experiment with rats to test the efficacy of daridorexant. Treiber et al. pointed out that the administration of daridorexant can decrease active wake time by 22% in comparison to the rats who was in the control subjects. Furthermore, the medication boosted REM and non-REM sleep, respectively, by 84% and 29% [7].

### 3.2. The Potency in Dosage and Efficacy of Daridorexant

Muehlan et al. carried out an experiment to explore the potency of daridorexant and the difference in efficacy of different doses of daridorexant. After analyzing the data, they found that daridorexant has the ability of reducing energy and concentration. Additionally, they found that doses of 5 mg had negligible effects, whereas doses of 25 mg or greater had significant effects on the central nervous system. While the highest effect happened almost 1.5 hours after taking 100 mg, all these effects happened an hour after dose. After 200 mg, the greatest benefits were seen two hours later. Within 3-6 hours and 6-8 hours, respectively, daridorexant's side effects at dosages of 25 and 50 mg returned to normal [8].

### 3.3. The Potency in Improving Sleep Structure of Daridorexant

Another experiment demonstrated that daridorexant has no effect on sleep itself, it mainly relies on reducing wakefulness. In the experiments, as shown in Table 2 which concluded the data in physiological proportions after administering daridorexant, scientists gave daridorexant to rats at the beginning of their dormant stage. However, this treatment didn't prolong the time rats spend on sleep. So, scientists realized that daridorexant will not affect the architecture of sleep [9].

**Table 2**. The data in physiological proportions after administering daridorexant

| group | dosage(*10mg/kg) | active weak | quiet weak | NREM sleep | REM sleep |
|---|---|---|---|---|---|
| 1 | Vehicle | 39.9 | 35.9 | 18 | 6.2 |
| 2 | 1 | 35.3 | 35.5 | 21.7 | 7.4 |
| 3 | 3 | 31.1 | 35.1 | 24 | 9.8 |
| 4 | 10 | 27.3 | 34.2 | 27.5 | 11 |
| 5 | 30 | 27.3 | 30.1 | 33.4 | 9.2 |

### 3.4. The Potency in Pharmaceutical Residues of Daridorexant

Finally, scientists didn't observe any leftover sleepiness or any memory and attention problems in the morning of the next day, which indicated that daridorexant is unlikely to produce sequelae the

next morning [10]. Overall, darodorexant is an efficient and safe drug. It has a promising development in the future.

### 3.5. The Adverse Events (AEs) and Abuse Potential of Daridorexant

Although daridorexant is safe in clinical practice, excessive dosage can still lead to some adverse effects. These side effects include somnolence, nausea, dizziness, fatigue, accidental overdose, headache and nasopharyngitis [11]. Scientists carried out several other experiments, in the experiment, they gave the volunteers a placebo, 25 and 50 milligrams of daridorexant, respectively. The outcomes validated their former conclusions. The phenomenon of hypnagogic and hypnopompic hallucinations, which happened in 0.6% of patients treated with daridorexant 25 mg but not in any of the patients treated with higher doses of daridorexant or placebo, was a distinctive quality [12]. From Table 3 and Fig 2, we can find that for these diseases, daridorexant promoted their morbidity relative to placebo.

**Table 3**. Summary of adverse events

| Diseases doses | placebo | 25mg | 50mg |
|---|---|---|---|
| nasopharyngitis | 6% | 7% | 6% |
| headache | 4% | 5% | 6% |
| accidental overdose | 2% | 1% | 3% |
| dizziness | 1% | 2% | 2% |
| nausea | 1% | <1% | 2% |
| somnolence | 2% | 4% | 2% |
| sleep paralysis | 0 | 0.5% | 0.3% |

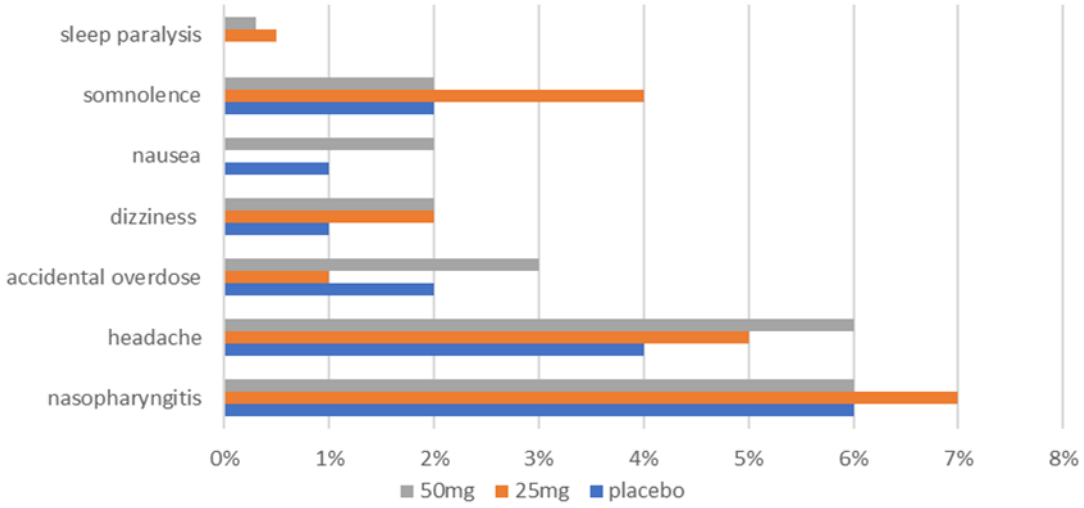


**Fig. 2** Probability of disease emergence of different doses of daridorexnat

In nonclinical tests, daridorexant did not show any traits of a common problem for traditional hypnotics that the development of tolerance. There was no elicit self-administration in rats of daridorexant prove that the abuse potential will be low on human [13]. As the well score of daridorexant in clinical trials, the abuse potential of daridorexant is low. In a study that lasted 52 weeks and included 804 participants, the most common reported Treatment Emergent Adverse Event (TEAE) about drug abuse is accidental overdose. In these reports, patients did not receive a euphoria feeling, and all the TEAEs were non-serious. After a 52-week treatment, participants did not have a withdrawal symptom, or rebound insomnia [14]. All those evidence shows that the abuse potential of daridorexant is low.

### 3.6. The Potency of Suvorexant

Joseph Herring et al. conducted a phase III clinical trial to explore the improvement of different doses (40/30 mg and 20/15 mg) of suvorexant. As shown in Table 4 and 5, the high dose group and low one was revealed to be overall superior to placebo in 1-month and 3-month Mean Subjective Total Sleep Time (sTSTm), Wakefulness After Persistent Sleep Onset (WASO), and Latency to Onset of Persistent Sleep (LPS) measurements, despite the data for LPS in the suvorexant 40/30 mg is low than that for placebo.

**Table 4**. Baseline scores of three treatment plans

| Treatment | | 40/30 mg | 20/15 mg | Placebo |
|---|---|---|---|---|
| Mean (SD) Baseline Scores | sTSTm, min | 316.1 (67.2) | 322.4 (57.3) | 315.7 (65.1) |
| | WASO, min | 117.7 (49.6) | 119.2 (46.5) | 114.9 (45.7) |
| | LPS, min | 61.8 (39.1) | 68.9 (49.7) | 66.2 (44.1) |

**Table 5**. Adjusted mean change from baseline (95% CI) in least squares.

| Numble | | 40/30 mg | 20/15 mg | Placebo |
|---|---|---|---|---|
| Mouth 1 | sTSTm, min | 42.6 (37.3 to 48.0) | 39.4 (32.8 to 45.9) | 23.1 (17.7 to 28.4) |
| | WASO, min | -45.0 (-50.1 to -39.9) | -45.0 (-51.2 to -38.9) | -18.7 (-23.7 to -13.6) |
| | LPS, min | -34.5 (-38.1 to -30.9) | -33.6 (-37.9 to -29.2) | -23.3 (-26.9 to -19.7) |
| Mouth 3 | sTSTm, min | 60.3 (54.8 to 65.8) | 51.2 (44.4 to 58.1) | 40.6 (35.0 to 46.1) |
| | WASO, min | -47.9 (-53.2 to -42.6) | -41.6 (-48.0 to -35.2) | -25.0 (-30.3 to -19.8) |
| | LPS, min | -36.0 (-39.7 to -32.4) | -34.7 (-39.1 to -30.2) | -26.6 (-30.2 to -22.9) |

According to the data about the difference (95% CI), they found that high dose group appeared to be slightly more effective than low one for most measurements and time points. Suvorexant effects tended to be more prominent for sleep maintenance (sTSTm, WASO) than sleep onset (LPS) [15].

### 3.7. The Adverse Events and Abuse Potential of Suvorexant

Table 6 shows the serious adverse events and other (not including serious) adverse events reported in Treatment (TRT) and Extension (EXT) phases of this clinical trial. In the former phase, the incidence of serious adverse events in the suvorexant low dose group and the high dose one was similar, while the incidence of placebo group was higher. The number of other adverse events in the high dose group was nearly twice as high as in the low one. In the latter phase, only three serious events were in the group of suvorexant 40/30 mg, whose number of other adverse events was over twice as high as in the suvorexant 20/15 mg and more than 4 times higher in the placebo group.

**Table 6**. Summary of adverse events-number (%)

| Group | | TRT Phase | | | EXT Phase | | |
|---|---|---|---|---|---|---|---|
| | | Low dose | High dose | Placebo | Low dose | High dose | Placebo |
| Serious Adverse Events | Total | 1 (0.39) | 0 | 20 (5.21) | 0 | 4 (2.33) | 0 |
| Other Adverse Events | Total | 51 (20.08) | 107 (27.94) | 76 (19.79) | 6 (6.00) | 17 (9.89) | 3 (1.99) |
| | nasopharnygitis | 18 (7.09) | 33 (8.62) | 35 (9.11) | 4 (4.00) | 10 (5.81) | 1 (0.66) |
| | headache | 19 (7.48) | 33 (8.62) | 28 (7.29) | 1 (1.00) | 4 (2.33) | 1 (0.66) |
| | somnolence | 14 (5.51) | 41 (10.70) | 13 (3.39) | 1 (1.00) | 3 (1.74) | 1 (0.66) |

This means that increasing the dose of the drug may be more likely to cause adverse effects. Among the records, the most common adverse event was nasopharyngitis. In the nonclinical trial of suvorexant, according to the data of rats and non-human primates, suvorexant does have a sign for abuse potential or dependance. In a clinical trial, less than 4 percent participants reported AEs that correlate with drug abuse. This shows that the possibility of drug abuse of suvorexant can be ignored. However, the alcohol or other drugs abuse history may have a negative effect on the abuse potential on suvorexant [16].

## 4. Conclusion

The available treatments for persistent insomnia have not been found to be effective for all people. However, diridorexant serves a variety of distinct purposes, and the introduction of daridorexant may alter this phenomenon. Overall, the hypnotic medications daridorexant and suvorexant are both successful. They are both highly utilized as medicines in the treatment of insomnia. Suvorexant is already a familiar drug in common households, while daridorexant is a relatively new drug that just enter the market in 2022. As a promising new drug, daridorexant has less side-effects compared to suvorexant in clinical trials, which is more stable for patients to use. In addition, daridorexant includes a new function that pervious drugs do not included, which is the ability to improving the sleeping structure. Thanks to the discovery of daridorexant, people can get through second day without any drug residue influencing people. Daridorexant has a very minimal potential for abuse, is intended to sustain cognitive function, does not develop tolerance with prolonged usage, and does not rebound. In the future, researchers will dig deeper in the field of daridorexant, and other former hypnotic drugs may be replaced by daridorexant because of its effectiveness.

## Authors Contribution

All the authors contributed equally, and their names were listed in alphabetical order.

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