IZDEBSKA, Wiktoria, SORNEK, Patrycja, STANEK, Jakub, KAŹMIERCZAK, Anna, PERKOWSKA, Klaudia, BORKOWSKA, Agata, KIEŁB, Anna, PAWLAK, Igor, MICH, Anna, CIESIELSKI, Radosław. Daridorexant as a new dual orexin receptor antagonist for insomnia – a literature review. Quality in Sport. 2024;30:55710. eISSN 2450-3118.
https://dx.doi.org/10.12775/QS.2024.30.55710
https://apcz.umk.pl/QS/article/view/55710

The journal has been 20 points in the Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 19.10.2024. Revised: 20.10.2024. Accepted: 26.10.2024. Published: 27.10.2024.

Daridorexant as a new dual orexin receptor antagonist for insomnia – a literature review

Wiktoria Izdebska

ORCID: https://orcid.org/0009-0005-0242-141X

E-mail: wiktoriaxizdebska@gmail.com

J. Gromkowski Regional Specialist Hospital in Wrocław

Koszarowa 5, 51-149 Wrocław, Poland

Patrycja Sornek

ORCID: https://orcid.org/0009-0003-9630-055X

E-mail: sornekpatrycja5@gmail.com

Military Medical Academy Memorial Teaching Hospital - Central Veteran Hospital

Stefana Żeromskiego 113, 90-549 Lodz, Poland

Jakub Stanek
ORCID: https://orcid.org/0000-0002-9450-7261
E-mail: jakubstanek22@gmail.com
Medical University of Lodz
Tadeusza Kościuszki 4, 90-419 Lodz, Poland

Anna Kaźmierczak
ORCID: https://orcid.org/0009-0000-8435-6685
E-mail: a.kazmierczak.1998@o2.pl
4th Military Clinical Hospital in Wrocław
Weigla 5, 53-114 Wrocław, Poland

Klaudia Perkowska
ORCID: https://orcid.org/0009-0001-7362-4995
E-mail: dr.kperkowska@gmail.com
Military Medical Institute
Szaserów 128, 04-349 Warsaw, Poland

Agata Borkowska
ORCID: https://orcid.org/0009-0008-7347-7762
E-mail: agata.borkowska.ab@wp.pl
Military Institute of Aviation Medicine
Zygmunta Krasińskiego 54/56, 01-755 Warsaw, Poland

Anna Kiełb
ORCID: https://orcid.org/0009-0005-3152-5429
E-mail: akielb97@gmail.com
5th Military Clinical Hospital in Krakow
Wrocławska 1-3, 30-901 Krakow, Poland

Igor Pawlak
ORCID: https://orcid.org/0009-0003-1942-9296
E-mail: igor.a.pawlak@gmail.com
Independent Public Hospital in Mińsk Mazowiecki
Szpitalna 37, 05-300 Mińsk Mazowiecki, Poland

Anna Mich
ORCID: https://orcid.org/0009-0004-6299-5506
E-mail: aniamich97@icloud.com
Independent Public Hospital in Mińsk Mazowiecki
Szpitalna 37, 05-300 Mińsk Mazowiecki, Poland

Radosław Ciesielski
ORCID: https://orcid.org/0000-0002-3458-2024
E-mail: radoslaw.ciesielski@yahoo.com
Independent Public Hospital in Mińsk Mazowiecki
Szpitalna 37, 05-300 Mińsk Mazowiecki, Poland

Corresponding author: Wiktoria Izdebska, wiktoriaxizdebska@gmail.com

Abstract

Introduction and purpose of review: Insomnia is a prevalent disorder responsible for multiple negative effects on human health. Its treatment involves both non pharmacological and pharmacological methods, however many common insomnia medications are recommended not to be used long term. Daridorexant is a new dual orexin receptor inhibitor, recently approved by the EMA for use in the European Union. The aim of this study is to present current knowledge concerning daridorexant safety, efficacy and general characteristics.
Methods: Pubmed database literature review has been performed. Relevant studies regarding daridorexant and insomnia have been assessed. Product characteristics available on EMA, FDA and Idorsia Pharmaceuticals websites have also been inspected.
Current state of knowledge: Studies suggest that daridorexant is generally safe and significantly improves the night-time and daytime functioning of people suffering from

insomnia, by enabling them to fall asleep in shorter periods of time and stay asleep for longer. It increases time spent in both REM and non-REM phases proportionally and does not disturb physiological sleep architecture. It shows no residual effects in the morning and can be used long-term, with no reduced efficacy and with no signs of physical dependence or withdrawal symptoms. It rarely leads to serious adverse effects and is contraindicated only in a few groups of patients.

Conclusions: Daridorexant is a recently approved dual orexin receptor inhibitor with a promising long-term use safety and efficacy profile. As it is a new medication, further investigation concerning the side effects observed over time should be advised.

Keywords: daridorexant; DORAs; dual orexin receptor antagonists; orexin; insomnia; treatment

Introduction

Insomnia is a prevalent disorder [1] associated with difficulty initiating sleep, maintaining sleep or early-morning awakenings [2]. It causes negative effects on daytime functioning such as fatigue, irritability, memory impairment and reduced motivation and is associated with deterioration of academic and work performance [1, 3, 4]. It is estimated that the annual loss of quality-adjusted life years from insomnia might be higher than the loss caused by many other common medical conditions such as depression, arthritis and hypertension [5, 6].

Despite the fact that insomnia often coexists with other medical comorbidities such as respiratory and gastrointestinal disorders, it is a distinct condition and should be treated as such [3, 7]. Insomnia treatment involves both pharmacological and non pharmacological ways. Its suggested first-line approach is a cognitive behavioral therapy (CBT-I) which is a fully non pharmacological method, now extended to a digital version - digital behavioral therapy (dCBT-I). CBT-I combines cognitive therapy with behavioral and educational interventions [5, 8]. Pharmacological insomnia treatment includes numerous off-label and over-the-counter

substances as well as medications approved by the U.S. Food and Drug Administration (FDA). FDA approved drugs involve GABA receptors agonists (benzodiazepines and non-benzodiazepine Z-drugs), ramelton - melatonin receptor agonist, doxepin - tricyclic antidepressant and DORA's - dual orexin receptor antagonists. Commonly used over-the-counter and off-label medications, as well as other substances used for insomnia treatment, include antidepressants (trazodone, mirtazapine), anticonvulsants (pregabalin, gabapentin), antipsychotics (quetiapine, olanzapine), antihistamines (doxylamine, diphenhydramine), melatonin and alcohol [3, 1]. Many above-mentioned substances offer relief for either sleep-maintenance or initial insomnia, but rarely for the two of them and are often associated with drug dependence and adverse effects [9, 3, 7].

Pathophysiology of insomnia and sleep physiology

Due to its complex nature and frequent presence of comorbid conditions it is impossible to define one insomnia mechanism. Many factors such as family history of sleep disorders, advanced age, female gender, stressful events, depressed mood and substance abuse are known to predispose to its formation [1, 10], however the exact pathophysiology is still unclear. It is thought that the main cause of insomnia is associated with cognitive arousal and dysregulation of circadian and homeostatic mechanisms [3, 5].

There are two main systems responsible for wakefulness and sleep control. Wakefulness is promoted by the reticular activation system (RAS) nuclei [11, 5]. In large part they are activated by a neuropeptide orexin, which is synthesized in the lateral hypothalamus and perifornical areas [12, 13]. There are two known kinds of orexin neuropeptides - orexin A (OXA) and orexin B (OXB). They activate RAS nuclei through two receptors: OX1R and OX2R. OX1 receptor has a higher affinity to orexin A, while OX2 receptor bonds both orexin A and orexin B with similar affinity [12, 14]. RAS neurons release such neurotransmitters as norepinephrine, acetylcholine, histamine and serotonin which play an important role in regulating arousal [15, 11, 16]. Additionally, orexin receptors are linked to other psychiatric disorders such as binge eating, substance abuse and anxiety [17, 18, 19].

Orexin inhibition and deactivation of the orexin system is known to initiate sleep during the night. Neurotransmitters responsible for RAS inhibition are γ-aminobutyric acid (GABA) and

galanin, which are released by the ventrolateral preoptic region (VLPR) [5, 20, 21]. It is demonstrated that orexin deficiency is associated with narcolepsy type 1, sleep disorder characterized by excessive daytime sleepiness [12, 22, 23]. Studies suggest that orexin mimetic can safely stimulate wakefulness through the orexin receptors agonism and orexin receptors antagonists can play an important role in promoting sleep during the night [12].

Dual orexin receptor antagonists

There are two kinds of orexin receptor antagonists - selective orexin receptor antagonists, which bind with one specific orexin receptor (1-SORAs - antagonists for OX1 receptor and 2-SORAs - antagonists for OX2 receptor) and dual orexin receptor antagonists (DORAs) which bind with both OX1 and OX2 receptors [22]. There are three dual receptor antagonists approved by FDA for treating insomnia: suvorexant (approved in 2014 [24]), lemborexant (approved in 2019 [25]) and daridorexant (approved in 2022 [26]). Daridorexant is the only DORA approved by the European Medicines Agency (EMA) for use in the European Union [27].

Daridorexant - clinical development

Daridorexant is a new dual orexin receptor antagonist, developed by Idorsia Pharmaceutical under the trade name Quviviq® [9, 26]. It was approved by the Food and Drug Administration and European Medicines Agency in 2022 [28] and is currently being introduced into the European market. In the European Union daridorexant is indicated for treating adult patients whose insomnia symptoms last for at least three months and are significantly affecting patients daytime activity [28]. Daridorexant underwent a clinical pharmacologic program which included 18 completed Phase 1 studies, 3 Phase 2 studies and 2 Phase 3 studies. The phase 3 studies have been supported by additional double-blind phase 3 extension studies which lasted 9 months (12 months in total) [29]. Clinical trials have shown detailed information about long-term safety and efficacy of daridorexant and are rated as high quality in accordance with the Cochrane risk of bias assessment criteria [9, 30].

Daridorexant - way of action

Daridorexant crosses the blood-brain-barrier and competitively bonds to the active site of both orexin receptors (OX1 and OX2) [31, 32]. It inhibits wakefulness, enables patients to fall asleep in shorter periods of time, stay asleep for longer and improves daytime functioning [28, 33]. Unlike common insomnia medications, such as benzodiazepines and Z-drugs, it elongates both REM and non-REM sleep phases proportionally and enables patients to maintain a physiological sleep architecture [9, 34, 35]. It is suggested that due to the OX1 receptor antagonism, daridorexant may have a positive effect on reducing patients anxiety about their ability to fall asleep [9, 34, 36].

Daridorexant does not affect receptors other than OX such as GABAergic or opioid, what results in reduced risk of substance dependency [9, 34, 32]. Studies demonstrate that even when used long-term, patients treated with daridorexant do not show signs of physical dependence and withdrawal symptoms [33]. Moreover, data suggest that daridorexant does not cause effects typical for GABA-A receptor modulators and preserves muscle coordination and strength, as well as shows no negative effects on memory and cognition [31, 34].

Daridorexant - pharmacodynamics and pharmacokinetics

Daridorexant is recommended to be taken approximately 30 minutes before going to bed, as its onset of action (for doses 25mg and 50mg) is between 30 and 40 minutes, while its estimated time to peak maximum plasma concentrations is reached within 1 and 2 hours [26, 37, 30]. If daridorexant is taken during or after a high calorie meal the time needed to reach maximum plasma concentration might be elongated [38, 39]. Daridorexant's terminal half-life time is approximately 8 hours and it is advised not to be taken, if the time prior to waking is less than 7 hours [26]. Because of the 8 hours terminal half-life time, daridorexant shows no residual effects in the morning if taken as recommended [9, 34]. Also, daridorexant shows dose proportional plasma exposure from 25 mg to 50 mg and does not accumulate after single or multidose administration [26]. Daridorexant is mainly metabolized by the cytochrome P450 (CYP3A4) and its metabolites are mostly excreted in feces (~57%) and urine (~28%) [26].

Daridorexant - safety and efficacy assessed in clinical trials

Safety and efficacy of daridorexant have been examined in multiple clinical trials, including phase 2 and phase 3 studies, which were extended to 40 weeks in total. They demonstrate that daridorexant is generally safe and significantly improves the night-time and daytime functioning of patients suffering from insomnia, even when used long-term [33].

The main parameters used to assess the efficacy of daridorexant were WASO (wake after sleep onset), TST (total sleep time) and LPS (latency to persistent sleep). The tool used to evaluate patients daytime functioning was The Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ). Details and results of phase 2 and phase 3 studies are shown in tables below.

Authors, study ID	Study objectives [29]	Study details [29]
Dauvilliers et al. [40], AC-078A201 [29]	Efficacy, pharmacokinetics and safety of daridorexant in adult patients with insomnia disorder	- Participants: 360 adult (<65 years old [41]) patients - Duration: 29 days - Treatment: 5/10/25/50 mg daridorexant; 10 mg zolpidem; placebo - Type of study: Placebo, double blind phase 2 trial
Zammit et al. [42], AC-078A202 [29]	Efficacy, pharmacokinetics and safety of daridorexant in elderly patients	- Participants: 58 elderly patients (65-85 years old [43]) - Duration: 5 periods lasting 2 days, separated by wash-out 5-12 days periods - Treatment: 5/10/25/50 mg daridorexant; placebo - Type of study: Placebo, double blind phase 2 trial
Mignot et al., [30] ID-078A301 [29]	Efficacy and safety of daridorexant in adult and elderly patients with insomnia disorder	- Participants: 930 adult and elderly patients - Duration: 3 months - Treatment: 25/50 mg daridorexant; placebo - Type of study: Placebo, double blind phase 3 trial
Mignot et al., [30] ID-078A302 [29]	Efficacy and safety of daridorexant in adult and elderly patients with insomnia disorder	- Participants: 924 adult and elderly patients - Duration: 3 months - Treatment: 10/25 mg daridorexant; placebo - Type of study: Placebo, double blind phase 3 trial

Authors, study ID	Study objectives [29]	Study details [29]
Kunz et al. [33] ID-078A303 (extension of ID-078A301 and ID-078A302) [29]	Long-term safety and efficacy of daridorexant	- Participants: 804 adult and elderly patients who completed phase 3 studies - Duration: 9 months (12 months in total) - Treatment: 10/25/50 mg daridorexant; placebo - Type of study: Placebo, double blind phase 3 trial

Table 1. Details of phase 2 and phase 3 clinical trials which assess daridorexant efficacy and safety.

Authors, study ID	Efficacy - study results	Safety - study results
Dauvilliers et al., AC-078A201	Significant dose-response relationship in the reduction of WASO and LPS from baseline to days 1 and 2 with daridorexant, the reductions were sustained through to 28th and 29th day (p=0.050 and p=0.042) [40]	No clinically relevant daridorexant-related serious adverse effects have been observed [40]
Zammit et al., AC-078A202	Significant reduction of WASO (-32.0, -45.1, -61.4 minutes for 10, 25, and 50 mg, respectively) and LPS (-44.9, -43.8, -45.4 minutes for 10, 25, and 50 mg, respectively) with daridorexant in comparison to placebo ($p \leq 0.025$) [42]	Daridorexant-related reported adverse effects were similar to placebo-related reported adverse effects with the most common being fatigue, nasopharyngitis, gait disturbance, and headache [42]

Authors, study ID	Efficacy - study results	Safety - study results
Mignot et al., ID-078A301	Significant reduction of WASO at month 1 and month 3 in comparison to placebo with both 25 mg and 50 mg doses of daridorexant ($p<0.0001$). Significant reduction of LPS at month 1 and month 3 in comparison to placebo with 50 mg ($p<0.001$) and 25 mg ($p=0.0005$ at month 1 and $p=0.0015$ at month 3) doses of daridorexant. Significant improvement of self-reported TST at month 1 and month 3 with 50 mg ($p<0.0001$) and 25 mg ($p=0.0013$ at month 1 and $p=0.033$ at month 3) of daridorexant when compared with placebo. Significant improvement of IDSIQ sleepiness domain scores at month 1 and month 3 with 50 mg ($p<0.0001$ at month 1 and $p=0.0002$ at month 3) daridorexant when compared to placebo but no significant IDSIQ sleepiness domain scores improvement with 25 mg ($p=0.055$ at month 1 and $p=0.053$ at month 3) of daridorexant when compared to placebo [30]	Daridorexant-related reported adverse effects were similar to placebo-related adverse effects with the most common being nasopharyngitis and headache [30]
Mignot et al., ID-078A302	Significant reduction of WASO at month 1 ($p=0.0001$) and month 3 ($p=0.0028$) and improvement in self-reported TST at month 1 and month 3 ($p<0.0001$ for both) with 25 mg daridorexant when compared to placebo. No significant changes in LPS ($p=0.030$ at month 1 and $p=0.0053$ at month 3) and IDSIQ sleepiness domain scores ($p=0.073$ at month 1 and $p=0.012$ at month 3) with 25 mg of daridorexant in comparison to placebo. No significant WASO ($p=0.37$ at month 1 and $p=0.57$ at month 3), self-reported TST ($p=0.0009$ at month 1 and $p=0.0028$ at month 3), LPS ($p=0.38$ at month 1 and $p=0.32$ at month 3) and IDSIQ sleepiness domain scores ($p=0.30$ at month 1 and $p=0.14$ at month 3) changes with 10 mg of daridorexant when compared to placebo [30]	Daridorexant-related reported adverse effects were similar to placebo-related adverse effects with the most common being nasopharyngitis and headache [30]

Authors, study ID	Efficacy - study results	Safety - study results
Kunz et al. ID-078A303 (extension of ID-078A301 and ID-078A302)	Daridorexant, when compared to placebo, provided sustained efficacy in improving self-reported TST and decreasing IDSIQ scores observed in the 12 weeks studies. Improvements in night-time insomnia symptoms and daytime functioning were mostly seen with daridorexant 50 mg and included increases in self-reported TST from the 12-week study baseline when compared to placebo (p=0.014 at week 12, p=0.063 at week 24, p=0.055 at week 36) and decreases in the IDSIQ total score from the baseline when compared to placebo (p=0.0015 at week 12, p=0.0019 at week 24 and p=0.0058 at week 36) [33]	The overall incidence and severity of daridorexant-related adverse effects was similar across groups (including placebo group). Mostly reported adverse effects were mild or moderate (91.2%) and the most common was nasopharyngitis. Other adverse effects included falls, headache, somnolence, dizziness and fatigue. Serious adverse effects were reported in less than 5.5% patients of all groups. No sign of tolerance, physical dependance or rebound has been observed [33]

Table 2. Results of clinical trials mentioned in Table 1.

Daridorexant - side effects

The incidence of adverse effects in clinical trials was similar in daridorexant and placebo groups. Main side effects reported by participants were nasopharyngitis, headache, falls, somnolence, dizziness, and fatigue [42, 30, 33]. During clinical trials, no sign of drug tolerance, physical dependance or rebound has been observed [33, 38, 44]. Phase 1 clinical trial has demonstrated no effect of daridorexant on QT interval prolongation in healthy participants [45]. Daridorexant should be used with caution in patients attempting to drive the following day, until individual reaction to daridorexant is assessed [46]. Presence of other side effects such as

CNS-depressant effects, sleep paralysis, hypnagogic/hypnopompic hallucinations or cataplexy-like symptoms should also be monitored in patients treated with daridorexant [47].

Daridorexant - drug interactions

Daridorexant is mainly metabolized by the cytochrome P450 (CYP3A4) and its coadministration with strong CYP3A4 inhibitors, as well as moderate and strong CYP3A4 inducers should be avoided [26]. Daridorexant should not be taken in doses higher than 25 mg if moderate CYP3A4 inhibitors are also administered. Such medications include diltiazem, erythromycin, ciprofloxacin, cyclosporine and others [47]. Concurrent use of daridorexant with gastric acid secretion modifiers can alter daridorexant pharmacokinetic parameters, however dose adaptation is not required [48]. If used together, ethanol might prolong time to reach maximum plasma concentration of daridorexant. Due to potential additive effects, dose modifications might be needed if daridorexant is coadministered with CNS depressants [49, 47].

Daridorexant - recommended use in patients with comorbid diseases

Daridorexant is not recommended in patients suffering from severe hepatic impairment. Lower amounts of daridorexant should be administered if moderate hepatic impairment is present [50,47]. There is no need for dose adjustment in patients with renal function impairment [51, 47]. Daridorexant does not impair night-time respiratory function in patients with moderate chronic obstructive pulmonary disease and mild to moderate obstructive sleep apnea [52, 53, 54]. It should be used with caution in patients exhibiting symptoms of depression or with pre-existing psychiatric conditions, as isolated cases of suicidal ideation have been observed in phase 3 clinical study [33, 47]. Daridorexant should not be administered to patients suffering from narcolepsy and patients hypersensitive to the active substance or any of the excipients [47].

Daridorexant - recommended dosing

Daridorexant is available in a form of 25 mg and 50 mg tablets [26]. Its dosage should be determined individually, however studies suggest that improved night-time and daytime

symptoms of insomnia are mostly pronounced with 50 mg daridorexant [33]. Despite the fact that daridorexant appears to be generally safe at both 25 mg and 50 mg doses [33], there are cases where higher dosing is contraindicated, such as with concurrent use of moderate inhibitors of CYP3A4 or in patients with moderate hepatic impairment [50, 47]. Dose adjustments might be required if daridorexant is co-administered with CNS depressants [49, 47]. The maximum daily dose of daridorexant is 50 mg [47].

Summary

Insomnia is a prevalent disorder, associated with multiple negative health consequences. Despite the availability of many insomnia medications, its treatment is often limited by drug dependence and adverse effects. Daridorexant is a new dual orexin receptor inhibitor which reduces insomnia symptoms by inhibiting wakefulness. It decreases time needed to fall asleep and increases total sleep time with proportional effect on both REM and non-REM phases and so does not affect physiological sleep architecture. It shows positive effects on day-time functioning and does not cause morning sleepiness. Patients treated with daridorexant do not exhibit signs of physical dependence or withdrawal symptoms. Studies show that daridorexant administered for up to 12 months is generally safe and does not lose efficacy over time. Its main side effects include nasopharyngitis, headache, falls, somnolence, dizziness and fatigue, while severe adverse effects are rarely observed. Daridorexant use should be avoided in patients suffering from hepatic impairment or treated with strong CYP3A4 inhibitors as well as with moderate and strong CYP3A4 inducers. In view of the fact that daridorexant is a recently developed medication, further investigation concerning daridorexant long term safety should be advised.

Disclosures

Author's contribution

Conceptualization - Wiktoria Izdebska and Patrycja Sornek; methodology - Jakub Stanek, Anna Kiełb; software - Anna Kaźmierczak, Agata Borkowska; check Igor Pawlak, Anna Mich, Radosław Ciesielski; formal analysis - Wiktoria Izdebska, Patrycja Sornek; investigation - Wiktoria Izdebska, Patrycja Sornek and Klaudia Perkowska; resources - Wiktoria Izdebska, Patrycja Sornek, Klaudia Perkowska; data curation - Agata Borkowska, Anna Kaźmierczak and Anna Kiełb; writing - rough preparation - Wiktoria Izdebska, Patrycja Sornek; writing - review and editing - Agata Borkowska, Anna Kaźmierczak, Anna Kiełb; visualization Wiktoria Izdebska, Jakub Stanek; supervision - Igor Pawlak, Anna Mich and Radosław Ciesielski; project administration - Wiktoria Izdebska, Patrycja Sornek, Jakub Stanek; receiving funding not applicable. All authors have read and agreed with the published version of the manuscript.

Funding Statement:

This Research received no external funding.

Institutional Review Board Statement:

Not applicable.

Informed Consent Statement:

Not applicable.

Data Availability Statement:

The authors confirm that the data supporting the findings of this study are available within the article’s bibliography.

Conflicts of Interests:

Authors declare no conflict of interests.

References

1. Naha S, Sivaraman M, Sahota P. Insomnia: A Current Review. *Missouri Medicine*. 2024;121(1):44-51.
2. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, VA, American Psychiatric Association, 2013. DOI: https://doi.org/10.1176/appi.books.9780890425596
3. Shaha DP. Insomnia Management: A Review and Update. *The Journal of Family Practice*. 2023;72(6 Suppl):S31-S36. DOI: https://doi.org/10.12788/jfp.0620
4. Kyle SD, Espie CA, Morgan K. "...Not just a minor thing, it is something major, which stops you from functioning daily": quality of life and daytime functioning in insomnia. *Behavioral Sleep Medicine*. 2010;8(3):123-140. DOI: https://doi.org/10.1080/15402002.2010.487450
5. Dopheide JA. Insomnia overview: epidemiology, pathophysiology, diagnosis and monitoring, and nonpharmacologic therapy. *The American Journal of Managed Care*. 2020;26(4 Suppl):S76-S84. DOI: https://doi.org/10.37765/ajmc.2020.42769
6. Olfson M, Wall M, Liu SM, Morin CM, Blanco C. Insomnia and Impaired Quality of Life in the United States. *The Journal of Clinical Psychiatry*. 2018;79(5):17m12020. Published 2018 Sep 11. DOI: https://doi.org/10.4088/JCP.17m12020
7. Rosenberg RP, Benca R, Doghramji P, Roth T. A 2023 Update on Managing Insomnia in Primary Care: Insights From an Expert Consensus Group. *The Primary Care Companion for CNS Disorders*. 2023;25(1):22nr03385. Published 2023 Jan 24. DOI: https://doi.org/10.4088/pcc.22nr03385
8. Qaseem A, Kansagara D, Forciea MA, Cooke M, Denberg TD. Clinical Guidelines Committee of the American College of Physicians. Management of Chronic Insomnia Disorder in Adults: A Clinical Practice Guideline From the American College of Physicians. *Annals of Internal Medicine*. 2016;165(2):125-133. DOI: https://doi.org/10.7326/M15-2175
9. Álamo C, Sáiz Ruiz J, Zaragozá Arnáez C. Orexinergic Receptor Antagonists as a New Therapeutic Target to Overcome Limitations of Current Pharmacological Treatment of Insomnia Disorder. *Actas Españolas de Psiquiatría*. 2024;52(2):172-182. DOI: https://doi.org/10.62641/aep.v52i2.1659

10. Krystal AD, Prather AA, Ashbrook LH. The assessment and management of insomnia: an update. *World Psychiatry*. 2019;18(3):337-352. DOI: https://doi.org/10.1002/wps.20674
11. Arguinchona JH, Tadi P. Neuroanatomy, Reticular Activating System. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing; July 24, 2023.
12. Toor B, Ray LB, Pozzobon A, Fogel SM. Sleep, Orexin and Cognition. *Frontiers of Neurology and Neuroscience*. 2021;45:38-51. DOI: https://doi.org/10.1159/000514960
13. Sakurai T, Amemiya A, Ishii M, Matsuzaki I, Chemelli RM, Tanaka H, Williams SC, Richardson JA, Kozlowski GP, Wilson S, Arch JR, Buckingam RE, Haynes AC, Carr SA, Annan RS, McNulty DE, Liu WS, Terrett JA, Elshourbagy NA, Bergsma DJ, Yanagisawa M. Orexins and orexin receptors: a family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior. *Cell*. 1998;92(4):573-585. DOI:https://doi.org/10.1016/S0092-8674(00)80949-6
14. Xu TR, Yang Y, Ward R, Gao L, Liu Y. Orexin receptors: multi-functional therapeutic targets for sleeping disorders, eating disorders, drug addiction, cancers and other physiological disorders. *Cellular Signalling*. 2013;25(12):2413-2423. https://doi.org/10.1016/j.cellsig.2013.07.025
15. Lie JD, Tu KN, Shen DD, Wong BM. Pharmacological Treatment of Insomnia. *P&T*. 2015;40(11):759-771.
16. Siegel JM. The neurotransmitters of sleep. *The Journal of Clinical Psychiatry*. 2004;65 Suppl 16(Suppl 16):4-7.
17. Glen A, Bürli RW, Livermore D, Buffham W, Merison S, Rowland AE, Newman R, Fieldhouse C, Miller DJ, Dawson LA, Matthews K, Carlton MB, Brice NL. Discovery and first-time disclosure of CVN766, an exquisitely selective orexin 1 receptor antagonist. *Bioorganic & Medicinal Chemistry Letters*. 2024;100:129629. DOI: https://doi.org/10.1016/j.bmcl.2024.129629
18. Piccoli, L., Micioni Di Bonaventura, M., Cifani, C. *Costantini VJA, Massagrande M, Montanari D, Martinelli P, Antolini M, Ciccocioppo R, Massi M, Merlo-Pich E, Di Fabio R, Corsi M.* Role of Orexin-1 Receptor Mechanisms on Compulsive Food Consumption in a Model of Binge Eating in Female Rats. *Neuropsychopharmacology*. 37, 1999–2011 (2012). DOI: https://doi.org/10.1038/npp.2012.48
19. Ten-Blanco M, Flores Á, Cristino L, Pereda-Pérez I, Berrendero F. Targeting the orexin/hypocretin system for the treatment of neuropsychiatric and neurodegenerative

diseases: From animal to clinical studies. *Frontiers in Neuroendocrinology*. 2023;69:101066. DOI: https://doi.org/10.1016/j.yfrne.2023.101066

20. Fuller PM, Gooley JJ, Saper CB. Neurobiology of the sleep-wake cycle: sleep architecture, circadian regulation, and regulatory feedback. *Journal of Biological Rhythms*. 2006;21(6):482-493. DOI: https://doi.org/10.1177/0748730406294627
21. Saper CB, Fuller PM, Pedersen NP, Lu J, Scammell TE. Sleep state switching. *Neuron*. 2010;68(6):1023-1042. DOI: https://doi.org/10.1016/j.neuron.2010.11.032
22. Sun Y, Tisdale RK, Kilduff TS. Hypocretin/Orexin Receptor Pharmacology and Sleep Phases. *Frontiers of Neurology and Neuroscience*. 2021;45:22-37.DOI: https://doi.org/10.1159/000514963
23. Nishino S, Ripley B, Overeem S, Lammers GJ, Mignot E. Hypocretin (orexin) deficiency in human narcolepsy. *The Lancet*. 2000;355(9197):39-40. DOI:https://doi.org/10.1016/S0140-6736(99)05582-8
24. Merck Sharp & Dohme Corp. BELSOMRA® Medication Guide. U.S. Food and Drug Administration. Available from https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/204569s008lbl.pdf#page=1 (access: 30.05.2024)
25. Eisai Inc. DAYVIGO® Medication Guide. U.S. Food and Drug Administration. Available from https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/212028s008lbl.pdf#page=1 (access: 30.05.2024)
26. Idorsia Pharmaceuticals US Inc. QUVIVIQ® Medication Guide. U.S. Food and Drug Administration. Available from https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/214985s007s008lbl.pdf#page=1 (access: 30.05.2024)
27. European Medicines Agency website medicines search available from https://www.ema.europa.eu/en/medicines (access: 30.05.2024)
28. European Medicines Agency. An overview of Quviviq and why it is authorised in the EU. 2022. Available from https://www.ema.europa.eu/en/documents/overview/quviviq-epar-medicine-overview_en.pdf (access: 30.05.2024)
29. European Medicines Agency. Quiviviq Assessment Report. 2022. Available from https://www.ema.europa.eu/en/documents/assessment-report/quviviq-epar-public-assessment-report_en.pdf (access 30.05.2024)

30. Mignot E, Mayleben D, Fietze I, Leger D, Zammit G, Bassetti CLA, Pain S, Seboek Kinter D, Roth T. Safety and efficacy of daridorexant in patients with insomnia disorder: results from two multicentre, randomised, double-blind, placebo-controlled, phase 3 trials [published correction appears in Lancet Neurol. 2022 Jan 20;:] [published correction appears in Lancet Neurol. 2022 Jun;21(6):e6]. *The Lancet Neurology*. 2022;21(2):125-139. DOI: https://doi.org/10.1016/S1474-4422(21)00436-1
31. Robinson CL, Supra R, Downs E, Kataria S, Parker K, Kaye AD, Viswanath O, Urits I. Daridorexant for the Treatment of Insomnia. *Health Psychology Research*. 2022;10(3):37400. Published 2022 Aug 30. DOI: https://doi.org/10.52965/001c.37400
32. Treiber A, de Kanter R, Roch C, Gatfield J, Boss C, Raumer M, Schindelholz B, Muehlan C, Gerben J, Jeck F. The Use of Physiology-Based Pharmacokinetic and Pharmacodynamic Modeling in the Discovery of the Dual Orexin Receptor Antagonist ACT-541468. *The Journal of Pharmacology and Experimental Therapeutics*. 2017;362(3):489-503. DOI: https://doi.org/10.1124/jpet.117.241596
33. Kunz D, Dauvilliers Y, Benes H, García-Borreguero D, Plazzi G, Seboek Kinter D, Coloma P, Rausch M, Sassi-Sayadi M, Thein S. Long-Term Safety and Tolerability of Daridorexant in Patients with Insomnia Disorder. *CNS Drugs*. 2023;37(1):93-106. DOI: https://doi.org/10.1007/s40263-022-00980-8
34. Roch C, Bergamini G, Steiner MA, Clozel M. Nonclinical pharmacology of daridorexant: a new dual orexin receptor antagonist for the treatment of insomnia. *Psychopharmacology*. 2021;238(10):2693-2708. DOI: https://doi.org/10.1007/s00213-021-05954-0
35. Boss C, Gatfield J, Brotschi C, Heidmann B, Sifferlen T, Raumer M, Schmidt G, Williams JT, Treiber A, Roch C. The Quest for the Best Dual Orexin Receptor Antagonist (Daridorexant) for the Treatment of Insomnia Disorders. *ChemMedChem*. 2020;15(23):2286-2305. DOI: https://doi.org/10.1002/cmdc.202000453
36. Steiner MA, Gatfield J, Brisbare-Roch C, Dietrich H, Treiber A, Jenck F, Boss C. Discovery and characterization of ACT-335827, an orally available, brain penetrant orexin receptor type 1 selective antagonist. *ChemMedChem*. 2013;8(6):898-903. DOI: https://doi.org/10.1002/cmdc.201300003
37. Onge ES, Phillips B, Rowe C. Daridorexant: A New Dual Orexin Receptor Antagonist for Insomnia. *Journal of Pharmacy Technology*. 2022;38(5):297-303. DOI: https://doi.org/10.1177/87551225221112546

38. Krause A, Lott D, Brussee JM, Muehlan C, Dingemanse J. Population pharmacokinetic modeling of daridorexant, a novel dual orexin receptor antagonist. *CPT: Pharmacometrics & Systems Pharmacology*. 2023;12(1):74-86. DOI: https://doi.org/10.1002/psp4.12877
39. Boof ML, Alatrach A, Ufer M, Dingemanse J. Interaction potential of the dual orexin receptor antagonist ACT-541468 with CYP3A4 and food: results from two interaction studies. *European Journal of Clinical Pharmacology* 75, 195–205 (2019). DOI: https://doi.org/10.1007/s00228-018-2559-5
40. Dauvilliers Y, Zammit G, Fietze I, Mayleben D, Seboek Kinter D, Pain S, Hedner J. Daridorexant, a New Dual Orexin Receptor Antagonist to Treat Insomnia Disorder [published correction appears in Ann Neurol. 2020 Sep;88(3):647-651]. *Annals of Neurology*. 2020;87(3):347-356. DOI: https://doi.org/10.1002/ana.25680
41. Idorsia Pharmaceuticals Ltd. Efficacy and Safety of ACT-541468 in Adult Subjects With Insomnia Disorder. Available from https://classic.clinicaltrials.gov/ct2/show/study/NCT02839200 (access: 31.05.2024)
42. Zammit G, Dauvilliers Y, Pain S, Sebök Kinter D, Mansour Y, Kunz D. Daridorexant, a new dual orexin receptor antagonist, in elderly subjects with insomnia disorder. *Neurology*. 2020;94(21):e2222-e2232. DOI: https://doi.org/10.1212/WNL.0000000000009475
43. Idorsia Pharmaceuticals Ltd. Efficacy and Safety of ACT-541468 in Elderly Subjects With Insomnia Disorder. Available from https://classic.clinicaltrials.gov/ct2/show/results/NCT02841709 (access: 31.05.2024)
44. Muehlan C, Vaillant C, Zenklusen I, Kraehenbuehl S, Dingemanse J. Clinical pharmacology, efficacy, and safety of orexin receptor antagonists for the treatment of insomnia disorders. *Expert Opinion on Drug Metabolism & Toxicology*. 2020;16(11):1063-1078. DOI: https://doi.org/10.1080/17425255.2020.1817380
45. Schilling U, Henrich A, Muehlan C, Krause A, Dingemanse J, Ufer M. Impact of Daridorexant, a Dual Orexin Receptor Antagonist, on Cardiac Repolarization Following Bedtime Dosing: Results from a Thorough QT Study Using Concentration-QT Analysis. *Clinical Drug Investigation*. 2021;41(8):711-721. DOI: https://doi.org/10.1007/s40261-021-01062-1
46. Muehlan C, Brooks S, Vaillant C, Meinel M, Jacobs GE, Zuiker RG, Dingemanse J. Driving Performance after Bedtime Administration of Daridorexant, Assessed in a Sensitive Simulator. *Clinical Pharmacology & Therapeutics*. 2022;111(6):1334-1342. DOI: https://doi.org/10.1002/cpt.2592

47. Idorsia Pharmaceutical Ltd. QUIVIVIQ Summary of Product Characteristics. Available from https://www.idorsia.com/dam/jcr:1dfbe824-089e-4aeb-9e7e-c314d3b63928/quviviq-smpc.pdf (access: 30.05.2024)
48. Gehin M, Wierdak J, Sabattini G, Sidharta PN, Dingemanse J. Effect of gastric pH and of a moderate CYP3A4 inducer on the pharmacokinetics of daridorexant, a dual orexin receptor antagonist. *British Journal of Clinical Pharmacology*. 2022;88(2):810-819. DOI: https://doi.org/10.1111/bcp.15029
49. Berger B, Brooks S, Zuiker R, Richard M, Muehlan C, Dingemanse J. Pharmacological Interactions between the Dual Orexin Receptor Antagonist Daridorexant and Ethanol in a Double-Blind, Randomized, Placebo-Controlled, Double-Dummy, Four-Way Crossover Phase I Study in Healthy Subjects. *CNS Drugs*. 2020;34(12):1253-1266. DOI: https://doi.org/10.1007/s40263-020-00768-8
50. Berger B, Dingemanse J, Sabattini G, Delahaye S, Duthaler U, Muehlan C, Krähenbühl S. Effect of Liver Cirrhosis on the Pharmacokinetics, Metabolism, and Tolerability of Daridorexant, A Novel Dual Orexin Receptor Antagonist. *Clinical Pharmacokinetics*. 2021;60(10):1349-1360. DOI: https://doi.org/10.1007/s40262-021-01028-8
51. Berger B, Muehlan C, Klein G, Dingemanse J. Pharmacokinetics of daridorexant, a dual orexin receptor antagonist, are not affected by renal impairment. *Clinical and Translational Science*. 2021;14(6):2132-2138. DOI: https://doi.org/10.1111/cts.13079
52. Boof ML, Dingemanse J, Brunke M, Esselmann A, Heymer P, Kestermann O, Lederer K, Fietze I, Ufer M. Effect of the novel dual orexin receptor antagonist daridorexant on night-time respiratory function and sleep in patients with moderate chronic obstructive pulmonary disease. *Journal of Sleep Research*. 2021;30(4):e13248. DOI: https://doi.org/10.1111/jsr.13248
53. Boof ML, Dingemanse J, Lederer K, Fietze I, Ufer M. Effect of the new dual orexin receptor antagonist daridorexant on nighttime respiratory function and sleep in patients with mild and moderate obstructive sleep apnea. *Sleep*. 2021;44(6):zsaa275. DOI: https://doi.org/10.1093/sleep/zsaa275
54. Boof ML, Ufer M, Fietze I, Pépin JL, Guern AS, Lemoine V, Dingemanse J. Assessment of the effect of the dual orexin receptor antagonist daridorexant on various indices of disease severity in patients with mild to moderate obstructive sleep apnea. *Sleep Medicine*. 2022;92:4-11. DOI: https://doi.org/10.1016/j.sleep.2021.11.015