Full title: Orexin Receptor Antagonists in the Treatment of Depression: A Leading Article summarising Pre-clinical and Clinical Studies.

Running title: Leading Article on Orexin Receptor Antagonists in the Treatment of Depression.

Harry Fagan1,2\*, Edward Jones3, David S Baldwin1,2,4

1. Clinical and Experimental Sciences (CNS and Psychiatry), Faculty of Medicine, University of Southampton, Southampton, UK
2. Southern Health NHS Foundation Trust, Southampton, UK
3. Tees, Esk and Wear Valleys NHS Foundation Trust, Darlington, UK
4. Department of Psychiatry and Mental Health, University of Cape Town, Cape Town, South Africa.

\*Corresponding Author

Dr Harry Fagan, (email: h.fagan@soton.ac.uk)

Department of Psychiatry, College Keep, 4-12 Terminus Terrace, Southampton, SO14 3AL

ORCiD numbers

Harry Fagan **0000-0001-8573-3024**

**David Baldwin 0000-0003-3343-0907**

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Abstract

The orexin (hypocretin) system comprises two neuropeptides (orexin-A and orexin-B) and two G-protein coupled receptors (the orexin type 1 and the orexin type 2 receptor). The system regulates several biological functions including appetite, the sleep-wake cycle, the stress response, and motivation and reward processing*.* Dysfunction of the orexin system has been implicated in the pathophysiology of depression in human and animal studies, although the exact nature of this dysfunction remains unclear.

Orexin receptor antagonists (ORAs) are a class of compounds developed for the treatment of insomnia and have demonstrated efficacy in this area. Three dual orexin receptor antagonists (DORAs) have received licences for treatment of primary insomnia and some ORAs have since been investigated as potential treatments for major depressive disorder (MDD).

In this leading article, we summarise the existent literature on use of ORAs in depression, in pre-clinical and clinical studies. In rodent models of depression, investigated ORAs have included the DORA almorexant and TCS1102, the selective orexin 1 receptor antagonists SB334867 and SB674042, and the selective orexin 2 receptor antagonists LSN2424100, MK-1064 and TCS-OX2-29. These pre-clinical studies suggest a possible antidepressant effect of systemic DORA treatment, however the evidence from selective ORAs is conflicting. To date, four published RCTs (one with the DORA filorexant and three with the selective orexin 2 receptor antagonist seltorexant), have compared an ORA to placebo in the treatment of MDD. Only one of these demonstrated a statistically significant difference relative to placebo.

Key Points

The orexinergic system has been implicated in the pathophysiology of MDD.

Pre-clinical rodent studies suggest a possible antidepressant-like effect of the DORA almorexant, however evidence from studies with selective ORAs is conflicting.

The limited number of clinical studies, using the DORA filorexant and the selective orexin 2 receptor antagonist seltorexant, have not demonstrated consistent effectiveness.

Further clinical studies are needed to fully appraise the potential of orexin-modulating compounds in MDD.

1. Depression and the orexin neurotransmitter system

Major depressive disorder (MDD) is a common mental disorder and a leading cause of global disability [1]. Despite a wide range of treatments, a substantial proportion of patients do not enter symptom remission and there remains a pressing need to develop new, effective treatments [1].

An area of interest in depression research is the orexin neurotransmitter system. Orexins are two neuropeptides (orexin-A and orexin-B) synthesised by hypothalamic neurons, with widespread projections through the brain [2-5]. Orexin signalling is mediated through two different G-protein coupled receptors: orexin type 1 receptors (OX1R) and orexin type 2 receptors (OX2R) [3]. These receptors show differing affinity to orexin-A and orexin-B: OX1R has greater affinity to orexin-A than orexin-B, while OXR2 has similar affinity to both [3]. These receptors are widely expressed in the brain, but largely in differing regions [6]. The orexin system plays an important regulatory role in the sleep-wake cycle, the stress response, and motivation and reward processing. [7, 8]. Recognising the wide range of regulatory roles, it has been argued that the underlying function of the orexin system is the facilitation of adaptive, motivated behaviour in response to threats or opportunities in the environment [9].

Several lines of evidence, implicate the orexin system in the pathophysiology of MDD [10, 11]. Reduced levels of orexins in multiple brain regions have been observed in rat models of depression; in chronic clomipramine administration and in social isolation followed by repeated social defeat [12, 13]. However, in mice, depressive behaviour in the forced swim test (FST) has been associated with increased levels of orexin-A and increased expression of OX1R mRNA in the amygdala [14] and mice exposed to repeated restraint also demonstrate increased orexin mRNA expression in the basolateral amygdala (BLA) [15]. In addition, mice exposed to chronic treatment with hydrocortisone (a model of stress-induced depression) also demonstrate an increased number of hypothalamic orexin neurons [16]. In clinical populations, genetic studies have also associated the orexin system with MDD. Two case control studies demonstrated an association between variants of the OX1R gene and MDD [17, 18]. Further studies have measured orexin-A concentrations in cerebrospinal fluid (CSF) in depressed patients. CSF concentrations of orexin-A after suicide attempts are higher in MDD versusdysthymia or adjustment disorder, and the level of orexin-A is negatively correlated with overall severity of illness [19, 20]. However, other studies have demonstrated no difference in overall orexin-A CSF levels in depressed patients [21-24]. In summary, while orexin system dysfunction has been implicated in the pathophysiology of MDD, the exact nature of the dysfunction remains unclear.

2. Orexin receptor antagonists (ORAs)

Following the description of the orexin system, many compounds demonstrating affinity for orexin receptors have been identified [25]. Due to the role of orexin in regulating the sleep-wake cycle, ORAs were investigated as potential hypnotic agents for treatment of insomnia, with the initial focus on the development of dual orexin receptor antagonists (DORAs) [25]. Clinical trials have demonstrated the efficacy of several DORAs in the treatment of primary insomnia in adults [26-34]. DORAs have demonstrated improvement in a range of sleep-related outcomes, with greatest evidence for suvorexant and lemborexant [34]. Reported adverse effects for these compounds versusplacebo include daytime somnolence, abnormal dreams, fatigue, and dry mouth [34]. DORAs do not appear to demonstrate the dependence that can commonly develop with the chronic use of benzodiazepines or ‘Z-drugs’ such as zopiclone and zolpidem [29, 32, 35-37]. To date, three DORAs (suvorexant, lemborexant, and daridorexant) have received a license for the treatment of primary insomnia in at least one country [38-40].

1. ORAs in the treatment of depression – animal studies

Several animal studies have investigated the antidepressant effect of ORAs (Table 1). All studies have used rodent models and have included DORAs and/or selective OX1R and OX2R antagonists.

* 1. Studies using DORAs.

In two mouse studies, Nollet et al. [41, 42] investigated the effect of the DORA almorexant and the selective serotonin reuptake inhibitor (SSRI) fluoxetine on depressive behaviours, hypothalamic-pituitary-adrenal (HPA) axis activity and hippocampal neurogenesis. The authors utilised unpredictable chronic mild stress (UCMS) over a 9-week period to model depression, and almorexant was provided orally. UCMS induced several depression-like physical changes and behavioural changes (notably increased immobility in the tail suspension test [TST]) which were reversed by both agents. The TST is a widely used model for assessing antidepressant efficacy, which involves subjecting an animal to the acute stress of being suspended by its tail [43]. Over time the subject animal will tend to adopt an immobile position, but the timing of this is sensitive to antidepressant treatment [43]. UCMS also resulted in increased hyperactivity of the HPA axis, which was reversed by both agents. Finally, UCMS resulted in reductions in hippocampal cell proliferation and neurogenesis, which were reversed by fluoxetine but not almorexant.

Fitch et al. [44] assessed almorexant in a mouse and rat study using the delayed reinforcement of low-rate (DRL) assay, an experimental model demonstrated to be sensitive to currently used classes of antidepressants [45]. The DRL assay involves assessing the response of animals to an operant condition paradigm, where a particular response is rewarded only if it follows a previous response beyond a certain length of time [45]. Both almorexant and imipramine were administered orally. The authors demonstrated that almorexant showed an antidepressant response in the DRL assay, similar to that induced by imipramine in both rats and mice. The authors further assessed the effect of almorexant in separate mice populations with knock out of both OX1R and OX2R.

However, a rat study by Ji et al. [46], which investigated the effect of orexin signalling in the ventral palladium (VP), found contrasting results. The VP is a component of the basal ganglia, associated with reward processing and motivation [47] which has been implicated in the pathophysiology of depression [48]. Intracerebral injections of the DORA TCS1102 into the VP resulted in a pro-depressive response, with increased immobility in the FST and reduced sucrose intake in the sucrose preference test (SPT). An opposite response in the FST and SPT, was seen when intracerebral injections of orexin-B were given.

* 1. Studies using selective OX1R antagonists

In a mouse study, Scott et al. [49] assessed the effect of the selective OX1R antagonist SB334867 on depressive behaviours: intraperitoneal injections of SB334867, showed an antidepressant effect with reduced immobility in the FST and TST.

In a mouse study, Yaeger et al. [50] assessed the role of orexin signalling in the basolateral amygdala, which plays a crucial role in the regulation of fear and anxiety [51]. The authors utilised the Stress-Alternatives Model, a naturalistic model of anxiety and depression [52]. In this model, the studied animal was placed in an enclosure with a larger, aggressive mouse for a 5-minute period on 4 consecutive days. A small escape route was present, large enough to allow the escape of the study animal but not the second larger mouse. Mice were defined as showing either “Escape” or “Stay” behavioural phenotypes, dependent on whether they escaped or remained in the enclosure with the second mouse. On the third day, mice received treatment with either intracerebral injection of the OX1R antagonist SB674042 or a combination of orexin-A and an OX2R antagonist (to selectively stimulate OX1R) into the bilateral BLA. Selective OX1R antagonism in the BLA resulted in increased escape behaviour in previously “Stay” mice, while selective OX1R stimulation resulted in reduced escape behaviour in both previously “Stay” and “Escape” mice.

However, in a rat study by Deats et al. [53] an opposite finding was noted: intraperitoneal injections of SB334867 showed a pro-depressant result, with increased immobility in the FST and decreased preference for sucrose in the SPT.

In a further two studies by Fitch et al. [44] and Stanquini et al. [54], SB334867 was not seen to have any impact on depressive behaviours. In the previous discussed rat and mouse study, Fitch et al. [44] found intraperitoneal injections of SB334867 did not result in antidepressant-like responses in the DRL assay in either animal group. In a rat study, Stanquini et al. [54] investigated the effect of localised OX1R antagonism in the ventromedial prefrontal cortex (vmPFC), a cortical region involved in decision making, emotional regulation and social cognition [55]. Intracerebral injections of SB334867 into vmPFC did not alter behaviour in the FST. However, injections of orexin-A into this region did result in an antidepressant response (reduced immobility time); and this was abolished when orexin-A was administered with SB334867.

* 1. Studies using selective OX2R antagonists

In the previously described rat and mouse study from Fitch et al. [44], intraperitoneal injections of the selective OX2R antagonist LSN2424100 produced an antidepressant-like response in the DRL assay.

One mouse study by Staton et al. [56] investigated the role of OX2R agonism or antagonism using the previously described Stress-Alternatives Model. Intracerebroventricular injections of a selective OX2R agonist (the modified orexin-B peptide: [Ala**11**, D-Leu**15**]-orexin-B) and the selective OX2R antagonist MK-1064 were given on the third day. OX2R agonism resulted in an increased tendency to escape the enclosure, in previously “Stay” mice, while OX2R antagonism reduced the tendency to escape the enclosure in previously “Escape” mice. On day 5, the mice underwent a social interaction test (SIT) where a perforated, transparent container containing a novel mouse was placed into their enclosure. OX2R agonism increased the time spent near the novel mouse, in “Stay” mice. OX2R antagonism, reduced the time spent near the novel mouse, in “Escape” mice.

In a mouse study by Wang et al. [57], the authors investigated the function of a specific orexinergic projection to the lateral habenula, a densely innervated structure in the basal forebrain involved in the regulation of motivation and implicated in the pathophysiology of depression [58, 59]. Mice received intracerebral injections of either a OX1R and OX2R agonist (orexin-A) or a selective OX2R antagonist (TCS-OX2-29) into the lateral habenula, bilaterally. Orexin-A resulted in anti-depressive behaviour with reduced social avoidance behaviour in the SIT and decreased immobility in both the FST and TST. However, selective OX2R antagonism resulted in depressive behaviour with increased social avoidance behaviour in the SIT and greater immobility in both the FST and TST.

1. ORAs in the treatment of MDD – clinical studies

Several clinical studies have investigated ORAs in the treatment of MDD. To date, five randomised controlled trials (RCT) have been conducted [60-64], although one of these [64] remains unpublished (Table 2). Three further clinical trials with seltorexant are currently recruiting [65-67].

4.1 Filorexant study

Connor et al. [60] published a phase II double-blind RCT, comparing filorexant as an augmentation to current antidepressant treatment (n=64) with matching placebo (n=64) over a 6-week duration. All patients had a diagnosis of moderate or severe MDD, with a previous partial response to antidepressant therapy. The filorexant dose was given at bedtime. The study had significant recruitment challenges and only recruited approximately 40% of the participants required (n=129) based on their initial power calculation. The estimated treatment difference for the primary outcome measure (change in Montgomery-Asberg Depression Rating Scale, [MADRS], [68] from baseline to end of study) for filorexant versus placebo was -0.7, favouring filorexant (least squares [LS] mean difference) (95% CI -3.8, 3.5). This difference was not statistically significant. A greater proportion of patients in the filorexant group reported at least 1 adverse effect (42% versus 27% in the placebo group). The most common adverse effects over-represented in the filorexant group were suicidal ideation (7.8% versus1.6% in the placebo group) and somnolence (8% versus 0% in the placebo group) and one participant in the filorexant group dropped out of the study due to somnolence.

4.2 Seltorexant studies

Brooks et al. [61] reported a 4-way crossover trial which compared a single dose of 10, 20 and 40 mg, or placebo, as an augmentation to current antidepressant treatment, in 20 patients with MDD with self-reported insomnia symptoms. Each dose was given at bedtime. The primary outcome in this study was improved sleep outcomes including both total sleep time and sleep efficiency, measured using an 8-hour period of polysomnography recording after the medication was taken. Depressive symptoms were measured as a secondary outcome via the Quick Inventory of Depressive Symptomatology- Self Report (QIDS-SR) [69] at baseline and the following day. All dosages of seltorexant showed a decrease in QIDS-SR for post-dose versuspre-dose (greatest at 40 mg: mean change of -2.1 [95% CI -3.54, -0.66]). However, no dosage caused a statistically significant decrease relative to placebo. Common adverse effects included sedation, particularly at the higher dose of 40 mg. Four patients reported somnolence at the higher dose, while at doses of 10 and 20 mg and placebo treatment only a single patient reported somnolence.

Recourt et al. [62] compared a daily dose of 20 mg seltorexant (n=22) against the antihistamine diphenhydramine (n=13) and placebo (n=12) in patients with MDD. Patients were treated for 28 days, or for 10 days if they were women of child-bearing potential (WOCBP). The authors justified this decision based on the limited reproductive toxicity data available for seltorexant. Most of the study participants (31/47) were WOCBP and thus only received 10 days of seltorexant. Most patients (79%) were not taking antidepressants, while the remainder were taking an SSRI or duloxetine, to which they had not responded. Each dose was given at bedtime. The primary outcomes were improvements in depressive symptoms measured both with the 17-item Hamilton Depression Rating Scale (HDRS-17) [70] and the QIDS-SR [69]. Seltorexant demonstrated a non-statistically significant reduction in the HDRS-17 versus placebo and diphenhydramine (-5.5 versus -3.6 and -4.1 respectively, mean change from pre-treatment versus day 11 score) after 10 days of treatment. There was also no statistically significant difference in the QIDS-SR between the seltorexant, diphenhydramine and placebo groups after 10 days of treatment. A statistically significant difference for seltorexant versusplacebo was seen in two HDRS-17 subsets; the HDRS-17 after removal of the 3 sleep-related items and the HAM-D6 which measured the severity of six core depressive symptoms from the HDRS-17 (specifically depressed mood, feelings of guilt, motor retardation, somatic symptoms, psychic anxiety and functional effects on work and interests) [71]. Differences between treatments in these latter two subsets were found to be statistically significant in *post hoc* analyses by the authors. Commonly reported adverse effects in the seltorexant group included somnolence (reported in 4/22 [18.1%] patients taking seltorexant, but none in the other two groups).

In a phase 2b study, Savitz et al., 2021 [63], compared seltorexant at daily doses of 10, 20 or 40 mg as an augmentation to current antidepressant treatment, to placebo for a 6-week period. Recruited patients had a diagnosis of MDD with an inadequate response to 1-3 antidepressants. Each dose was given at bedtime. The primary outcome was improvement in depressive symptoms, as measured by the MADRS. Initially patients were randomised to receive 20 or 40 mg seltorexant, however this was changed after a pre-specified interim analysis (occurring 6 weeks after randomisation of the 160th participant) to 10 and 20 mg. The authors reported that the interim analysis demonstrated higher efficacy for the 20 mg dosage over the 40 mg dosage. In total 138 patients received placebo treatment while 33, 63 and 53 received seltorexant at dosages of 10, 20 and 40 mg respectively. The authors reported a statistically significant treatment difference in the MADRS for seltorexant versus placebo at 6 weeks of -3.1 (LS mean difference) (90% CI -6.13, -0.16) for the 20 mg dosage. There was no significant difference at the 10 mg or 40 mg dosage versusplacebo. The overall treatment difference for all doses was not provided. A greater proportion of participants in the seltorexant arm reported at least one adverse effect versusplacebo (40.9% versus37.7%). Particular adverse effects more common in the seltorexant group included somnolence (6.2% versus5.0%), abnormal dreams (2.7% versus0.7%), nightmares (1.4% versus0%) and sleep paralysis (1.4% versus0.7%).

In a further unpublished study, Savitz et al., 2020 [64] reported a phase 1 trial comparing monotherapy seltorexant at 20 and 40 mg to placebo for a 5-week period. This study was published as a conference abstract and only a limited subset of the methodology and results were presented. Recruited patients had a diagnosis of MDD and were not on any other antidepressant during the trial, however the authors did not specify whether this population had previously been treated with antidepressant treatment with no or partial response. The primary outcome was improvement in depressive symptoms, as measured by the HDRS-17. The authors reported a statistically significant difference in the HDRS-17 for seltorexant versus placebo of -2.9 (LS mean difference) (80% CI -4.37, -1.48) at 20 mg. There was no significant difference at the 40 mg dosage versusplacebo. Commonly reported adverse effects in both groups were headache and nasopharyngitis, but the respective incidences were not reported.

5. Discussion

Several studies in rodent models of depression have investigated the antidepressant effect of ORAs, however the studies are relatively heterogenous in the depressive models employed and the type and administration route of the used ORA. Most of these studies included widely used ‘classical’ models of depression and anxiety in animals, particularly the TST and FST. These models have received criticism for their lack of validity and their widespread use has been suggested to contribute to the current failure to develop new effective antidepressants [72-74]. The use of DRL assay in the Fitch et al. [44] study, although it has demonstrated good predictive validity for currently used antidepressant classes [45], may also lack the face and contrast validity for an animal model of depression. There has been a recent emphasis on the development of animal models, which are designed to be ethologically relevant to the species used [73]. The Stress-Alternatives Model, used by Staton et al. [56] and Yaeger et al. [50] has been argued to model stress-related animal behaviour in a species appropriate manner [52] and may be likely to provide stronger evidence for the findings of these studies.

Four of the studies used localised administration of an ORA into specific regions of the rodent brain: VP [46], vmPFC [54], BLA [50] and lateral habenula [57], all regions with established orexinergic innervation [5, 6]. In all four regions, orexin receptor stimulation was associated with an antidepressant response in behavioural tests while orexin receptor antagonism was associated with an increase in depressive behaviour (except for the vmPFC study [54] where OX1R antagonism had no effect alone). Although these studies are of interest in understanding the role of orexin signalling in different brain regions, they may be less helpful at understanding the likely effect of these agents in clinical practice where medications will be administered systemically.

The reminder of the studies administered an ORA systemically. Three studies using systemic administration of the DORA almorexant demonstrated an antidepressant effect [41, 42, 44], although it did not result in the increased hippocampal cell proliferation and neurogenesis seen with fluoxetine [42]. This suggests that the antidepressant effect of almorexant is independent of hippocampal neurogenesis and is consistent with a previous mouse study [75] which demonstrated that orexin-A promoted hippocampal neurogenesis. Of interest in one study [44], the antidepressant effect of almorexant was sustained in OX1R knock-out mice but abolished in OX2R knock-out mice, suggesting that the antidepressant effect of almorexant is mediated by OX2R antagonism, at least in mice. The findings from studies using OX1R antagonists are more conflicting. Fitch et al. demonstrated no antidepressant effect from SB334867 using the DRL assay [44]. The opposing pro depressive and anti-depressive behavioural changes in the FST reported by Deats et al. [53] and Scott et al. [49], may reflect species differences between mice and rats, or be related to the low light conditions the study animals were kept (in Deats et al). The findings from OX2R antagonists also produced conflicting results. Systemic administration of LSN2424100 resulted in an antidepressant effect in the DRL in mice and rats, but the issues with the validity of this test remain. Stronger evidence from Staton et al. [56] in mice associated systemic OX2R antagonism via MK-1064 with depressive responses in the Stress-Alternatives Model.

At present, the available evidence from human studies of the potential antidepressant action of ORAs is limited. Only the DORA filorexant and the selective OX2R antagonist seltorexant have been investigated. All published studies are relatively small, early phase, industry-funded studies. Two studies only assessed the effect of a single dose of the ORA [61] or a 10-day course in most participants [62], which is unlikely to allow a valid assessment of antidepressant effect. One study remains unpublished [64] and we have been unable to fully appraise this, based on the limited information currently available. From the two remaining studies, the phase II DORA trial with filorexant [60] failed to show any significant difference between filorexant and placebo after 6 weeks. However, this trial was not adequately powered as per the authors original power calculation, which raises questions concerning the validity of its findings. The Savitz et al. trial [63], the largest of the included clinical trials, did demonstrate a statistically significant difference for one of three seltorexant doses. Of note, in this study no significant difference versusplacebo was seen at 10 mg or 40 mg of seltorexant. However, this difference is likely to lie at the margins of clinical significance. The minimal importance difference (MID) defines the smallest difference in score that a patient would perceive as beneficial and is a common standard to assess the clinical significance of antidepressant treatment effects. A variety of MIDs for both the MADRS and HDRS-17 are described in the literature, but several have suggested at least a difference of 3 points on the scale [76].

An additional important consideration is the extent by which improvements on depression scales are mediated by improved sleep symptoms. Several depression rating scales contain sleep items, and an effective hypnotic agent, without any additional antidepressant action, could cause a significant improvement solely by improving insomnia. For the HDRS-17, three of the 17 items are related to sleep [70] and 1 of the 10 items on the MADRS scores reduced sleep [68]. One of the trials [62] did report subsets of the HDRS-17 which excluded the sleep items (an adjusted HDRS-17 which excluded the 3 sleep items, and the 6-item HAMD-D6 which only includes 6 core depression symptoms). However, no such analysis was performed for the one trial [63] which reported a statistically significant difference for 20 mg seltorexant versusplacebo. It is therefore difficult to determine whether this difference was related to an antidepressant effect, independent of the hypnotic effect of seltorexant.

A final point is to consider the role of the orexin system in other psychiatric conditions, beyond MDD and sleep disorders. The orexin system has further been recognised to play a role in several additional psychiatric conditions, including anxiety disorders [77-85], post-traumatic stress disorder [86, 87] and substance misuse disorders [88-93]. This is perhaps, unsurprising considering the orexinergic innervations of many brain regions involved in the neurocircuitry of fear, anxiety, and addiction [5, 51, 91]. In clinical populations, MDD is frequently co-morbid with other psychiatric comorbidities [94, 95] and the role orexin-modulating agents, may have on other psychiatric conditions, should be considered when assessing their effect.

6. Conclusion

This leading article has summarised the animal and clinical research investigating the potential antidepressant role of ORAs. Overall, animal studies have generated conflicting results, however there is some evidence to suggest an antidepressant effect of systemic administration of the DORA almorexant. Four published RCTs have compared an ORA (either the DORA filorexant or the OX2R antagonist seltorexant) to placebo in a population with depression. Only one published study with seltorexant [63], demonstrated a statistically significant difference versusplacebo, but this difference (3.1 points on the MADRS) was only noted at a particular dosage (20 mg) and lies on the border of proposed levels of clinical significance. Considering the lack of consistent support for the antidepressant effect of OX2R antagonists in clinical trials and the evidence for a pro-depressive effect of OX2R antagonism in some animal studies, we would suggest considering whether OX2R antagonism is the best treatment strategy in depression. Further pre-clinical work could continue to examine the effect of selective agonism at orexin receptors, with the consideration of translating selective agonists into clinical trials if they show promise.

7. References

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Table 1: Summary of discussed studies investigating the effect of orexin receptor antagonists in animal models of depression

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Authors/year of publication | Animal model  | Model of depression used  | Type of ORA used  | Comparator compounds used | Route of drug administration  | Principal results |
| Nollet et al., 2011 [41] | Mouse | UCMS model, mice exposed for 8 weeks. TST | Almorexant (DORA) | Fluoxetine (SSRI)  | Almorexant administered orally, fluoxetine intraperitoneally  | Fluoxetine reversed the physical and behavioural effects of UCMS.Almorexant decreased immobility in the TST.  |
| Scott et al., 2011 [49] | Mouse | FST, TST | SB334867 (selective OX1R antagonist) | None | Intraperitoneal  | SB334867 caused a decrease in depressive behaviour (reduced immobility in the FST and TST) |
| Nollet et al., 2012 [42] | Mouse  | UCMS model, mice exposed for 9 weeks and TST  | Almorexant (DORA) | Fluoxetine (SSRI)  | Oral (dissolved in water) | Fluoxetine and almorexant reversed the physical and behavioural depressive features of UCMS.Fluoxetine and almorexant reversed the HPA axis hyperactivity seen in UCMS Fluoxetine but **not** almorexant reversed the fall in hippocampal cell proliferation and neurogenesis seen in UCMS. |
| Deats et al., 2014 [53] | Rat  | FST, SPT | SB334867 (a selective OX1R antagonist) | None  | Intraperitoneal | SB334867 caused an increase in depressive behaviour (increased immobility in the FST and decreased preference for sucrose in the SPT)  |
| Fitch et al., 2014 [44] | Mouse and rat  | DRL assay  | Almorexant (DORA), SB334867 (selective OX1R antagonist), LSN2424100 (selective OX2R antagonist) | Imipramine (TCA) | Almorexant and imipramine administered orally, others given intraperitoneally  | Almorexant and LSN2424100 but **not** SB334867 showed antidepressant like properties in the DRL assay in mice and rats.The effect of almorexant and LSN2424100 was abolished in OX2R knockout mice.  |
| Ji et al., 2018 [46] | Rat  | FST, SPT, SIT  | TCS1102 (DORA), SB334867 (a selective OX1R antagonist) | Orexin-A, orexin-B  | Intracerebral injections into bilateral ventral palladia  | TCS1102 caused an increase in depressive behaviour (increased immobility in the FST and decreased sucrose intake in the SPT).Orexin-A caused a decrease in depressive behaviour (reduced immobility in the FST, increased sucrose intake in the SPT and increased time spent by an unfamiliar rat in the SIT.) |
| Staton et al., 2018 [56] | Mouse  | SAM, SIT | MK-1064 (selective OX2R antagonist) | Modified orexin-B peptide  | Intracerebroventricular  | MK-1064 reduced escape behaviour from a hostile mouse.Orexin-B increased escape behaviour from a hostile mouse. |
| Stanquini et al., 2020 [54] | Rat  | FST  | SB334867 (selective OX1R antagonist) | Orexin-A and non-selective tyrosine kinase inhibitor | Intracerebral injections into the ventromedial prefrontal cortex | Orexin-A alone reduced immobility in the FST.SB334867 alone had no effect on the FST. When SB334867 was given with orexin-A it abolished the effect of orexin-A on the FST.  |
| Wang et al., 2021 [57]  | Mouse | FST, SIT, TST | TCS-OX2-29 (selective OX2R antagonist) | Orexin-A  | Intracerebral injections into bilateral lateral habenula.  | Orexin-A resulted in reduced social avoidance behaviour and decreased immobility in the FST and TST. TCS-OX2-29 resulted in increased social avoidance behaviour and greater immobility in the FST and TST.  |
| Yaeger et al., 2022 [50] | Mouse | SAM | SB674042 (selective OX1R antagonist) and MK-1064 (selective OX2R antagonist) | Orexin-A | Intracerebral injections in bilateral BLA | OX1R antagonism increased escape behaviour and reduced fear responses to a hostile mouse.OX1R stimulation reduced escape behaviour from a hostile mouse.  |

Abbreviations used; BLA: Basolateral amygdala; DORA: Dual orexin receptor antagonist, DRL: Delayed reinforcement of low-rate assay, FST: Forced swim test, HPA: Hypothalamic-pituitary-adrenal, OFT: Open-field test, OX1R: Orexin 1 receptor, OX2R: Orexin 2 receptor, SAM: Stress-Alternatives Model, SIT: Social interaction test, SPT: Sucrose preference test, SSRI: Selective serotonin reuptake inhibitor, TCA: Tricyclic antidepressant, TST: Tail suspension test, UCMS: Unpredictable chronic mild stress

Table 2: Summary of included clinical trials

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Authors/year of publication | Clinical population  | ORA used as monotherapy or augmentation  | Sample size | Intervention: type of ORA, dosage, and duration of treatment  | Comparator  | Depression rating scale used  | Principal clinical result and statistical outcomes  |
| Connor et al., 2017 [60] | MDD | Augmentation to SSRIs, SNRIs or bupropion | 128  | Filorexant, 10 mg at bedtime, 6 weeks  | Matching placebo  |  MADRS | Mean treatment difference (filorexant versus placebo) was -0.7 (95% CI -3.8, 3.5).  |
| Brooks et al., 2019 [61] | MDD with self-reported insomnia  | Augmentation to (SSRI or SNRI) | 20 | Seltorexant, 10/20/40 mg at bedtime, 1 day  | Placebo  | QIDS-SR | All dosages of seltorexant showed a decrease in QIDS-SR, greatest difference was -2.1 (95% CI -3.54, -0.66) for 40 mg seltorexant.  |
| Recourt et al., 2019 [62] | MDD | Either monotherapy (n=37) or augmentation to SSRI or duloxetine (n=10)  | 47 | Seltorexant, 20 mg at bedtime, 28 days in men/woman of non-child-bearing age (n=16) and 10 days for woman of child-bearing age (n=31)  | Placebo and diphenhydramine (25 mg)  | HDRS-17, QIDS-SR | Mean treatment difference after 10 days of treatment (seltorexant versus placebo) was -1.9 for HDRS-17 and- 0.2 for QIDS-SR.  |
| Savitz et al., 2020 [64] | MDD  | Monotherapy  | 128 | Seltorexant, 20/40 mg (time of administration not specified), 5 weeks | Placebo  | HDRS-17  | Mean treatment difference (seltorexant versus placebo) was -2.9\* (80% CI -4.37, -1.48) for 20 mg and -0.9 (80% CI -2.32, 0.61) for 40 mg.  |
| Savitz et al., 2021 [63] | MDD | Augmentation to antidepressant (SSRI or SNRI) | 287 | Seltorexant, 10/20/40 mg at bedtime, 6 weeks | Placebo  |  MADRS | Mean treatment difference for seltorexant versusplacebo was -3.1\* (90% CI -6.13, -0.16) for 20 mg and -1.5 (90% CI−4.70; 1.63) for 40 mg.  |

Abbreviations used; CI: confidence interval, HDRS-17: 17-item Hamilton depression rating scale, MADRS: Montgomery-Asberg depression rating scale, MDD: Major depressive disorder, QIDS-SR: Quick inventory of depressive symptomatology self-report, SNRI: Serotonin-noradrenaline reuptake inhibitor, SSRI: Selective serotonin reuptake inhibitor; \*Reported as statistically significant