The Discovery of Suvorexant: Lessons Learned That Can Be Applied to Other CNS Drug Development Efforts

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ABSTRACT: The development of therapeutics for central nervous system (CNS) disorders has many challenges that result in low probability of success and longer-than-typical development timelines. Suvorexant (Belsomra), the first dual orexin receptor antagonist used for insomnia, was approved by the United States Food and Drug Administration ~10 years after the initial high-throughput screen was conducted to identify orexin receptor antagonists. What accounted for this success and speed? Here we suggest that this program was unique and set up for success by (1) having a robust and high-throughput pharmacodynamic readout that was translatable across species, including humans, (2) a well-validated target with a defined product profile, resulting in a highly energized team with a can-do attitude, and (3) a highly executable and streamlined clinical strategy. The utility of Belsomra for insomnia, as well as other neurological and psychiatric diseases, continues to be explored, most recently for insomnia associated with Alzheimer's disease.

KEYWORDS: orexin, sleep, Belsomra, Suvorexant, insomnia, drug discovery

The development of novel medicines to treat central nervous system (CNS) disorders has multiple unique challenges. First, the mechanisms that underlie complex psychiatric and neurodegenerative disorders are poorly understood and very complex. Relative to other tissues, the brain has evolved more dramatically from preclinical species to human, making it difficult to model disease and predict CNS drug effects using preclinical species. Finally, unlike other systems where pathology can typically be evaluated with biopsies or relatively noninvasive procedures, assessing CNS function typically requires use of complex biomarkers and/or subjective measurements of function. Therefore, it is not surprising that the development of novel treatments for CNS disorders typically takes much longer than for other indications and that failure due to lack of efficacy is the norm rather than the exception.^{1,2}

Despite these challenges, Merck & Co., Inc. (Kenilworth, NJ) has remained dedicated to treating CNS disorders. One of our company's major accomplishments in the neuroscience space has been the discovery and development of Suvorexant (Belsomra), the first dual orexin receptor antagonist (DORA) to be approved for insomnia. The DORA program at our company was initiated in the early 2000s, in part because insomnia was identified as a major unmet medical need for which the standard of care was unsatisfactory. Characterized by difficulty falling or staying asleep, or poor sleep quality, insomnia is a highly prevalent CNS disorder, affecting ~4–33% of the U.S. population depending on the population studied and diagnostic criteria used.^{3–8} Poor sleep not only affects the individual's quality of life but also has significant societal and economic costs. For example, insufficient sleep is linked to many of the leading causes of death, such as cardiovascular, hypertension, cancer, cerebrovascular, diabetes,

and accidents,⁹ as well as negatively impacting work productivity.^{10,11} A comprehensive analysis conducted by RAND regarding the economic cost of insufficient sleep suggests an ca. \$680 billion loss of economic output every year for the five OECD countries (US, UK, Japan, Germany, and Canada).⁴

In addition to the significant unmet medical need, the fundamental biology underlying sleep and wake processes was also beginning to be better understood around this time. In 1998 the orexin peptides OXA and OXB and their cognate receptors OX1R and OX2R were discovered independently by two groups,^{12,13} although their role in modulating sleep and wakefulness was not fully appreciated at the time of discovery. One year later, Lin and Mignot et al.¹⁴ showed that inheritable canine narcolepsy was due to OX2R mutations, suggesting the importance of the orexins in wakefulness, and in 2000, the link to human wakefulness was established when human narcolepsy was demonstrated to be due to diminished orexin-containing neurons and orexin CSF levels.^{15,16} The potential therapeutic benefit of modulating orexin receptor activity to treat sleep disorders rapidly caught the attention of drug discovery researchers as over 50 applications for patents were filed to identify orexin receptor antagonists between 1999 and 2007.¹⁷

Against this backdrop, what allowed for the discovery of Belsomra and how can those lessons be applied to other neuroscience drug discovery efforts? Here we will suggest that

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it was not one factor but a combination of elements that allowed for the rapid discovery of this novel CNS therapeutic. (The high-throughput screen to identify orexin receptor antagonists was conducted in 2005, and Suvorexant was approved by the United States Food and Drug Administration for the treatment of primary insomnia in 2014.)

■ THE VALUE OF A TRANSLATABLE AND ROBUST PRECLINICAL PHARMACODYNAMIC MEASUREMENT

A challenge to developing treatments for many CNS disorders is that disease cannot be easily modeled in preclinical species. For example, measuring neuropsychiatric symptoms such as mood, cognition, or anxiety in preclinical species is not straightforward. Typical preclinical measures of mood in rodents include assays that are sensitive to standard-of-care antidepressants, but the duration of time a mouse struggles when hung by its tail or is placed in a water tank is hardly an assay that would seem an appropriate measure of mood or one that will translate well to humans. Thus, it is not clear whether such assays will be valuable for identifying novel antidepressants with unique mechanisms of action. Likewise, assays used to measure cognition in rodents, such as novel object recognition, Pavlovian conditioning to an electric shock, and locating a submerged platform in a water tank are not all that similar to the methods for assessing cognition in humans. The need for measures with greater construct, predictive, and face validity is well-known in the neuroscience field, and many efforts have been undertaken to help remedy this problem.^{18–20} Nevertheless, given the current battery of assays being used by most pharmaceutical companies, it is not entirely surprising that most novel compounds developed to treat these neuropsychiatric symptoms have failed for lack of efficacy despite demonstrating preclinical effects. For this reason, many neuroscience companies are moving away from using rodent behavioral models to identify targets and predict human efficacy and moving toward developing relevant human models, such as inducible pluripotent stem cells (iPSCs) from patients, as a way of predicting drug effects.

In contrast to the end points mentioned above such as mood and cognition, sleep can be measured in preclinical species in an almost identical way as it can be measured clinically. When mammals sleep, the brain shows distinct changes in electrical activity that can be measured using an electroencephalograph (EEG) with noninvasively placed recording electrodes on the scalp. The polysomnogram (PSG) provides more detailed information on sleep-stage by combining EEG with other biological measurements, including eye movements and muscle activity. PSG can be used to measure circadian changes in sleep and wakefulness in humans and preclinical species, as well as pharmacologically induced changes.

Given our interest in insomnia at Merck & Co., we invested in building a start-of-the-art preclinical PSG facility that enabled us to characterize the sleep and wake pharmacology of molecules with differing biological mechanisms in ambulatory rodents, canines, and rhesus monkeys. Historically, PSGs have been time-consuming to analyze because of the need to remove artifacts, extract relevant features, and classify many hours of data. However, as computational capabilities have increased, the ability to automate PSG analysis has improved. We took advantage of these technological advances and built an automated analysis pipeline in the early 2000s that allowed for rapid analysis with greatly reduced need for human

oversight. At the time, this was a unique capability and allowed us to record data from hundreds of animals simultaneously so that we could rapidly assess dose–effect relationships of investigational compounds and establish correlations between the *in vitro* and *in vivo* properties of orexin receptor antagonists. As we gained more experience translating the effects of orexin receptor antagonists from mouse and rat to dog and rhesus, we were able to gain additional confidence that this mechanism would be effective in humans, and we also gained greater certainty in predicting what might be a relevant dose. This attribute of using relevant preclinical measures in a relatively high-throughput manner was one reason we were able to move so quickly and confidently into the clinic. Identifying other functionally relevant end-points and biomarkers that could be useful in a manner similar to that of EEG for sleep and insomnia should be a goal to enable future drug discovery efforts in the CNS space.

■ THE IMPORTANCE OF A WELL-DEFINED PRODUCT PROFILE AND AN ENERGIZED/INTEGRATED PROJECT TEAM

At the outset of most drug discovery projects, the desired product profile is typically quite poorly defined due to a lack of understanding of the biology/confidence in the mechanism, desired pharmacokinetic (PK) properties, or structure–activity relationship (SAR). The DORA program was fortunate because we had a strong rationale to believe that blocking both OX1 and OX2 receptors would promote sleep since the double-receptor-knockout mouse showed a stronger sleep phenotype than individual knockouts, and we had the capabilities to quickly assess the relationship between chemical structure, *in vitro* properties, PK, and *in vivo* pharmacodynamic effects using preclinical polysomnography. As the team generated preclinical data that supported the promise of orexin antagonists to treat sleep disorders, the program team was further energized and operated with increased urgency.

We started our drug discovery program by initiating a high-throughput screen of the Merck & Co., Inc. sample collection and assayed over 2 million compounds for their ability to block orexin-A signaling in recombinant cells that overexpressed human OX1R and OX2R. From that screen, we identified multiple hit classes with distinct chemical structures and varying degrees of OX2R and OX1R activity. Our initial inspection of these new hit classes revealed some attractive starting points for a drug discovery campaign. Many of our initial hits had good levels of potency against OX1R and OX2R while having physicochemical properties that were favorable for CNS penetration. A key liability of many of these nascent series was the fact that many of these compounds had very high levels of lipophilicity, metabolic instability, and poor solubility. We focused much of our early efforts on increasing the polarity of our newly synthesized antagonists while preserving good brain penetration properties.

One of the most attractive hits to emerge from our screening campaign was compound **1** which possessed a seven-membered diazepane ring as a key feature (Figure 1). This diazepane series was appealing to us because it possessed excellent starting potency against OX1R/OX2R while possessing a modular structure. That modular structure permitted us to apply parallel synthesis techniques to prepare large compound libraries. Separately we developed radioligand displacement binding assays for both OX2R and OX1R that could be run in a high-throughput fashion to drive molecule

Figure 1. Early high-throughput screen (HTS) hit Diazepane, **1**, and more optimized molecule Diazepane In Vivo Tool, **2**, which was appropriate for initial in vivo testing.

optimization. These efforts led to the identification of compound **2** which had enhanced potency with improved physicochemical properties.²¹ As we studied compound **2**, we became more excited about the prospects for this series. Indeed, compound **2** had many of the attributes we desired in a lead molecule: clean off-target profile, favorable brain penetration, and good permeability/solubility. Downsides of compound **2** included poor oral bioavailability and extensive first-pass hepatic metabolism. Furthermore, when incubated in human liver microsomes, compound **2** produced abundant glutathione adducts suggesting the generation of reactive metabolites that could emerge as a potential safety risk for the molecule. Despite the low oral bioavailability, we could administer compound **2** to rats via an interperitoneal (i.p.) injection and achieve reasonable plasma and brain levels. We were delighted to see strong dose-dependent reductions in locomotor activity for the rats over a period of 6 h with clear evidence of sedation and recovery, all consistent with the compound promoting sleep.

This early result energized the team, who focused their efforts on fixing the ADME issues associated with compound **2**. We began to characterize our lead molecules directly in rat EEG studies to build a correlation between brain exposure and pharmacological activity. In those early studies, we initially dosed our test molecules via the i.p. route because of poor oral PK and the in vivo efficacy not as impressive as we anticipated. We subsequently realized that administering test compounds via the i.p. route blunted much of the initial efficacy of our orexin antagonists, and we observed a more profound effect in the EEG studies when we switched to dosing orexin antagonists by oral gavage. Furthermore, given that orexin antagonists block *wakefulness* versus forcing sleep, we found a more substantial effect of our molecules on rat EEG when they

were dosed in the "lights out" period when the rodents are more active, as compared to when the lights were on and vehicle-treated animals had high levels of sleep. These observations taken together allowed us to refine our in vivo testing protocols and build a clearer understanding of the PK–PD relationships for investigational DORA molecules.

We understood that compounds like **2** were rapidly metabolized in vitro and in vivo and as a result were generating reactive, electrophilic species. We postulated that the seven-membered ring could be a "soft-spot" for hepatic metabolism. Alternately, we considered that the heterocycles that are present in these analogs could be sites for oxidative metabolism. With these considerations in mind, the team synthesized hundreds of analogs with varying central ring structures and alternative heterocycles in search of a molecule with more favorable pharmacokinetic properties. Ultimately we found that the quinazoline in **2** was highly prone to metabolic oxidation and generation of an arene oxide reactive species. Replacing the quinazoline in compound **2** with a chlorobenzoxazole (vide infra) afforded a dramatic improvement in pharmacokinetic and suppression of reactive metabolites.

We postulated that these diazepane DORA's adopt a U-shaped conformation when bound to orexin receptors.²² Further studies performed by the team tested the hypothesis that this U-shaped conformation was critical for receptor binding. These findings led to a design strategy where the team designed more rigidified cores that could either enforce or minimally not disfavor the U-shaped conformation.²³ This ligand-based design principle guided much of the subsequent efforts (Figure 2).²⁴

With these design principles in mind, substitutions on the seven-membered diazepane ring were studied to assess impacts on binding affinity, PK properties, receptor potency, brain penetration, and in vivo efficacy. Introduction of a 7-methyl substituent on the diazepane core provided further improvements in potency and PK. When combined with the chlorobenzoxazole, a profound improvement in dog pharmacokinetics was observed with near full reduction of metabolic activation and glutathione adduct formation observed in vitro. When evaluated in EEG-telemetered rodents, dogs, and rhesus monkeys, compound **3** provided a dose-dependent reduction in wakefulness while increasing both REM and non-REM sleep. After establishing a favorable preclinical toxicology profile, compound **3** advanced into clinical studies as the investigational drug, suvorexant (Figure 3).²⁵

Figure 2. Structural information allowed for more hypothesis-driven design principles.

Suvorexant (Belsomra) 3

hOX1R bind = 0.65 nM

hOX2R bind = 0.24 nM

Brain-penetrant

Bioavailable in preclinical species

Low bioactivation

Efficacious in rat, mouse, dog,

rhesus EEG studies

Figure 3. Suvorexant achieves the product profile that the team had defined at the outset of the program.

■ THE VALUE OF TRANSLATABLE END-POINTS AND AN EXECUTABLE AND STREAMLINED CLINICAL STRATEGY

The clinical development program supporting suvorexant registrations comprised 36 studies, of which 32 were Phase 1 studies and 4 were Phase 2/3 studies in people with insomnia.²⁶ Characterization of suvorexant pharmacokinetics at clinically meaningful doses established that peak concentrations occur at ~2 h under fasted conditions, which can be prolonged by ~1.5 h if administered with consumption of a high-fat meal. Suvorexant's mean absolute bioavailability is ~80%, and it is largely eliminated via CYP3A-mediated metabolism.²⁷ Suvorexant demonstrates linear systemic pharmacokinetics, with an accumulation of ~1- to 2-fold with QD administration, with achievement of steady-state at 3 days. Suvorexant's mean plasma terminal $t_{1/2}$ is approximately 12 h.²⁸

Consistent with effects characterized in preclinical species,²⁹ the observation of sleep promoting effects in Phase 1 healthy volunteer studies²⁸ accelerated suvorexant's development into four Phase 2–3 studies in patients meeting the definition of insomnia according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV): a 4 week Phase 2B dose-ranging trial,³⁰ two 3 month pivotal Phase 3 trials³¹ and a 1 year Phase 3 trial.³² In each study, a diary was utilized to measure outcomes recorded by patients including sleep maintenance (subjective total sleep time) and sleep onset (subjective time to sleep onset). In the Phase 2 and pivotal Phase 3 trials, objective sleep laboratory polysomnography (PSG) data was also collected, allowing for measures of sleep duration (total sleep time [TST]), sleep maintenance (wake after sleep onset [WASO]), and sleep onset (latency to persistent sleep). In total, suvorexant was administered to patients for >275 000 nights.

In the 4 week Phase 2 crossover study of 10, 20, 40, and 80 mg ($n = 254$), all doses were significant relative to placebo for the primary end point of sleep efficiency [SE], as assessed by PSG both on the first night and at the end of 4 weeks of treatment [where SE = TST/fixed time in bed (8 h) $\times$ 100].³⁰ The 4 week SE improvements correspond to TST changes of 90, 92, 98, and 95 min from baseline for the 10, 20, 40, and 80 mg doses, respectively (versus 60 min for placebo). WASO was also reduced across the doses evaluated. Improvement in latency to persistent sleep was noted at 80 mg, as were improvements in patient reported measures for subjective time to sleep onset, subjective total sleep time, and subjective

quality of sleep, for the 40 and 80 mg doses on both night 1 and at the end of week 4. Suvorexant was generally well-tolerated, with no reports of rebound insomnia, cataplexy, amnesia, or complex unwanted behaviors (e.g., sleep-walking, sleep eating). Somnolence was the most frequent adverse event reported. Analysis of power spectral density of the EEG data from this first patient study showed that the increased TST mediated by suvorexant results in minimal perturbation from sleep on placebo, in either NREM- or REM-phase,³³ a feature further confirmed and shown to be differentiated from the profile of zolpidem in a head-to-head study in healthy volunteers.³⁴

The Phase 3 program included three double-blind, randomized, placebo-controlled studies that enrolled both nonelderly and elderly insomnia patients: two replicate pivotal studies with core 3 month treatment periods,³¹ and a 1 year efficacy and safety study with a 2 month randomized discontinuation.³¹ On the basis of the Phase 2 results, doses of 40 and 20 mg were included for evaluation in the pivotal Phase 3 trials.³¹ In the elderly, doses of 30 mg (instead of 40 mg) and 15 mg (instead of 20 mg) were included to account for anticipated exposure differences based on the available data at the time studies were initiated.

The primary results from the two pivotal Phase 3 trials were reported separately, with results of pooled data for the approved 20/15 mg doses combined.³⁵ Across the randomized studies, 775 patients received 40/30 mg, 494 received 20/15 mg, and 772 received placebo. Suvorexant was effective versus placebo from the earliest time points on all measures (night 1 for objective measures, and week 1 for subjective measures) that was generally sustained over the 3 months (except for latency to persistent sleep at the 20/15 mg dose, which appeared to be the result of an increase in placebo response, rather than a decrease in the response to suvorexant). Suvorexant tended to produce greater efficacy on patient reported sleep maintenance measures as compared to sleep-onset measures; for example, suvorexant 20/15 mg at 3 months produced a standardized effect size of 29% for subjective total sleep time and 17% for subjective time to sleep onset.³⁵ Suvorexant appeared to produce greater effects on objective measures compared to subjective measures; for example, at 3 month standardized effect sizes for measures of sleep maintenance were 54% for WASO with suvorexant 20/15 mg and 29% for subjective TST.³⁵ Last, regarding dose response, although on most measures suvorexant 40/30 mg appeared to be more effective than 20/15 mg, the difference was modest (i.e., 40/30 mg was not twice as effective as 20/15 mg), and the 20/15 mg dose produced the majority of efficacy for most end points.

To further characterize the nature of the suvorexant-mediated benefits observed for maintenance of sleep, analyses of WASO using PSG was conducted. These showed that the effects of suvorexant in reducing WASO was apparent from ~2 h of sleep initiation, which was sustained over the remainder of the 8 h recording. Interestingly, this reduction in WASO was not accompanied by a change in awakenings during the night,³⁰ a finding consistent with preclinical data indicating suvorexant does not affect the ability of salient cues to cause awakening.³⁶ Additional characterization of suvorexant's effects on WASO and awakenings found that suvorexant affects consolidation of sleep by decreasing the total time spent in and total number of "long" awakenings (>2 min), and that this effect appeared to increase patient-reported good/excellent

sleep quality by 2-fold,³⁷ consistent with other data indicating long awakenings are more impactful than short awakenings for patients with insomnia.³⁸ Importantly, suvorexant helped patients return to sleep from their longest awakening more than twice as fast as those on placebo. With respect to overall sleep architecture and normal sleep physiology, analyses of the pooled Phase 3 PSG data indicate that the increased time spent asleep (TST) associated with suvorexant is accompanied by proportional increases in time spent in all sleep stages (REM and NREM) compared to placebo.³⁹

Beyond the results observed on core sleep measures in the pivotal trials, other analyses such as assessments of insomnia severity and improvement and responder analyses further confirm the consistency and relevance of the global benefits experienced by patients treated with suvorexant.^{31,35} For example, when responders are defined as those showing ≥ 6 point improvement⁴⁰ at 3 months on the patient-rated Insomnia Severity Index,⁴¹ the responder percentage was 56% for suvorexant 20/15 mg compared to 42% for placebo with an odds ratio of 1.8, indicating that patients taking suvorexant were nearly twice as likely to be a responder than patients taking placebo.³⁵

With regard to sustained efficacy in patients requiring chronic use of pharmacologic agents for effective management of their insomnia, a 1 year randomized placebo controlled trial was conducted primarily designed to assess safety but also to characterize the long-term efficacy of suvorexant 40/30 mg ($N = 522$) versus placebo ($N = 259$).³² Importantly, suvorexant effects on sleep onset and maintenance were maintained over 12 months. During a 2 month randomized discontinuation phase following 1 year of treatment, insomnia symptoms (difficulty falling asleep and staying asleep) returned in patients switched to placebo versus those continued on suvorexant, supporting the continued benefit of suvorexant treatment for insomnia. Although the approved 20/15 mg dose was not included, a similar pattern of sustained efficacy would be expected for that dose in the setting of chronic treatment, based on its performance in the 3 month pivotal trials and further supported by evidence for continued efficacy for up to 6 months in a postmarketing survey study conducted in Japan.⁴²

Regarding suvorexant safety, most patients completed the planned 3 months of treatment in the pooled analysis of the two pivotal Phase 3 trials, with relatively few discontinuations resulting from adverse events (3.0% for 20/15 mg versus 5.2% for placebo).³⁵ Somnolence was the most common adverse event associated with suvorexant (6.7% for 20/15 mg versus 3.3% for placebo). Reports of somnolence occurred most often early in treatment (first 1–2 weeks), were generally mild-to-moderate, and rarely resulted in discontinuation. Severe and impairing daytime somnolence was infrequent in patients on suvorexant 20/15 mg (0.6%).

Because narcolepsy has been shown to be associated with loss of orexin neurons¹⁶ and the subsequent theoretical suggestion that antagonism of orexin receptors could produce symptoms of narcolepsy, particularly cataplexy, the Phase 3 program included prespecified evaluation of adverse events that could be considered mechanism-based. However, based on adjudication of suspect events by an external independent expert committee, no events in the Phase 2–3 trials, including falls, were confirmed to be consistent with cataplexy. However, as patients with narcolepsy were excluded from the Phase 3 trials and no systematic data exists regarding the effects of

suvorexant in patients with narcolepsy, suvorexant is contraindicated in these patients.

Other potential sleep-associated adverse events were also systematically assessed in the suvorexant Phase 3 development program (e.g., hallucinations, sleep paralysis, and complex sleep-related behaviors). A small number of reports of sleep-related hallucinations (2/493, 0.4%) and sleep paralysis (1/493, 0.2%) were associated with suvorexant 20/15 mg, with no such reports for placebo. Because of the small numbers of patients experiencing these effects, both sleep-related hallucinations and sleep paralysis can occur in the general population, and hallucinations have been reported with use of other sleep-promoting medications (i.e., zolpidem), it is unknown whether this effect is mechanism-based.^{43,44} No complex sleep behavior events were reported for suvorexant 20/15 mg.³⁵ For the higher 40/30 mg dose, there were 2/1291 (0.2%) events reported^{31,32} that appeared qualitatively similar to those reported for other sleep treatments.⁴⁵

All centrally acting drugs pose concerns for effects on mood and suicidality, and patients with major psychiatric disorders were generally excluded from the development program. In the Phase 3 trials, suicidal ideation was infrequent but dose-related: 1/493 (0.2%) on suvorexant 20/15 mg and 6/1291 (0.5%) on suvorexant 40/30 mg.^{31,32} Insomnia and mood disorders, as well as suicidal ideation, have a high comorbidity and, consequently, as with other hypnotics, it is possible that worsening of depression or suicidal thinking may occur with suvorexant.

In aggregate, the clinical trial experience with suvorexant demonstrated that it improved sleep onset and maintenance and was generally safe and well-tolerated. Although the suvorexant clinical program evaluated higher doses than those ultimately recommended, in some instances higher-dose data has been mentioned here to provide full context of the impact of dual orexin receptor antagonism, however, the 10–20 mg data are most informative from a clinical perspective. No direct head-to-head insomnia studies comparing suvorexant sleep efficacy and safety with other sleep medications have yet been conducted.

As of this writing, Belsomra R (suvorexant) is the first and currently the only approved orexin receptor antagonist for the treatment of insomnia. Suvorexant was approved in Japan and the USA in 2014 and in Australia in 2016. In the USA, the approved doses are 5, 10, 15, and 20 mg with a recommended starting dose of 10 mg, which can be increased to a maximum of 20 mg if the lower dose is well-tolerated but not satisfactorily effective. The USA dosing recommendations were based on the FDA view that the lowest effective dose of any insomnia treatment should be used. In Japan and Australia, regulatory opinion favored a more direct-to-most-effective dose approach, with approval of 15 mg for elderly patients and 20 mg for nonelderly patients, without titration from a lower dose.

Beyond its established role in sleep–wake regulation, accumulating evidence points to the involvement of the orexin system in the pathology of a variety of neuropsychiatric disorders including Alzheimer's disease (AD), Parkinson's disease (PD), anxiety, stress, posttraumatic stress disorder (PTSD), substance abuse disorders, depression, and pain.^{46–49} Since regulatory approval of suvorexant as the first orexin receptor antagonist nearly 5 years ago as of this review, the therapeutic landscape for strategies aimed at modulating orexinergic signaling is growing rapidly. In fact, a number of

clinical studies with suvorexant are either ongoing or continue to be initiated in a variety of conditions.⁵⁰

The incidence of sleep disturbances and insomnia in patients with AD is high, which combined with inadequate treatment options places a particularly heavy burden on their caregivers and is a major cause of institutionalization.⁵¹ Preclinical studies suggest that sleep time is correlated with brain changes consistent with AD development. For example, shorter sleep duration has been demonstrated to be correlated with higher levels of A β and its aggregation.^{52,53} Of additional interest are data showing that an AD mouse model made deficient in orexin peptide expression showed a significant improvement in A β pathology, and this improvement was attributed to sleep prolongation.⁵³ Furthermore, intracerebroventricular (IVC) infusion of orexin neuropeptide produced consolidated wakefulness and increased interstitial A β .⁵² Preclinical observations such as these mirror clinical data suggesting an inverse relationship between A β in the cerebrospinal fluid (CSF) and duration of sleep.^{54–56} Furthermore, patients with moderate to severe AD showed greater sleep disruptions and higher CSF orexin levels compared to healthy controls.⁵⁷ On the basis of these accumulating data, the orexin pathway has become an interesting target to explore for the potential treatment of AD; indeed, IVC infusion of a DORA has been shown to decrease interstitial A β in mice.⁵²

In light of these intriguing preclinical and preliminary clinical data, a Phase 3 clinical study to examine the sleep efficacy and safety of suvorexant in AD patients has recently been completed (NCT02750306). In this four-week study, 142 patients with both probable mild-to-moderate AD dementia and DSM-V insomnia received suvorexant (10 or 20 mg, dose adjusted based on clinical response), and 143 patients received placebo. Similar to what has been reported in other populations with insomnia, suvorexant increased TST in AD patients by 28 min compared to placebo, an improvement corresponding to a 73 min increase from a baseline of 278 min.⁵⁸ Patients taking suvorexant were also twice as likely to experience an improvement of ≥ 60 min relative to those taking placebo. Suvorexant also reduced WASO relative to placebo, consistent with observations in prior insomnia studies. The adverse effect profile of suvorexant in patients with probable AD was similar to what has been reported in prior insomnia studies, with somnolence being most frequent (6/142, 4.2%) versus placebo (2/143, 1.4%). Notably, based on end-of-treatment week 4 assessments, suvorexant neither improved nor impaired next-day cognitive or psychomotor performance (by the Mini Mental Status Exam and Digit Symbol Tests, respectively). Larger long-term studies will be required to address whether sleep improvements mediated by suvorexant could lead to improvements over time from a baseline of impaired cognition. Future studies aimed at addressing such questions and understanding the broader relevance of sleep and orexin signaling to insomnia in AD dementia and AD disease progression are warranted^{52,59} and are expected to be followed with excitement over the coming years.

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Notes

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REFERENCES

- (1) CNS Drugs Take 20% Longer to Develop and to Approve vs. Non-CNS Drugs. *Tufts CSDD Impact Rep.* 2018, 20, 5–8.
- (2) DiMasi, J. A.; Hansen, R. W.; and Grabowski, H. G. (2003) The price of innovation: new estimates of drug development costs. *J. Health Econ.* 22 (2), 151–85.
- (3) Ohayon, M. M.; Lemoine, P.; Arnaud-Briant, V.; and Dreyfus, M. (2002) Prevalence and consequences of sleep disorders in a shift worker population. *J. Psychosom. Res.* 53 (1), 577–83.
- (4) Hafner, M.; Stepanek, M.; Taylor, J.; Troxel, W. M.; and van Stolk, C. (2017) Why Sleep Matters-The Economic Costs of Insufficient Sleep: A Cross-Country Comparative Analysis. *Rand Health Q.* 6 (4), 11.
- (5) Mai, E.; and Buysse, D. J. (2008) Insomnia: Prevalence, Impact, Pathogenesis, Differential Diagnosis, and Evaluation. *Sleep Med. Clin* 3 (2), 167–174.
- (6) Morin, C. M.; Belanger, L.; LeBlanc, M.; Ivers, H.; Savard, J.; Espie, C. A.; Merette, C.; Baillargeon, L.; and Gregoire, J. P. (2009) The natural history of insomnia: a population-based 3-year longitudinal study. *Arch. Intern. Med.* 169 (5), 447–53.
- (7) Ohayon, M. M.; Guilleminault, C.; and Chokroverty, S. (2010) Sleep epidemiology 30 years later: where are we? *Sleep Med.* 11 (10), 961–2.
- (8) Roth, T.; Coulouvrat, C.; Hajak, G.; Lakoma, M. D.; Sampson, N. A.; Shahly, V.; Shillington, A. C.; Stephenson, J. J.; Walsh, J. K.; and Kessler, R. C. (2011) Prevalence and perceived health associated with insomnia based on DSM-IV-TR; International Statistical Classification of Diseases and Related Health Problems, Tenth Revision; and Research Diagnostic Criteria/International Classification of Sleep Disorders, Second Edition criteria: results from the America Insomnia Survey. *Biol. Psychiatry* 69 (6), 592–600.
- (9) Kochanek, K. D.; Murphy, S. L.; Xu, J.; and Arias, E. (2014) Mortality in the United States, 2013. *NCHS Data Brief* No. 178, 1–8.
- (10) Nuckols, T. K.; Bhattacharya, J.; Wolman, D. M.; Ulmer, C.; and Escarce, J. J. (2009) Cost implications of reduced work hours and workloads for resident physicians. *N. Engl. J. Med.* 360 (21), 2202–15.
- (11) Pack, A. I. (1995) The prevalence of work-related sleep problems. *J. Gen Intern Med.* 10 (1), 57.
- (12) de Lecea, L.; Kilduff, T. S.; Peyron, C.; Gao, X.; Foye, P. E.; Danielson, P. E.; Fukuhara, C.; Battenberg, E. L.; Gautvik, V. T.; Bartlett, F. S., 2nd; Frankel, W. N.; van den Pol, A. N.; Bloom, F. E.; Gautvik, K. M.; and Sutcliffe, J. G. (1998) The hypocretins: hypothalamus-specific peptides with neuroexcitatory activity. *Proc. Natl. Acad. Sci. U. S. A.* 95 (1), 322–7.
- (13) Sakurai, T.; Amemiya, A.; Ishii, M.; Matsuzaki, I.; Chemelli, R. M.; Tanaka, H.; Williams, S. C.; Richardson, J. A.; Kozlowski, G. P.; Wilson, S.; Arch, J. R.; Buckingham, R. E.; Haynes, A. C.; Carr, S. A.; Annan, R. S.; McNulty, D. E.; Liu, W. S.; Terrett, J. A.; Elshourbagy, N. A.; Bergsma, D. J.; and Yanagisawa, M. (1998) Orexins and orexin receptors: a family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior. *Cell* 92 (4), 573–85.
- (14) Lin, L.; Faraco, J.; Li, R.; Kadotani, H.; Rogers, W.; Lin, X.; Qiu, X.; de Jong, P. J.; Nishino, S.; and Mignot, E. (1999) The sleep

disorder canine narcolepsy is caused by a mutation in the hypocretin (orexin) receptor 2 gene. *Cell* 98 (3), 365–76.

(15) Mignot, E., Lammers, G. J., Ripley, B., Okun, M., Nevsimialova, S., Overeem, S., Vankova, J., Black, J., Harsh, J., Bassetti, C., Schrader, H., and Nishino, S. (2002) The role of cerebrospinal fluid hypocretin measurement in the diagnosis of narcolepsy and other hypersomnias. *Arch. Neurol.* 59 (10), 1553–62.

(16) Thannickal, T. C., Moore, R. Y., Nienhuis, R., Ramanathan, L., Gulyani, S., Aldrich, M., Cornford, M., and Siegel, J. M. (2000) Reduced number of hypocretin neurons in human narcolepsy. *Neuron* 27 (3), 469–74.

(17) Roecker, A. J., Cox, C. D., and Coleman, P. J. (2016) Orexin Receptor Antagonists: New Therapeutic Agents for the Treatment of Insomnia. *J. Med. Chem.* 59 (2), 504–30.

(18) Rupniak, N. M. (2003) Animal models of depression: challenges from a drug development perspective. *Behav. Pharmacol.* 14 (5–6), 385–390.

(19) Berton, O., and Nestler, E. J. (2006) New approaches to antidepressant drug discovery: beyond monoamines. *Nat. Rev. Neurosci.* 7 (2), 137–51.

(20) Bussey, T. J., Holmes, A., Lyon, L., Mar, A. C., McAllister, K. A., Nithianantharajah, J., Oomen, C. A., and Saksida, L. M. (2012) New translational assays for preclinical modelling of cognition in schizophrenia: the touchscreen testing method for mice and rats. *Neuropharmacology* 62 (3), 1191–203.

(21) Whitman, D. B., Cox, C. D., Breslin, M. J., Brashear, K. M., Schreier, J. D., Bogusky, M. J., Bednar, R. A., Lemaire, W., Bruno, J. G., Hartman, G. D., Reiss, D. R., Harrell, C. M., Kraus, R. L., Li, Y., Garson, S. L., Doran, S. M., Prueksaritanont, T., Li, C., Winrow, C. J., Koblan, K. S., Renger, J. J., and Coleman, P. J. (2009) Discovery of a potent, CNS-penetrant orexin receptor antagonist based on an n, n-disubstituted-1,4-diazepane scaffold that promotes sleep in rats. *ChemMedChem* 4 (7), 1069–74.

(22) Cox, C. D., McGaughey, G. B., Bogusky, M. J., Whitman, D. B., Ball, R. G., Winrow, C. J., Renger, J. J., and Coleman, P. J. (2009) Conformational analysis of N,N-disubstituted-1,4-diazepane orexin receptor antagonists and implications for receptor binding. *Bioorg. Med. Chem. Lett.* 19 (11), 2997–3001.

(23) Coleman, P. J., Schreier, J. D., Roecker, A. J., Mercer, S. P., McGaughey, G. B., Cox, C. D., Hartman, G. D., Harrell, C. M., Reiss, D. R., Doran, S. M., Garson, S. L., Anderson, W. B., Tang, C., Prueksaritanont, T., Winrow, C. J., and Renger, J. J. (2010) Discovery of 3,9-diazabicyclo[4.2.1]nonanes as potent dual orexin receptor antagonists with sleep-promoting activity in the rat. *Bioorg. Med. Chem. Lett.* 20 (14), 4201–5.

(24) McGaughey, G., Bayly, C. I., Cox, C. D., Schreier, J. D., Breslin, M. J., Bogusky, M., Pitznerberger, S., Ball, R., and Coleman, P. J. (2014) Shaping suvorexant: application of experimental and theoretical methods for driving synthetic designs. *J. Comput.-Aided Mol. Des.* 28 (1), 5–12.

(25) Cox, C. D., Breslin, M. J., Whitman, D. B., Schreier, J. D., McGaughey, G. B., Bogusky, M. J., Roecker, A. J., Mercer, S. P., Bednar, R. A., Lemaire, W., Bruno, J. G., Reiss, D. R., Harrell, C. M., Murphy, K. L., Garson, S. L., Doran, S. M., Prueksaritanont, T., Anderson, W. B., Tang, C., Roller, S., Cabalu, T. D., Cui, D., Hartman, G. D., Young, S. D., Koblan, K. S., Winrow, C. J., Renger, J. J., and Coleman, P. J. (2010) Discovery of the dual orexin receptor antagonist [(7R)-4-(5-chloro-1,3-benzoxazol-2-yl)-7-methyl-1,4-diazepan-1-yl][5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl]methanone (MK-4305) for the treatment of insomnia. *J. Med. Chem.* 53 (14), 5320–32.

(26) Herring, W. J., Connor, K. M., Snyder, E., Snively, D. B., Morin, C. M., Lines, C., and Michelson, D. (2019) Effects of suvorexant on the Insomnia Severity Index in patients with insomnia: analysis of pooled phase 3 data. *Sleep Med.* 56, 219–223.

(27) Cui, D., Cabalu, T., Yee, K. L., Small, J., Li, X., Liu, B., Maciolek, C., Smith, S., Liu, W., McCrea, J. B., and Prueksaritanont, T. (2016) In vitro and in vivo characterisation of the metabolism and disposition of suvorexant in humans. *Xenobiotica* 46 (10), 882–95.

(28) Sun, H., Kennedy, W. P., Wilbraham, D., Lewis, N., Calder, N., Li, X., Ma, J., Yee, K. L., Ermlich, S., Mangin, E., Lines, C., Rosen, L., Chodakewitz, J., and Murphy, G. M. (2013) Effects of suvorexant, an orexin receptor antagonist, on sleep parameters as measured by polysomnography in healthy men. *Sleep* 36 (2), 259–267.

(29) Winrow, C. J., Gotter, A. L., Cox, C. D., Doran, S. M., Tannenbaum, P. L., Breslin, M. J., Garson, S. L., Fox, S. V., Harrell, C. M., Stevens, J., Reiss, D. R., Cui, D., Coleman, P. J., and Renger, J. J. (2011) Promotion of sleep by suvorexant: a novel dual orexin receptor antagonist. *J. Neurogenet.* 25 (1–2), 52–61.

(30) Herring, W. J., Snyder, E., Budd, K., Hutzelmann, J., Snively, D., Liu, K., Lines, C., Roth, T., and Michelson, D. (2012) Orexin receptor antagonism for treatment of insomnia: a randomized clinical trial of suvorexant. *Neurology* 79 (23), 2265–74.

(31) Herring, W. J., Connor, K. M., Ivgy-May, N., Snyder, E., Liu, K., Snively, D. B., Krystal, A. D., Walsh, J. K., Benca, R. M., Rosenberg, R., Sangal, R. B., Budd, K., Hutzelmann, J., Leibenberger, H., Froman, S., Lines, C., Roth, T., and Michelson, D. (2016) Suvorexant in Patients With Insomnia: Results From Two 3-Month Randomized Controlled Clinical Trials. *Biol. Psychiatry* 79 (2), 136–48.

(32) Michelson, D., Snyder, E., Paradis, E., Cheng-Liu, M., Snively, D. B., Hutzelmann, J., Walsh, J. K., Krystal, A. D., Benca, R. M., Cohn, M., Lines, C., Roth, T., and Herring, W. J. (2014) Safety and efficacy of suvorexant during 1-year treatment of insomnia with subsequent abrupt treatment discontinuation: a phase 3 randomised, double-blind, placebo-controlled trial. *Lancet Neurol.* 13 (5), 461–71.

(33) Ma, J., Svetnik, V., Snyder, E., Lines, C., Roth, T., and Herring, W. J. (2014) Electroencephalographic power spectral density profile of the orexin receptor antagonist suvorexant in patients with primary insomnia and healthy subjects. *Sleep* 37 (10), 1609–19.

(34) Struyk, A., Gargano, C., Drexel, M., Stoch, S. A., Svetnik, V., Ma, J., and Mayleben, D. (2016) Pharmacodynamic effects of suvorexant and zolpidem on EEG during sleep in healthy subjects. *Eur. Neuropsychopharmacol.* 26 (10), 1649–56.

(35) Herring, W. J., Connor, K. M., Snyder, E., Snively, D. B., Zhang, Y., Hutzelmann, J., Matzura-Wolfe, D., Benca, R. M., Krystal, A. D., Walsh, J. K., Lines, C., Roth, T., and Michelson, D. (2016) Suvorexant in Patients with Insomnia: Pooled Analyses of Three-Month Data from Phase-3 Randomized Controlled Clinical Trials. *J. Clin. Sleep Med.* 12 (9), 1215–25.

(36) Tannenbaum, P. L., Stevens, J., Binns, J., Savitz, A. T., Garson, S. L., Fox, S. V., Coleman, P., Kuduk, S. D., Gotter, A. L., Marino, M., Tye, S. J., Uslaner, J. M., Winrow, C. J., and Renger, J. J. (2014) Orexin receptor antagonist-induced sleep does not impair the ability to wake in response to emotionally salient acoustic stimuli in dogs. *Front. Behav. Neurosci.* 8, 182.

(37) Svetnik, V., Snyder, E. S., Tao, P., Scammell, T. E., Roth, T., Lines, C., and Herring, W. J. (2018) Insight Into Reduction of Wakefulness by Suvorexant in Patients With Insomnia: Analysis of Wake Bouts. *Sleep* 41 (1), zsx178.

(38) Winsor, M. A., McBean, A. L., and Montgomery-Downs, H. E. (2013) Minimum duration of actigraphy-defined nocturnal awakenings necessary for morning recall. *Sleep Med.* 14 (7), 688–91.

(39) Snyder, E., Ma, J., Svetnik, V., Connor, K. M., Lines, C., Michelson, D., and Herring, W. J. (2016) Effects of suvorexant on sleep architecture and power spectral profile in patients with insomnia: analysis of pooled phase 3 data. *Sleep Med.* 19, 93–100.

(40) Yang, M., Morin, C. M., Schaefer, K., and Wallenstein, G. V. (2009) Interpreting score differences in the Insomnia Severity Index: using health-related outcomes to define the minimally important difference. *Curr. Med. Res. Opin.* 25 (10), 2487–94.

(41) Bastien, C. H., Vallieres, A., and Morin, C. M. (2001) Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Med.* 2 (4), 297–307.

(42) Asai, Y., Sano, H., Miyazaki, M., Iwakura, M., Maeda, Y., and Hara, M. (2019) Suvorexant (Belsomra(R)) Tablets 10, 15, and 20 mg): Japanese Drug-Use Results Survey. *Drugs R&D* 19 (1), 27–46.

- (43) Ohayon, M. M. (2000) Prevalence of hallucinations and their pathological associations in the general population. *Psychiatry Res.* 97 (2–3), 153–64.
- (44) Ohayon, M. M., Zulley, J., Guilleminault, C., and Smirne, S. (1999) Prevalence and pathologic associations of sleep paralysis in the general population. *Neurology* 52 (6), 1194–200.
- (45) Dolder, C. R., and Nelson, M. H. (2008) Hypnosedative-induced complex behaviours: incidence, mechanisms and management. *CNS Drugs* 22 (12), 1021–36.
- (46) Matsuki, T., and Sakurai, T. (2008) Orexins and orexin receptors: from molecules to integrative physiology. *Results Probl Cell Differ* 46, 27–55.
- (47) Li, J., Hu, Z., and de Lecea, L. (2014) The hypocretins/orexins: integrators of multiple physiological functions. *Br. J. Pharmacol.* 171 (2), 332–50.
- (48) Aston-Jones, G., Smith, R. J., Moorman, D. E., and Richardson, K. A. (2009) Role of lateral hypothalamic orexin neurons in reward processing and addiction. *Neuropharmacology* 56, 112–121.
- (49) Lim, M. M., Gerstner, J. R., and Holtzman, D. M. (2014) The sleep-wake cycle and Alzheimer's disease: what do we know? *Neurodegener Dis Manag* 4 (5), 351–62.
- (50) Herring, W. J., Roth, T., Krystal, A. D., and Michelson, D. (2019) Orexin receptor antagonists for the treatment of insomnia and potential treatment of other neuropsychiatric indications. *J. Sleep Res.* 28 (2), No. e12782.
- (51) Urrestarazu, E., and Iriarte, J. (2016) Clinical management of sleep disturbances in Alzheimer's disease: current and emerging strategies. *Nat. Sci. Sleep* 8, 21–33.
- (52) Kang, J. E., Lim, M. M., Bateman, R. J., Lee, J. J., Smyth, L. P., Cirrito, J. R., Fujiki, N., Nishino, S., and Holtzman, D. M. (2009) Amyloid-beta dynamics are regulated by orexin and the sleep-wake cycle. *Science* 326 (5955), 1005–7.
- (53) Roh, J. H., Huang, Y., Bero, A. W., Kasten, T., Stewart, F. R., Bateman, R. J., and Holtzman, D. M. (2012) Disruption of the sleep-wake cycle and diurnal fluctuation of beta-amyloid in mice with Alzheimer's disease pathology. *Sci. Transl. Med.* 4 (150), 150ra122.
- (54) Spira, A. P., Gamaldo, A. A., An, Y., Wu, M. N., Simonsick, E. M., Bilgel, M., Zhou, Y., Wong, D. F., Ferrucci, L., and Resnick, S. M. (2013) Self-reported sleep and beta-amyloid deposition in community-dwelling older adults. *JAMA Neurol* 70 (12), 1537–1543.
- (55) Ooms, S., Overeem, S., Besse, K., Rikkert, M. O., Verbeek, M., and Claassen, J. A. (2014) Effect of 1 night of total sleep deprivation on cerebrospinal fluid beta-amyloid 42 in healthy middle-aged men: a randomized clinical trial. *JAMA Neurol* 71 (8), 971–7.
- (56) Ju, Y. E., McLeland, J. S., Toedebusch, C. D., Xiong, C., Fagan, A. M., Duntley, S. P., Morris, J. C., and Holtzman, D. M. (2013) Sleep quality and preclinical Alzheimer disease. *JAMA Neurol* 70 (5), 587–93.
- (57) Liguori, C., Romigi, A., Nuccetelli, M., Zannino, S., Sancesario, G., Martorana, A., Albanese, M., Mercuri, N. B., Izzì, F., Bernardini, S., Nitti, A., Sancesario, G. M., Sica, F., Marciani, M. G., and Placidi, F. (2014) Orexinergic system dysregulation, sleep impairment, and cognitive decline in Alzheimer disease. *JAMA Neurol* 71 (12), 1498–505.
- (58) Herring, W. J., Ceesay, P., Snyder, E., Bliwise, D., Budd, K., Hutzelmann, J., Stevens, J., and Michelson, D. (2019) Randomized Controlled Clinical Polysomnography Trial of Suvorexant for Treating Insomnia in Patients with Alzheimer's Disease. *Sleep* 42, A164.
- (59) Roh, J. H., Jiang, H., Finn, M. B., Stewart, F. R., Mahan, T. E., Cirrito, J. R., Heda, A., Snider, B. J., Li, M., Yanagisawa, M., de Lecea, L., and Holtzman, D. M. (2014) Potential role of orexin and sleep modulation in the pathogenesis of Alzheimer's disease. *J. Exp. Med.* 211 (13), 2487–96.