Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Suvorexant

Evidence Summary

Very likely a great option to protect against insomnia but little evidence or rationale to use outside of insomnia to protect against age-related disease or neurodegeneration.

Neuroprotective Benefit: Laboratory studies are conflicting on whether inhibition of orexin (e.g. with suvorexant) would protect or worsen neurodegeneration but successful treatment of insomnia may reduce dementia risk.

Aging and related health concerns: Limited evidence suggests orexin may decline with age, suggesting further reduction with suvorexant may be harmful for age-related heath, but the evidence is inconsistent across different models.

Safety: Good safety profile for up to 12 months but no data on long-term use of suvorexant. Animal research suggests that orexin is important for systems like appetite, lipid metabolism, and reward, thus inhibition could have long-term adverse effects.

What is it? Suvorexant (brand name Belsomra) is a dual-receptor antagonist of orexin. In other words, it is a drug that inhibits both of the 2 receptors known for orexin, reportedly with high specificity. Orexin, also called hypocretin, is a neuropeptide neurotransmitter generated in cells of the lateral hypothalamus. Orexin signaling is important for arousal, wakefulness, and appetite.

Neuroprotective Benefit: Laboratory studies are conflicting on whether inhibition of orexin (e.g. with suvorexant) would protect or worsen neurodegeneration but successful treatment of insomnia may to reduce dementia risk.

Types of evidence:

- 1 small observational study on incidence of Alzheimer's pathology in orexin-deficient people
- Conflicting small case-control studies testing whether orexin levels increase in patients
- Conflicting animal and *in vitro* studies reporting either protection or harm from orexin

Studies are rather mixed on whether orexin inhibition with suvorexant would protect or exacerbate neurodegeneration. Narcolepsy patients deficient in orexin do not appear to be protected from Alzheimer's pathology (Scammell 2012). But for people with insomnia, suvorexant may confer benefit, since sleep disturbance has been associated in some observational studies with an increased risk of dementia. While this relationship might be a symptom rather than a cause of incipient dementia, animal models have suggested that sleep may protect the brain in many ways, strengthening the synaptic connections that underlie memory, reducing the risk of metabolic impairment, and helping to clear toxic proteins like beta-amyloid from the brain (highlights in, Xie 2013, AlzForum June 2014).

Animal research from David Holtzman's lab reported that orexin antagonists can reduce beta-amyloid levels while orexin treatment can increase it but these effects mimicked that of changes to the sleep/wake cycle, suggesting the effects might occur via sleep (Kang 2009). However, several labs have reported that orexin is neuroprotective against several types of injuries, possibly by increasing HIF-1alpha (reviewed in Nixon 2015). Orexin can also promote hippocampal long-term potentiation, the molecular basis of memory (Akbari 2011, Wayner 2004, Walling 2004) although the opposite has also been reported (Aou 2003). In summary, animal studies are mixed on whether inhibition of orexin will protect or harm in terms of memory and neurodegeneration, and the benefits appear to be tied to sleep.

Whether orexin increases or decreases in Alzheimer's is also unclear. The levels of orexin in the CSF were increased in moderate to severe Alzheimer's patients in one study (Liquori 2014) and in mild cognitive impairment (MCI) patients due to Alzheimer's pathology in another study (Dauvilliers 2014).

However, these 2 studies are not consistent with each other or with a 3rd study (Schmidt 2013). Another study reported that CSF orexin levels correlated with tau and phosphorylated tau but these effects were even stronger in patients with depression than Alzheimer's disease, and Alzheimer's patients did not have higher orexin levels than patients with depression (Deuschle 2014). The number of orexin-labeled neurons was decreased in one autopsy study of dementia patients (Kasanuki 2014). In other words, whether CNS orexin levels increase or decrease with Alzheimer's or other dementia is still an open question.

APOE4 interactions: Whether APOE4 modifies the relationship of orexin to neurodegeneration has not been studied. Peripheral studies are not compelling. No effect of APOE4 was seen on CSF levels of hypocretin in a case-control comparison of Alzheimer's patients versus controls but that study did not detect an effect of Alzheimer's either, which is controversial (see above) (Schmidt 2013). APOE4 does not alter the risk of narcolepsy related to orexin signaling (Gencik 2001) and probably does not alter the risk of sleep apnea and disordered breathing (Varvarigou 2011, Kullkarni 2009).

Aging and related health concerns: Limited evidence suggests orexin may decline with age, suggesting further reduction with suvorexant may be harmful for age-related heath, but the evidence is inconsistent in different models.

Types of evidence:

- with suvorexant specifically, no studies
- with orexin, the target of suvorexant, animal and human studies on changes with age

For people with insomnia, suvorexant may be a relatively safe and effective treatment to reduce the many health risks of long-term sleep impairment. For people without insomnia, however, suvorexant has little rationale for protection from aging and related health risks.

Virtually no evidence is available on suvorexant use and aging but its target, orexin, has been studied. Aging reduces the magnitude of daily circadian changes in orexin levels in the brain in many animals although possibly not macaque monkeys (reviewed in Nixon 2015). Similarly, older humans have 10% fewer orexin-labeled neurons in their brain compared to young adults based on one small study (Hunt 2015). Paradoxically, plasma levels of orexin increase with both aging and menopause (Matsumura 2002, El-Sedeek 2010). The biological importance of plasma orexin relative to brain orexin is not yet clear.

None of these studies, whether on the brain or plasma, have tested whether orexin levels predict mortality or correlate with markers of biological age and function, making it difficult to predict whether

inhibiting orexin might be good or bad. More research is needed. Nixon and colleagues (2015) argued that the reduction in brain orexin with age might underlie age-related anorexia, weight gain, and sleep changes. If true, then further reduction of orexin with suvorexant might be harmful but the evidence for these conclusions is extremely weak at best.

Safety: Good safety profile for up to 12 months but no data on long-term use of suvorexant. Animal research suggests that orexin is important for systems like appetite, lipid metabolism, and reward, thus inhibition could have long-term adverse effects.

In Phase III trials, 3-12 months of suvorexant use in several hundred men and women was well tolerated. Long-term pharmacoepidemiology data does not yet exist because suvorexant is a new drug.

In trials, the most common side effect was somnolence (drowsiness), experienced by 10.7% of patients using 30-40mg and 6.7% of patients using 15-20mg versus 3% using placebo. Other adverse events, like headaches and dizziness, were not significantly increased, but more likely with suvorexant 15-20 mg compared to placebo (Citrome 2014 review). Sedation and cognitive disturbances are reportedly not side effects of suvorexant, although they are side effects of benzodiazepines.

Theoretically, orexin inhibition could have effects on many neuropsychiatric systems. Orexin, the target of suvorexant, appears to be important for reward processing, attention and appetite while dysfunction of orexin may be involved with depression, addiction, (e.g. Yeoh 2014, Nollet 2013, Aston-Jones 2010, Khoo 2014). Orexin may also influence metabolism (e.g. Gao 2014) and orexin-deficient narcolepsy patients often have higher body-mass index (reviewed in Nixon 2015). Orexin is also present in peripheral organs like the gastrointestinal tract, pituitary, pancreas, and male reproductive system (e.g. Leonard 2014 review). It is not yet clear whether pharmacological inhibition of orexin receptors will influence these various systems in the long-term.

Another dual-receptor orexin antagonist, almorexant, was discontinued in 2011 by GlaxoSmithKline and Actelion after unspecified "certain safety observations" in a phase III clinical trial. Unfortunately, information from the trial does not seem to have been released so it is difficult to evaluate whether the safety concerns were serious or whether they were due to a class effect (i.e. something that might happen with suvorexant at certain doses or duration of use) or due to something specific about almorexant (Forbes article 2013). Almorexant was also studied for effects on cognitive function but results were never posted (NCT01243060).

Drug interactions: Drugs that are metabolized by hepatic cytochrome P450 3A might be influenced by suvorexant, since that enzyme metabolizes suvorexant as well. Ketoconazole, an anti-fungal, is not

recommended for use along with suvorexant. Diltiazem should be used at a lower dose and rifampin at its maximum dose, if used alongside suvorexant (Reddy 2015). For a complete list, check out Drugs.com, which lists 77 major drug interactions, 598 moderate drug interactions, and 5 minor ones. Clinical trials tested doses between 15-40 mg/day.

Dosing and Sources:

Suvorexant is sold as Belsomra by Merck in 10, 15, and 20 mg tablets. The starting recommended dose is typically 15 mg for older patients and 20 mg for younger, taken before bed time. Doses up to 40 mg/day were well-tolerated for 12 months by most participants in a Phase III trial (Citrome 2014 review). No other dual orexin antagonist is currently on the market.

Future research:

No studies are listed at clinicaltrials.gov as underway. As more people use suvorexant clinically, epidemiologic information on its long-term use may be gathered and analyzed.

Long-term research is needed on the safety of suvorexant use and, specifically, how it influences orexin signaling and orexin receptor levels. Pharmacological inhibition of orexin receptors might eventually alter orexin signaling through homeostatic mechanisms. Also, studies are needed to address if and how suvorexant influences reward, depression, addiction, and obesity, whether for better or worse.

PubMed Search terms recorded:

- Belsomra separately with… Cognitive, Alzheimer, Dementia
- Suvorexant separately with… Dementia, cognitive, Alzheimer's, aging, mortality, lifespan, telomere, senescent, safety
- Orexin separately with … senescent, apolipoprotein e, lifespan, mortality, metabolism, reward, gastrointestinal
- Hypocretin & Alzheimer's
- Alzheimer's wake fragmentation orexin
- additional search strategy of identifying papers in reviews and using Pubmed to review papers that cite those
- Clinicaltrials.gov search for suvorexant

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