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.

Modafinil

Evidence Summary

Evidence suggests that modafinil may improve cognition in sleep-deprived or non-sleep deprived individuals with increasing benefits as tasks become more complicated.

Neuroprotective Benefit: Many studies suggest that modafinil may be beneficial for certain aspects of cognition, especially in instances of greater cognitive load or when sleep deprived. Its neuroprotective effects or effects in Alzheimer's patients are unknown.

Aging and related health concerns: Modafinil has not been studied for age-related diseases.

Safety: Some minor side effects are associated with modafinil, but serious adverse reactions are rare.

What is it?

Modafinil is a wake-promoting drug used to treat narcolepsy, shift work sleep disorder, and excessive daytime sleepiness associated with sleep apnea. It is also widely prescribed off-label as a cognitive enhancer and is used by militaries to enhance cognitive performance. It's mechanism of action is not completely understood, although it reportedly inhibits dopamine and noradrenaline uptake transporters and has indirect effects on other neurotransmitter systems such as serotonin, glutamate, histamine, orexin, and GABA (Battleday and Brem, 2015). Although it has never been studied in Alzheimer's patients, it slightly improves certain aspects of cognition in healthy adults and elderly – especially with more complex tasks.

Neuroprotective Benefit: Many studies suggest that modafinil may be beneficial for certain aspects of cognition, especially in instances of greater cognitive load or when sleep deprived. Its neuroprotective effects or effects in Alzheimer's patients are unknown.

Types of evidence:

- One systematic review in healthy non-sleep-deprived individuals for cognitive function
- Six additional studies in healthy non-sleep-deprived individuals for cognitive function

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?

A systematic review (Battleday and Brem, 2015) analyzed all of the studies in healthy non-sleep-deprived individuals to examine which elements of cognition were affected by modafinil. Most of these studies examine the acute effects of the drug and were conducted in young individuals (20s-30s). Specifically, the review examined modafinil's effects on attention, executive function, learning and memory, creativity, and task complexity.

Simple Tasks

Attention: Most studies report no effects on measures of simple attention including alertness, selective attention, sustained attention, and divided attention.

Executive function:

- Inhibitory control (the inhibition of irrelevant information) – mixed results depending on which tasks of inhibitory control are studied

- Working memory (the ability to hold and manipulate external and internal information) – no effects on simple working memory tasks, some benefits as working memory tasks became more difficult
- Cognitive flexibility (the ability to alternate the focus of attention in order to meet shifting task demands) – no benefits with simple cognitive flexibility tasks
- Planning, decision-making, and fluid intelligence – these are all tasks of high executive functionality. Most studies report benefits, especially at higher task difficulties

Learning and memory: mixed results with both non-verbal and verbal memory

Creativity: no benefits with convergent thinking and no effect or decreased performance with divergent thinking

Complex Tasks

The problem with studies using simple cognitive tests in young, healthy individuals is that there is usually a ceiling effect (i.e. individuals are already performing well). For instance, in a task measuring whether participants remember the order of numbers after a delay, they may already be performing at 95% accuracy and it is difficult to detect small changes. This is also why some studies report benefits only in individuals with low baseline performance or IQ (Randall et al, 2005; Muller et al, 2004).

Complex tasks measure multiple of the cognitive domains at once and may be better suited to test the effects of cognitive enhancers.

For instance, Pringle et al (2013) used a compound learning task to study implicit cognition. The task consisted of multiple blocks where a certain characteristic of a stimulus (e.g. color or shape) was predictive of a future probe location. Over multiple blocks, the predictive stimulus changed. This task requires increased attentional flexibility to both learn the new association and disregard the previous one. Both learning rate in terms of reaction time and accuracy were improved in the modafinil group.

In another example, Marchant et al (2009) conducted an attention-switching task. Participants sat in front of a computer screen and were presented with alternating colored squares (red/blue) and beeps (high/low). In the constant condition, they had to ignore the beeps and only hit a button when a red square appeared. In the alternating condition, they had to hit a button whenever a red square or low beep was presented. The second task required alternating attention between the colored squares and the sound. The modafinil group performed better than the placebo group in the constant condition

when the stimuli were presented faster, but not when they were presented slower. In the alternating task, the modafinil group performed better than the placebo group in both slower and faster conditions. This suggests that modafinil's benefits are more apparent in tasks that require a greater cognitive load.

All five studies reported in Battleday and Brem, 2015 using complex task paradigms reported that modafinil improved performance, especially in the domains of attention and memory, by enhancing higher cognitive functions. These studies suggest that modafinil is more beneficial as a task becomes more complex.

In another example of performance in a complex task, an RCT tested the effects of modafinil, methylphenidate, and caffeine in 39 male chess players in Germany. They played 3,059 timed chess games against a computer (20 minutes). Players taking modafinil took more reflection time per move and therefore lost a number of games due to taking too much time. In games that they players did not lose because of time, those taking modafinil and methylphenidate won significantly more games than placebo (51% modafinil vs 46% for placebo) (Franke et al, 2017).

Other paradigms of treatment

In a study looking at the effect of 10 day treatment with modafinil in young, non-sleep-deprived heathy adults, Gilleen et al (2014) reported that the combined effect of modafinil plus cognitive training was more effective than cognitive training alone. These benefits were due to within-day learning rather than improved memory between days, and these effects were greater at the beginning of the training period.

Most studies of the cognitive effects of modafinil were conducted in young adults. Two studies have looked in middle aged/elderly individuals. Randall et al (2004) reported no change in mood or most simple cognitive tests with 200mg of modafinil. Punzi et al (2017) reported an increase in functional connectivity between the visual and frontal cortex but did not measure cognitive performance.

Other recent studies report that modafinil improves attentional performance without inducing hyperarousal (Cope et al, 2017) and that it may do so by enhancing activity in brain regions associated with the 'alerting' network of attentional control (Ikeda et al, 2017).

Human research to suggest benefits to patients with dementia:

None

Mechanisms of action for neuroprotection identified from laboratory and clinical research:
The exact mechanism of action for modafinil is unclear. It putatively binds to dopamine uptake transporters and possibly norepinephrine uptake transporters, thus increasing extracellular concentrations of these neurotransmitters (Wisor, 2013; Battleday and Brem, 2015). This mechanism seems to have secondary effects on other transmitter systems such as elevation of extracellular serotonin, glutamate, histamine, and orexin, and reduced concentration of GABA (Battleday and Brem, 2015). It is not clear what implications this would have for patients with Alzheimer's disease.

The norepinephrine system is important for cognitive function, and the locus coeruleus, a major source of norepinephrine, starts to degenerate early in the disease progression (Robertson, 2013). Theoretically, then, modafinil may be beneficial at the early stages of the disease. On the other hand, excessive glutamate or norepinephrine may not be beneficial. In fact, some evidence suggests that beta-blockers may reduce the risk of Alzheimer's disease, but the evidence in not conclusive and this effect may be due to their anti-hypertensive effects.

APOE4 interactions: None reported.

Aging and related health concerns: Modafinil has not been studied for age-related diseases.

Safety: Some minor side effects are associated with modafinil, but serious adverse reactions are rare.

Types of evidence:

- 1 meta-analysis of modafinil in patients with sleep apnea
- 1 post-marketing analysis

Details:
Modafinil was associated with a number of mild-to-moderate side effects in patients with sleep apnea in studies up to 12 weeks including headache (~15%), nausea (~6%), dizziness (~5%), insomnia (~6%), and anxiety (~6%) (Sukhal et al, 2015). In 2007, the European Medicines Agency reviewed the post-marketing safety data on modafinil for concerns that it is associated with severe skin conditions (esp. in children) and potentially psychiatric disorders. They concluded that modafinil should only be used for narcolepsy and not for sleep apnea or shift-work disorder. However, post-marketing analyses suggest they are rare (Davies et al, 2013).

Modafinil does not have the addictive properties that other drugs effecting the dopaminergic system have and may be preferable than some other drugs. However, the long-term side effects of modafinil are not known. Drugs.com lists several other side effects that are less common.

Drug interactions:
Modafinil interacts with several neurotransmitter systems and likely has many drug interactions. Care should especially be taken when taking other drugs that act on the dopaminergic systems (e.g. amphetamines, Parkinson's disease drugs) or the norepinephrine system. Drugs.com lists 71 major and 236 moderate drug interactions including drugs containing codine, SSRIs, among many others (link).

Availability/Dosing: Modafinil is a prescription medicine available as a generic medication (Alertec, Modavigit, and Provigil) for narcolepsy, shift work sleep disorder, and excessive daytime sleepiness due to sleep apnea. Typical doses range from 100mg-200mg once/day in the morning.

Research underway:
There are currently 31 ongoing clinical trials using modafinil, primarily for fatigue due to cancer treatment or substance abuse.

Search terms:
Pubmed:

- **modafinil + alzheimer, cognition [meta-analysis], cognition elderly, longevity, aging, neuropathy, cardiovascular, osteoarthritis**

Clinicaltrials.gov:

- modafinil

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If you have suggestions for drugs, drugs-in-development, supplements, nutraceuticals, or food/drink with neuroprotective properties that warrant in-depth reviews by ADDF's Aging and Alzheimer's Prevention Program, please contact INFO@alzdiscovery.org. To view our official ratings, visit Cognitive Vitality's Rating page.