



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.

Nabilone

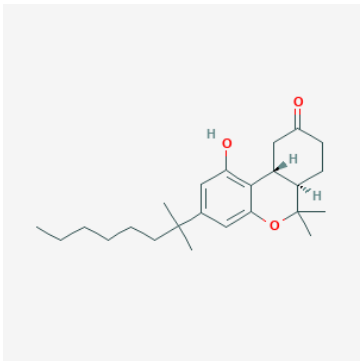
Evidence Summary

Effective in decreasing agitation in Alzheimer's patients, but can impair cognitive functions in healthy adults; side effects are common, including drowsiness, sedation, and increased heart rate.

Neuroprotective Benefit: Nabilone significantly decreased agitation in moderate-to-severe Alzheimer's patients, but impairs cognitive functions in healthy adults.

Aging and related health concerns: Minor benefits in pain relief and sleep have been observed in people with neuropathic pain. At high doses, nabilone may increase heart rate.

Safety: Side effects are common, including drowsiness, dizziness, dry mouth, disrupted cognitive performance, and sedation; at high doses, it may also increase heart rate.

<p>Availability: Prescription, approved for treating chemotherapy-induced nausea and vomiting</p>	<p>Dose: In cancer patients, 1 mg or 2 mg doses are taken orally, 1 to 3 hours before chemotherapy treatment. The mean therapeutic dose for treating agitation in moderate-to-severe Alzheimer's patients was 1.6 mg/day.</p>	<p>Chemical formula: C₂₄H₃₆O₃ MW: 372.549 g/mol</p>  <p>Source: PubChem</p>
<p>Half life: plasma half-life of nabilone is 2 hours (and 35 hours for its metabolites)</p>	<p>BBB: permeable</p>	
<p>Clinical trials: The largest meta-analysis included 6 RCTs testing nabilone, with a total of 277 cancer patients with chemotherapy-induced nausea and vomiting.</p>	<p>Observational studies: none</p>	

What is it? Nabilone is a synthetic cannabinoid mimicking the structure and activity of delta-9-tetrahydrocannabinol (THC), the primary psychoactive compound found in cannabis ([DrugBank](#)). However, its urinary metabolites are distinct from those of marijuana [1]. Nabilone was approved by the FDA in 1985 for the treatment of chemotherapy-induced nausea and vomiting in cancer patients who have failed to respond to other anti-emetic treatments. Nabilone has weak partial agonist activity at the cannabinoid 1 (CB1) and CB2 receptors. The endocannabinoid system is widely distributed throughout the central and peripheral nervous system and plays diverse roles, including learning and memory, pain, inflammation, cardiovascular function, and sleep/wake cycle ([DrugBank](#); [2]).

Neuroprotective Benefit: Nabilone significantly improved agitation in moderate-to-severe Alzheimer's patients, but impairs cognitive functions in healthy adults.

Types of evidence:

- 4 randomized controlled trials; 1 in healthy men, 1 in marijuana smokers, 1 in Alzheimer's patients, and 1 in Huntington's disease patients
- Numerous laboratory studies



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

Healthy adults: IMPAIRED COGNITIVE FUNCTIONS. In a small double-blind randomized trial in 24 healthy men, nabilone treatment (acute, 1-3 mg) resulted in impaired attention, psychomotor speed, and working and episodic memory [3]. For several measures, impairment (as measured by increased reaction time latencies and reduced performance accuracy) was dose-dependent. In addition, self-rated alertness was also reduced.

Statistically significant effects of nabilone were evident for at least one measure on every task in the CDR system battery, within all of the cognitive domains assessed (attention, psychomotor speed, working memory, and episodic memory) and for each of the composite scores [3]. Reductions in self-rated alertness and dose-dependent reductions in contentment with increasing dose were also observed. However, for self-rated calmness, the low dose (1 mg) was associated with increased ratings relative to placebo, while the high dose (2-3 mg) was associated with reduced calmness ratings. The cognitive deficits produced by nabilone were statistically reliable and marked in size. Effect sizes with the high doses (2-3 mg) were over 0.8 (considered to reflect large effect sizes) for power of attention, continuity of attention, numeric working memory, quality of episodic memory, and speed of memory. The deficits to the various CDR system cognition measures with the high doses (2-3 mg) of nabilone were roughly equivalent to or greater than those identified in other studies using the CDR system with 1 mg of lorazepam [4], 0.5 mg (s.c.) of scopolamine [5], 3 mg of haloperidol [6], and 0.5 g/kg of alcohol [7]. It is worth noting that this study was terminated due to the emergence of severe adverse events (see Safety section under **Healthy adults**).

Marijuana smokers: In a small double-blind randomized controlled trial of 14 marijuana smokers, nabilone treatment (4, 6, 8 mg) increased ratings of feeling a good effect, a strong effect and/or "high" relative to placebo [1]. Nabilone reduced psychomotor speed relative to placebo (and dronabinol), with nabilone (6, 8 mg) decreasing the total number of items attempted on the digit symbol substitution test (DSST) compared with placebo. Nabilone (6, 8 mg) also decreased the number of items correct as well as % correct on the DSST compared with placebo. The total tracking distance on the Divided Attention Task was lower after nabilone (2 mg) than placebo. There was no drug effect on the number of hits, hit latency or maximum tracking speed on the Divided Attention Task, the number of items entered in the Digit Span task, or on immediate or delayed recall or recognition scores. On the Repeated Acquisition Task (test of working memory), there was no effect of nabilone (or dronabinol) on the total number of

trials completed. The number of errors made in this task was actually higher on placebo relative to nabilone (4, 6 mg).

Human research to suggest benefits to patients with dementia:

Alzheimer's patients: DECREASED AGITATION. Results from a randomized double-blind clinical trial testing nabilone in moderate-to-severe Alzheimer's patients were presented at 2018 AAIC ([Press release](#)). This trial, led by Krista Lanctot, PhD, tested the efficacy of nabilone in treating agitation in Alzheimer's patients. Over the 14-week trial duration, 39 participants (77% male, average age 87) received nabilone in capsule form (mean therapeutic dose=1.6 +/- 0.5 mg) for 6 weeks, followed by 6 weeks of placebo, with 1 week between each treatment period. The primary outcome was a measure of agitation; other outcomes were also assessed, including overall behavioral symptoms, memory, physical changes, and safety. They found that agitation (as measured by the Cohen-Mansfield Agitation Inventory) improved significantly in those taking nabilone compared to placebo ($p=0.003$). Nabilone also significantly improved overall behavioral symptoms compared to placebo (as measured by the Neuropsychiatric Inventory; $p=0.004$). The researchers also observed small benefits in cognition and nutrition during the study, but a larger study is needed to validate these observations.

Huntington's patients: NO BENEFIT. In a pilot double-blind randomized controlled trial in 37 Huntington's disease patients, nabilone treatment (1 or 2 mg/day) did not affect the cognition subscore of the Unified Huntington's Disease Rating Scale (UHDRS) compared to placebo (3.57, 95% CI, -3.41 to 10.55; $p=0.3$) [8]. There was some evidence of improvement in chorea (1.68, 95% CI, 0.44 to 2.92; $p=0.009$) and neuropsychiatric inventory (6.43, 95% CI, 0.2 to 12.66; $p=0.04$) with nabilone treatment.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

The components of the endocannabinoid system have been investigated in brain samples of patients with Alzheimer's disease [2]. In the hippocampus and entorhinal/parahippocampal cortices of Alzheimer's patients, increased expression of CB2 receptors is observed in glial cells associated with senile plaques; in contrast, CB1 receptor density remained unchanged in the vicinity of these structures [9]. Other studies have found that CB1 expression is decreased in the brains of Alzheimer's patients [10]. A more recent study also noted higher expression of CB2 receptors in Brodmann area 10 (prefrontal cortex) of Alzheimer's patients, which correlated with A β 42 levels [11]. Lower levels of CB1 were also reported. It is not clear based on these postmortem studies whether altered levels of CB1 and/or CB2 receptors are causative or correlative to Alzheimer's pathology.

In a mouse model of Alzheimer's, CB2 receptor deletion resulted in higher levels of A β 42 and augmented plaque deposition, but the level of total tau was significantly decreased [12]. Several selective CB2 agonists (JWH-015, MDA-7) promoted removal of A β plaques in preclinical studies, suggesting that CB2 receptors may be involved in Alzheimer's neuropathology [2]. Since nabilone targets both CB1 and CB2 receptors, it is not clear whether it has similar disease-modifying properties as drugs selective for CB2. It is also not clear whether targeting cannabinoid receptors may increase tau pathology.

In normal rats, nabilone treatment (0.1, 0.5, and 1.0 mg/kg, i.p.) did not impair place learning in a water maze task, whereas THC disrupted this function [13]. At concentrations ranging from 1 nM to 10 μ M, nabilone did not influence basal glutamatergic neurotransmission, while this is decreased by THC. Although cannabinoids have been reported to affect synaptic plasticity, nabilone at 1 μ M concentration did not alter paired-pulse facilitation, long-term potentiation, or the magnitude of long-term depression.

APOE4 interactions: Unknown.

Aging and related health concerns: Minor benefits in pain relief and sleep have been observed in people with neuropathic pain. At high doses, nabilone may increase heart rate.

Types of evidence:

- 3 meta-analyses, 1 in chemotherapy-induced nausea/vomiting, 1 in neuropathic pain, and 1 in fibromyalgia
- 1 randomized controlled trial in marijuana smokers
- Numerous laboratory studies

Cardiovascular: UNKNOWN/INCREASED HEART RATE. It is not known whether nabilone produces cardiovascular benefits or harm in healthy individuals. In a small double-blind randomized controlled trial in 14 marijuana smokers, nabilone produced dose-dependent increases in heart rate: heart rate following nabilone administration (4, 6, 8 mg) was significantly higher than when placebo was given [1]. Also, nabilone (2 mg) resulted in decreased systolic blood pressure relative to placebo. In some individuals taking the higher dose of nabilone (8 mg), heart rate exceeded 100 beats per minute (bpm; up to 119 bpm), which could be medically significant in a clinical population. Heart rate did not exceed 100 bpm with the 4 mg dose, and at the 6 mg dose, there was only one reading over 100 bpm (106



bpm). It is worth noting that the doses tested in marijuana smokers were higher than those typically used in clinical populations (1-5 mg; [14; 15]).

Chemotherapy-Induced Nausea and Vomiting: BENEFIT. In a meta-analysis of 13 randomized controlled trials in cancer patients with chemotherapy-induced nausea and vomiting, 6 trials tested nabilone (total of 277 subjects) [16]. In terms of anti-emetic efficacy, there was not a statistically significant difference between nabilone and neuroleptics (RR = 0.88; 95% CI, 0.72–1.08; p=0.21), but a clinically significant difference was observed that favored nabilone. Doses tested ranged from 1-4 mg per dose (taken 1-5 times, depending on the study).

Neuropathic Pain: POTENTIAL BENEFIT BASED ON A SMALL STUDY. In a Cochrane meta-analysis of 16 randomized controlled trials in chronic neuropathic pain, 2 trials tested nabilone, one against placebo and the other against the pain killer dihydrocodeine [14]. The first study with 26 participants showed that there was no difference between nabilone (1-5 mg/day, orally, for 4 weeks) and placebo in the number of participants with a 50% pain relief or greater (31% versus 8%; p=0.12)[17]. Six of 13 participants in the nabilone and 1 of 13 participants in the placebo group reported to be much or very much improved (p=0.04). There was a difference between nabilone and placebo in the number of participants with pain relief of 30% or greater (85% versus 38%; p=0.006). The average pain intensity was 3.5 ± 1.3 in the nabilone and 5.4 ± 1.7 in the placebo group (p=0.005)(higher scores indicate more pain). The other trial included 73 participants and compared nabilone treatment (0.25-2 mg) against dihydrocodeine (30-240 mg), for 6 weeks each [18]. The Cochrane meta-analysis judged this study to have low quality of evidence due to indirectness, imprecision, and publication bias [14].

Overall, the reliability of the pooled results on nabilone was limited because the results of three clinical trials with nabilone have not been published (NCT00699634; NCT01035281; NCT01222468) [14]. The applicability of the evidence to routine clinical care is limited as the studies excluded people with current or historical substance abuse and major medical diseases. There is no high-quality evidence yet suggesting that nabilone is beneficial in treating people with chronic neuropathic pain [14].

Nabilone has weak partial agonist activity at the cannabinoid 1 (CB1) and CB2 receptors. CB1 receptors are expressed throughout the nervous system, including the spinal cord and peripheral sensory nerve endings [19]. Stimulation of CB1 receptors reduces neuronal excitability and the release of the neurotransmitters, GABA and glutamate, in the cortical, limbic, and other regions involved in nociception. In contrast, CB2 receptors are found mainly in immune tissues (e.g., spleen and tonsils) and immune cells (e.g., monocytes, B and T cells), but also in the brain. Stimulation of peripheral CB2



receptors results in anti-inflammatory and immunomodulating effects and therefore plays a role in alleviating inflammatory types of pain as well as neuropathic pain.

Fibromyalgia: NO BENEFIT. In a Cochrane meta-analysis of 2 randomized controlled trials in fibromyalgia (total of 72 patients), no convincing, unbiased, high quality evidence emerged that suggested nabilone (1 mg/day) is beneficial in treating people with fibromyalgia [15]. The authors noted that the quality of evidence for all outcomes of efficacy was very low. The tolerability of nabilone was also low in people with fibromyalgia.

Sleep: POTENTIAL/SMALL BENEFIT IN PATIENTS WITH PAIN. In a small randomized controlled trial in 26 patients with chronic neuropathic pain, the sleep problems score was lower in the nabilone group (27.1 ± 2.1 ; 1-5 mg/day, orally for 4 weeks) compared to the placebo group (33.0 ± 2.6), though this difference was not statistically significant (higher scores indicate more sleep problems)[17]. Third tier (very low quality) evidence suggested better effects of nabilone (1 mg/day) on sleep than amitriptyline (nerve pain medication and antidepressant) in patients with fibromyalgia [15].

Safety: Side effects are common, including drowsiness, dizziness, dry mouth, disrupted cognitive performance, and sedation; at high doses, it may also increase heart rate.

Types of evidence:

- 3 meta-analyses, 1 in chemotherapy-induced nausea/vomiting, 1 in chronic neuropathic pain, 1 in fibromyalgia
- 3 randomized controlled trials; 1 in healthy men, 1 in marijuana smokers, and 1 in Huntington's disease patients
- A few laboratory studies

Common adverse reactions include drowsiness (52-66%), dizziness (59%), vertigo (52-59%), euphoria (11-38%), dry mouth (22-36%), visual disturbance (13%), ataxia (13-14%), depression (14%), lack of concentration (12%), and sleep disorder (11%)(Drugs.com). Other adverse reactions include dysphoria (9%), hypotension (8%), anorexia (8%), weakness (8%), headache (6-7%), nausea (4%), sedation (3%), and increased appetite (2%)(Drugs.com). Nabilone may impair thinking or reactions, so extra care should be exercised when driving or doing anything that requires you to be alert (Drugs.com).



Healthy adults: SOME SEVERE CNS-RELATED ADVERSE EVENTS. In a small double-blind randomized trial in 24 healthy men, nabilone treatment at 3 mg produced severe CNS-related adverse events in 2 subjects (severe anxiety and aggression, along with a phobia of touch and altered body perception) [3]. These symptoms resolved within 48 hours, but following these events, the clinical trial was modified such that 2 mg was the highest dose tested and the low dose treatment consisted of 1 mg. The 2 subjects who experienced severe adverse events (SAEs) were withdrawn and replaced with 2 new volunteers. Later in the study, 2 more subjects experienced SAEs (becoming unconscious and stuporous, lasting 14 and 20 hours, respectively) and the study was terminated. All subjects except 1 experienced at least 1 adverse event during nabilone treatment. Most adverse events were classified as mild or moderate. The most common adverse events were dizziness, fatigue, tachycardia, postural dizziness, and dry mouth.

Alzheimer's patients: INCREASED SEDATION. In a randomized double-blind clinical trial testing nabilone in moderate-to-severe Alzheimer's patients, more people in the study experienced sedation on nabilone (45%) compared to placebo (16%) ([Press release](#)).

Chronic neuropathic pain patients: ADVERSE EVENT INCIDENCE SIMILAR TO PLACEBO. In a Cochrane meta-analysis of 16 randomized controlled trials in chronic neuropathic pain, 2 trials tested nabilone, one against placebo and the other against the pain killer dihydrocodeine [14]. No subjects experienced a serious adverse event in the nabilone (n=13) or placebo (n=13) group. At least one adverse event was experienced by 54% of those in the nabilone group and 46% of those in the placebo group (no significant group difference; p=1.0).

Cancer patients with chemotherapy-induced nausea and vomiting: MORE INTENSE ADVERSE EVENTS. Based on a meta-analysis of 13 randomized controlled trials, 6 trials tested the effects of nabilone. Adverse events were more intense and occurred more frequently among those treated with cannabinoids (nabilone, dronabinol, etc.) compared to placebo or neuroleptics [16]. Details of the types and frequencies of adverse events were not analyzed.

Fibromyalgia: INCREASED DROWSINESS, DIZZINESS, NAUSEA, AND DRY MOUTH. In a Cochrane meta-analysis of 2 randomized controlled trials in fibromyalgia (total of 72 patients), more participants dropped out due to adverse events in the nabilone groups (1 mg/day; 4/52 subjects) than in the control groups (1/20 in placebo and 0/32 in amitriptyline group) [15]. Neither study reported serious adverse events. In one study, 3 out of 20 participants in the nabilone group and 1 out of 20 participants in the placebo group dropped out due to adverse events [20]. The most frequent adverse events were

drowsiness (7 with nabilone, 1 with placebo), dry mouth (5 with nabilone, 1 with placebo), and vertigo (4 with nabilone, 0 with placebo). The other study reported that 1 out of 32 participants in the nabilone group and no participants in the amitriptyline group dropped out due to adverse events [21]. The most frequent adverse events were dizziness (10 with nabilone, 4 with amitriptyline), nausea (9 with nabilone, 1 with amitriptyline), dry mouth (7 with nabilone, 3 with amitriptyline), and drowsiness (6 with nabilone, 1 with amitriptyline).

Huntington's disease: INCREASED DROWSINESS AND FORGETFULNESS. In a pilot double-blind randomized controlled trial in 37 Huntington's disease patients, nabilone was well tolerated with no increase in chorea or psychosis [8]. There were 3 serious adverse events (SAEs), resulting in 2 patients withdrawing. One was considered treatment-related, concerning a patient taking temazepam, who experienced severe sedation on nabilone. The other 2 SAEs occurred during placebo treatment (1 patient had an asthma attack and experienced palpitations and the other had a seizure requiring hospitalization). Drowsiness and forgetfulness were the most frequently reported adverse effects; however, these were also reported with placebo. All other adverse effects including euphoria occurred infrequently.

Marijuana smokers: DISRUPTED COGNITIVE PERFORMANCE AND INCREASED HEART RATE AT HIGH DOSES. In a small double-blind randomized controlled trial of 14 marijuana smokers, higher doses of nabilone (6, 8 mg) produced the most robust positive subjective effects, disruption in cognitive performance, and cardiovascular changes [1]. Nabilone produced dose-dependent increases in heart rate such that in some individuals taking the higher dose of nabilone (8 mg), heart rate went as high as 119 bpm [1]. Heart rate did not exceed 100 bpm at the 4 mg dose, and at the 6 mg dose, there was only one reading over 100 bpm (106 bpm). Also, nabilone at 2 mg dose resulted in decreased systolic blood pressure relative to placebo.

Preclinical: ATAXIA AT HIGH DOSES. In a study in rats, ataxia appeared at 2.0 mg/kg, i.p., and showed a dose-dependent relationship up to the dose of 8.0 mg/kg, which was the highest dose tested [13]. These doses are much higher than what has been used in clinical trials in humans.

Drug interactions: Nabilone has major interactions with 7 drugs (acetaminophen/propoxyphene, aspirin/caffeine/propoxyphene, buprenorphine, buprenorphine/naloxone, levomethadyl acetate, propoxyphene, and sodium oxybate) and moderate interactions with 562 drugs ([Drugs.com](https://www.drugs.com)). Taking nabilone with other drugs that make you sleepy or slow your breathing can worsen these side effects



([Drugs.com](#)). Consult your doctor before taking nabilone with a sleep aid, narcotic pain medication, muscle relaxant, or anti-anxiety medication.

Sources and dosing: Nabilone (Cesamet®) was approved by the FDA in 1985 for the treatment of chemotherapy-induced nausea and vomiting in cancer patients who have failed to respond to other anti-emetic treatments. It is usually taken at 1 mg or 2 mg doses orally, 1 to 3 hours before chemotherapy treatment ([Drugs.com](#)). The mean therapeutic dose for treating agitation in moderate-to-severe Alzheimer's patients was 1.6 mg/day ([Press release](#)). For pain management, nabilone should be started at a low dose and titrated slowly; a typical starting dose is 0.5 mg/day [19].

Research underway: Several clinical trials are ongoing. Nabilone is being tested for non-motor symptoms in Parkinson's disease ([NCT03769896](#); [NCT03773796](#)), diabetic peripheral neuropathic pain ([NCT01035281](#)), acute pain in inflammatory bowel disease patients ([NCT03422861](#)), postoperative pain after knee replacement ([NCT03675971](#)), chronic pain and insomnia ([NCT00384410](#)), and anorexia in lung cancer ([NCT02802540](#)).

Search terms:

Pubmed, Google: nabilone

- + cognitive, + Alzheimer's, + amyloid, + APOE, + meta-analysis, + pain, + cardiovascular, + sleep

Websites visited for nabilone:

- [Clinicaltrials.gov](#)
- Examine.com (0)
- [Treato.com](#)
- DrugAge (0)
- Geroprotectors (0)
- [Drugs.com](#)
- [WebMD.com](#)
- [PubChem](#)
- [DrugBank.ca](#)
- Labdoor.com (0)
- ConsumerLab.com (0)
- Cafepharm (0)
- Pharmapro.com (0)



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