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.

Rotigotine

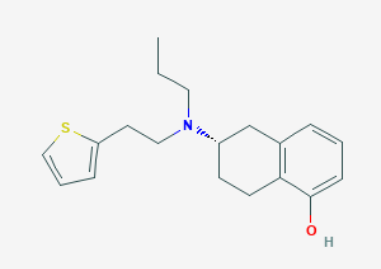
Evidence Summary

Rotigotine improves symptoms in Parkinson's and restless legs syndrome; modest benefits were seen in a pilot Alzheimer's trial. It may produce an inverted U-shaped response and impulse control issues.

Neuroprotective Benefit: Rotigotine improves various symptoms in PD and AD. But activation of D2-like receptors produces an inverted U-shaped response and can be inhibitory or facilitatory depending on endogenous activity and drug dose.

Aging and related health concerns: No evidence or rationale exists for the prevention or treatment of age-related conditions that are not neurological.

Safety: Nausea, vomiting, headache, dyskinesia, and impulse control issues have been reported with rotigotine, especially at high doses, though it is generally well-tolerated in clinical populations.

Availability: Rx, approved for Parkinson's disease and restless legs syndrome	**Dose**: Transdermal patch. For early-stage Parkinson's, initial dose is 2 mg/day, then increased to 4 or 6 mg/day. For advanced-stage Parkinson's, initial dose is 4 mg/day, then increased to 6 or 8 mg/day. For restless legs syndrome, initial dose is 1 mg/day and increased up to 3 mg/day.	**Chemical formula:** $C_{19}H_{25}NOS$ **MW**: 315.48  Source: PubChem
Half life: 5-7 hours	**BBB**: penetrant	
Clinical trials: Numerous meta-analyses including one that analyzed 8 RCTs with a total of 1,675 Parkinson's patients	**Observational studies**: none	

What is it? Rotigotine (Neupro®) is a non-ergoline dopamine agonist approved for the treatment of Parkinson's disease and restless legs syndrome. Dopamine receptors are classified as D1-like (D1 and D5 receptors) and D2-like (D2, D3, and D4 receptors). Rotigotine is an agonist at all dopamine receptor subtypes (D1-D5), though it binds preferentially to D2-like receptors; it binds to D3 receptors with the highest affinity (DrugBank.ca). It is also an antagonist at the α2-adrenergic receptor and an agonist at the 5HT-1A receptor. Rotigotine also inhibits dopamine uptake and prolactin secretion.

Neuroprotective Benefit: Rotigotine improves various symptoms in PD and AD. But activation of D2-like receptors produces an inverted U-shaped response and can be inhibitory or facilitatory depending on endogenous activity and drug dose.

Types of evidence:

- 2 meta-analyses, 1 in Parkinson's and 1 in Lewy body dementia
- 2 clinical studies in Alzheimer's patients
- Numerous laboratory studies

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

None available.

Human research to suggest benefits to patients with dementia:

Alzheimer's disease: POTENTIAL BENEFIT. In a placebo-controlled trial in 30 mild Alzheimer's patients and 10 age-matched healthy controls, the effects of rotigotine (4 mg/day for 4 weeks; transdermal Neupro®) and rivastigmine (acetylcholine esterase inhibitor; 4.6 mg/day for 4 weeks; transdermal Exelon®) on cortical plasticity were evaluated using transcranial stimulation (Koch et al., 2014). At baseline, Alzheimer's patients had impaired long-term potentiation (LTP)-like cortical plasticity as assessed by intermittent theta burst stimulation (TBS). These reduced levels of LTP-like cortical plasticity were normalized after rotigotine administration and motor-evoked potential (MEP) amplitudes were significantly increased compared to baseline at all time points. These effects were not observed with rivastigmine or placebo. Long-term depression (LTD)-like cortical plasticity was not affected with either rotigotine or rivastigmine. Cholinergic activity was increased by both rotigotine and rivastigmine.

For the 7 patients who were retested after 12 weeks of treatment (remaining on rotigotine, 4 mg/day, for 8 additional weeks), LTP-like cortical plasticity was increased, though the magnitude of effect appeared to be higher after 4 weeks of treatment than 12 weeks. In this group of 7 Alzheimer's patients who were treated with rotigotine, there were improvements in cognitive function [measured by MMSE; $t(6)=2.71$, $p<0.05$] and executive function [measured by frontal assessment battery; $t(6)=2.57$; $p<0.05$]. However, these data only emerged when paired t-tests were performed; no significant effects were seen with repeated measures ANOVA.

In a different study from 2013, 17 probable Alzheimer's patients and 8 age-matched controls were given rotigotine (2, 4, or 6 mg), and then their primary motor cortex excitability was measured using transcranial magnetic stimulation (TMS)(Martorana et al., 2013). Rotigotine treatment increased cortical excitability (decreased intracortical inhibition) and restored central cholinergic transmission (increased short latency afferent inhibition) in Alzheimer's patients. These results were unexpected as D2 receptor stimulation is expected to decrease cortical excitability and cholinergic transmission. In fact D3 receptor *antagonists* have been shown to produce cognitive-enhancing effects in monkeys (Arnsten and Jin, 2014). The authors of the Alzheimer's study speculate that the cholinergic changes in Alzheimer's patients are a result of D2-like receptor stimulation in the cell bodies and dendrites of cholinergic

neurons in the Meynert's nucleus or the nucleus accumbens (Martorana et al., 2013). But they were uncertain how rotigotine produced these paradoxical effects on cortical excitability and cholinergic transmission. Because rotigotine acts on many receptors outside of the dopamine system, it may be difficult to pinpoint the precise mechanisms of these observed beneficial effects.

Based on the preliminary findings suggesting that rotigotine may restore the altered cortical plasticity in Alzheimer's patients while possibly improving cognitive and executive functions, efforts are ongoing to validate these findings. A phase 2a study enrolling a total of 100 mild Alzheimer's patients was carried out and recently completed, but the results have not been published yet (NCT03250741; study details described under "**Research underway**" at the end).

Parkinson's disease: BENEFIT FOR MOTOR, APATHY, DEPRESSION, SLEEP, FATIGUE. In a 2018 meta-analysis of 8 randomized controlled trials including a total of 1,675 Parkinson's disease patients, treatment with rotigotine (2-16 mg/day, transdermal) for 12-27 weeks significantly improved scores for emotion/apathy (part of the Non-Motor Symptoms Scale; NMSS), depression (Beck Depression Inventory-II; BDI-II), apathy (Apathy Scale; AS), sleep/fatigue (part of the NMSS), and the Parkinson's disease Questionnaire (the 8-item and 39-item Parkinson's disease Questionnaire; PDQ-8 and PDQ-39) (Wang et al., 2018). Mean differences and 95% CI values were the following: emotion/apathy domain of the NMSS (MD=-2.5; 95% CI, -4.11 to 0.89), BDI-II (MD=-1.19; 95% CI, -2.30 to 0.08), AS (MD=-1.56; 95% CI, -2.67 to 0.45), sleep/fatigue domain of the NMSS (MD=-2.03; 95% CI, -3.08 to 0.98), PDQ-8: MD=-4.93; 95% CI, -6.79 to 3.07), PDQ-39 (MD=-3.52; 95% CI, -5.25 to 1.79), PDQ-8 and PDQ-39 (SMD=-0.36, 95% CI, -0.49 to 0.23)(Wang et al., 2018). The results of the Parkinson's Disease Sleep Scale 2nd version (PDSS-2) were heterogeneous, and those on the Snaith-Hamilton Pleasure Scale (SHAPS) were not statistically significant.

An older 2013 meta-analysis of 6 randomized controlled trials including 1,789 patients with Parkinson's disease also reported that the use of transdermal rotigotine resulted in greater improvements in Unified Parkinson's Disease Rating Scale (UPDRS) activities of daily living score (weighted mean difference [WMD]=-1.69; 95% CI, -2.18 to -1.19), motor score (WMD=-3.86; 95% CI, -4.86 to -2.86), and the activities of daily living and motor subtotal score (WMD=-4.52, 95% CI -5.86 to -3.17)(Zhou et al., 2013).

Lewy body dementia: UNKNOWN. In a 2015 meta-analysis of 42 studies examining 18 different treatments for Lewy body dementia and Parkinson's dementia, modest evidence of benefit with rotigotine emerged for Parkinson's dementia, but no studies of rotigotine for Lewy body dementia were identified (Stinton et al., 2015).

Progressive supranuclear palsy: NOT CLEAR. In a pilot open-label clinical study in 6 patients with progressive supranuclear palsy (PSP), treatment with rotigotine (up to 6 mg/day) for 42 weeks increased PSP rating scale and motor scores (UPDRS part 3 total) though these changes were not statistically significant (Schirinzi et al., 2019). Cognitive scores (measured by MoCA) were unchanged, possibly suggesting maintenance of cognitive functions. For PSP rating scale subitems, significant increase of bulbar ($p<0.05$) and gait ($p<0.05$) disturbances were seen. Worsening in history, ocular, and limb domains were not statistically significant. The clinical global expression (CGI-I) was not significantly changed. Since this was not a placebo-controlled study, it remains to be seen whether rotigotine has efficacy in treating PSP.

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

Dopamine is a neuromodulator that affects synaptic transmission including the probability of neurotransmitter release, the postsynaptic sensitivity to neurotransmitter, and the membrane excitability of the pre- and postsynaptic neurons (Tritsch and Sabatini, 2012). Its impact on motor cortical plasticity has been shown in both healthy individuals (Kuo et al, 2008; Monte-Silva et al, 2009) and patients with Parkinson's disease (Huang et al, 2011; Kishore et al, 2012). In the human motor cortex, dopamine agonists can exert inhibitory or facilitatory effects on neuroplasticity depending on the dose (Monte-Silva et al, 2009). In the cerebral cortex and the basal forebrain, dopamine modulates the activity of many types of neurons including the pyramidal cells, GABA interneurons, and also the diffuse cholinergic projections from neurons originating in the basal forebrain (Paspalas and Goldman-Rakic, 2005; Zhang et al, 2009).

In Alzheimer's patients: In postmortem brains of Alzheimer's patients, there is a preferential reduction of dopamine D2-like receptors in the prefrontal cortex and the hippocampus (Kemppainen et al, 2003; Kumar and Patel, 2007). Interestingly, most of the changes regarding the D2-like receptors were found at rostral and mid-levels of the temporal cortex, regions classically affected by Alzheimer's pathology (Joyce et al, 1998; Goldsmith and Joyce, 1996; Joyce et al, 1993; Ryoo and Joyce, 1994). In postmortem Alzheimer's brains, there is a significant reduction of D1, D3, and D4 receptors, but the D2 receptor expression was only moderately reduced. In a PET imaging study of D2 receptors, D2 receptor binding was significantly reduced in the striatum (involved in motor activities) of Alzheimer's patients, even in the absence of overt extra-pyramidal symptoms like dyskinesias (Pizzolato et al, 1996). In Alzheimer's patients, D2 receptor binding potentials are reduced in the hippocampus by 30% compared with healthy controls (Kemppainen et al, 2003). This reduction was found to be associated with both cognitive (Kemppainen et al, 2003) and behavioral abnormalities in Alzheimer's patients (Tanaka et al, 2003).

Although the dorsal striatum (involved in motor activities) is relatively spared in Alzheimer's disease, the nucleus accumbens (involved in the reward circuit) is highly affected; expressions of dopamine receptors (particularly D2-like receptors), dopamine transporters, and tyrosine hydroxylase (the enzyme that generates dopamine) are all reduced in the nucleus accumbens (Rinne et al., 1986; Allard et al., 1990; Murray et al., 1995; Joyce et al., 1997). Consequently, about half of Alzheimer's patients present with symptoms of apathy and one third with extrapyramidal signs in early-mid stage of the disease.

Preclinical studies: In animal models of Alzheimer's, dopamine agonists may improve memory and reduce neuronal amyloid deposition (Himeno et al, 2011). Stimulating D2/D3 receptors can have both positive and negative effects on synaptic plasticity and synaptic depression (LTP and LTD, respectively) (Manahan-Vaughan and Kulla, 2003), because D2-like receptor activation produces an inverted 'U'-shaped dose–response curve on plasticity (Arnsten et al., 1995). In studies in monkeys, systemic administration of a D2/3 receptor agonist has a triphasic effect on working memory performance, with low doses impairing performance likely through presynaptic D2 receptor actions, moderate doses improving performance through postsynaptic actions, and the highest doses impairing performance and inducing prominent side effects, including dyskinesias, hypotension, and occasional hallucinatory-like behaviors (Arnsten et al., 1995).

APOE4 interactions: Unknown

Aging and related health concerns: No evidence or rationale exists for the prevention or treatment of age-related conditions that are not neurological.

Types of evidence:

- None

No studies have specifically evaluated the effects of rotigotine on the prevention or treatment of age-related conditions outside of neurodegenerative conditions as discussed above (e.g., Parkinson's, Alzheimer's).

Safety: Nausea, vomiting, headache, dyskinesia, and impulse control issues have been reported with rotigotine, especially at high doses, though it is generally well-tolerated in clinical populations.

Types of evidence:

- 9 meta-analyses, 6 in Parkinson's, 2 in restless legs syndrome, and 1 in periodic limb movement
- 1 review

Parkinson's patients: APPLICATION SITE REACTION, NAUSEA, HEADACHE, DYSKINESIA, IMPULSE CONTROL DISORDER. In a 2018 meta-analysis of 8 randomized controlled trials including a total of 1,675 Parkinson's patients, rotigotine had an approximately 3-fold greater risk of developing application site reactions (Wang et al., 2018). Additionally, there was an approximately 5-fold greater risk of experiencing vomiting and a nearly 2-fold greater risk of experiencing nausea in early Parkinson's patients treated with rotigotine than in those treated with a placebo. Treatment with rotigotine also increased the risk of dyskinesia by approximately 2-fold in advanced Parkinson's patients. Rotigotine was also associated with a significantly increased risk of dizziness, insomnia, headache, and back pain but was not related to serious adverse events and did not increase the risk of diarrhea and constipation. Similar to other dopamine agonists, rotigotine may have neuropsychiatric side effects such as psychosis. These side effects are usually related to overdosing and high titration speeds. One study reported 3 cases of hallucinations, but the rate of this adverse event was lower for rotigotine than for ropinirole (Parkinson's medication). Another study reported 14 cases of hallucinations, which occurred at a rate that was lower than that for pramipexole (Parkinson's medication).

Other meta-analyses in Parkinson's disease patients have reported similar findings with regards to adverse events (Chen et al., 2017; Zhou et al., 2013). For example, rotigotine was associated with significantly higher rates of withdrawals due to adverse events (RR=1.82, 95% CI, 1.29 to 2.59), application site reactions (RR=2.92, 95% CI 2.29 to 3.72), vomiting (RR=5.18, 95% CI, 2.25 to 11.93), dizziness (RR=1.47, 95% CI, 1.12 to 1.95), and dyskinesia (RR=2.52, 95% CI, 1.47 to 4.32) compared with placebo (Zhou et al., 2013). However, rotigotine had a significantly lower withdrawal rate compared to placebo (Zhuo et al., 2017).

In a 2016 posthoc analysis of clinical trials evaluating open-label extensions of rotigotine treatment (2-16 mg/day) in over 750 patients with Parkinson's disease, 71 (9.0%) patients reported 106 adverse events of impulse control disorder (Antonini et al., 2016). Occurrence was similar across different categories: compulsive sexual behavior (2.5%), buying disorder (2.3%), compulsive gambling (2.0%), compulsive eating (1.7%), and punding behavior (1.7%). The percentage of new impulse control disorder

cases was relatively low and stable during the first 30 months of treatment (between 0.5% and 0.8% of patients reporting their first incidence each 6-month interval). The percentage of new impulse control disorder cases became higher over the following 30 months of treatment, ranging from 0.9% to 2.9% per 6-month interval, and peaked during the 54–60-month period. No impulse control disorder events were serious, and 97% were mild or moderate in intensity. Study discontinuation occurred in 7 (9.9%) patients due to impulse control disorders; these then resolved in 5 patients. There was an increase in overall adverse events of impulse control disorder with increasing dose of rotigotine. A noticeable increase in overall impulse control disorder incidents was first apparent at the 8 mg/24 h dose. It is worth noting that of the 71 patients who reported impulse control disorder, 94.4% had concomitant levodopa at any point during the studies.

Restless legs syndrome patients: NAUSEA, HEADACHE. In a 2017 meta-analysis of 35 randomized controlled trials including a total of 7,333 patients with restless legs syndrome, the most common side effects with dopaminergic drugs (pramipexole, ropinirole and rotigotine) were headache and nausea (Iftikhar et al., 2017). Nausea was most common with ropinirole (OR=6.70; 95% CI, 5.08–8.33), followed by rotigotine (OR=4.31; 95% CI, 2.65–5.98), and pramipexole (OR=3.56; 95% CI, 1.98–5.14) compared with placebo. Headache was most common with rotigotine (OR=2.93; 95% CI, 1.61–4.25) compared with placebo. In an older 2015 meta-analysis that examined rotigotine specifically (0.5-4.0 mg/day; 1-28 week-treatment), 6 randomized controlled trials were analyzed, and the most common adverse events were application site reactions, nausea, headache, and fatigue (Ding et al., 2015). Most were mild or moderate in intensity and in general, rotigotine was well-tolerated in patients with primary restless legs syndrome. Adverse events were typically increased with increasing rotigotine dose.

Periodic limb movement patients: NAUSEA, HEADACHE. In a 2018 meta-analysis of 5 controlled trials including a total of 197 patients with periodic limb movement, the rate of adverse effects was 60% in the rotigotine group and 50% in the placebo group (Wu et al., 2018). Of reported adverse events, nausea was the most common, followed by headache, nasopharyngitis, application site reaction, somnolence, and dizziness. Nausea was reported in 9% of patients receiving rotigotine and 0% of patients receiving placebo. The rates of headache, nasopharyngitis, application site reaction, somnolence, and dizziness were 8%, 8%, 5%, 9%, and 8%, respectively, in patients receiving rotigotine and 0%, 8%, 0%, 9.5%, and 0%, respectively, in patients receiving the placebo. Of the 5 reviewed studies, 2 reported no severe adverse events, one did not have data on severe adverse events, and 2 reported that the rate of severe adverse events was 7.5% in the rotigotine group and 2.5% in the placebo group.

Drug interactions: Rotigotine has 4 major drug interactions (acetaminophen/propoxyphene; aspirin/caffeine/propoxyphene; propoxyphene, and sodium oxybate) and 588 moderate drug interactions (Drugs.com). Caution needs to be exercised when taking other products that cause drowsiness including alcohol, marijuana, antihistamines (e.g., cetirizine, diphenhydramine), drugs for sleep or anxiety (e.g., alprazolam, diazepam, zolpidem), muscle relaxants, and narcotic pain relievers (e.g., codeine)(WebMD.com).

Sources and dosing: Rotigotine is a prescription transdermal patch approved for the treatment of Parkinson's disease and restless legs syndrome. It is marketed as Neupro® Film by UCB INC. The patches come in 6 different doses: 1 mg, 2 mg, 3 mg, 4 mg, 6 mg, and 8 mg per 24 hours. For early-stage Parkinson's, the initial dose is 2 mg/day, then increased to 4 or 6 mg/day (Drugs.com). For advanced-stage Parkinson's, the initial dose is 4 mg/day, then increased to 6 or 8 mg/day. For restless legs syndrome, the initial dose is 1 mg/day and increased up to 3 mg/day. The phase II clinical trial testing rotigotine in mild Alzheimer's patients used a dose of 4 mg/day (NCT03250741). To discontinue the use of rotigotine, the daily dose should be reduced by a maximum of 2 mg every 24 hours in Parkinson's disease patients (and a maximum of 1 mg every 24 hours in restless legs syndrome patients); if possible, the dose should be reduced every other day (Drugs.com).

Transdermal delivery of rotigotine has been shown to provide constant blood levels of the drug over 24 hours (Priano et al., 2006). The patch should be applied to clean, dry, intact skin, and to rotate application sites. If it is to be applied to a hairy area, the area needs to be shaved at least 3 days prior to application.

Research underway: There are 5 currently ongoing clinical trials that are testing rotigotine (ClinicalTrials.gov). Four are in Parkinson's disease patients and one is in people with restless legs syndrome.

One study in mild Alzheimer's patients (MMSE score between 18 and 24) was recently completed, but the results have not been published (NCT03250741). This trial was a phase 2a 24-week, prospective, randomized, double-blind, placebo-controlled study enrolling 100 patients total. The rotigotine transdermal patch dose was 4 mg in the active arm and placebo in the control group, as add-on to rivastigmine. The primary outcome was global cognition as measured by ADAS-Cog. Secondary outcomes included frontal cognitive functions (measured by frontal assessment battery), activities of daily living (ADCS-ADL), cortical activity (TEP amplitude over the prefrontal cortex), and neuropsychiatric evaluation (NPI).

Search terms:

Pubmed, Google:

- + meta-analysis, + Alzheimer's, + dementia, + APOE, + cardiovascular, + atherosclerosis, + diabetes , + neuropathy, + lifespan, + mortality

Websites visited for rotigotine:

- Clinicaltrials.gov
- DrugAge (0)
- Geroprotectors (0)
- Drugs.com
- WebMD.com
- PubChem
- DrugBank.ca
- Cafepharma (0)
- Pharmapro.com (0)