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.

Roflumilast

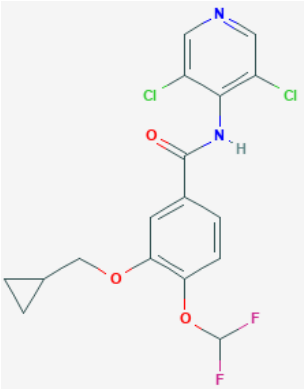
Evidence Summary

Possible cognitive enhancement ability at low doses that don't trigger gastrointestinal side effects. Has anti-inflammatory activity, and may promote metabolic regulation.

Neuroprotective Benefit: May boost cognitive function for verbal memory. Neuroprotection may be mediated by induction of neurotrophic factors and reduction of neuroinflammation.

Aging and related health concerns: May reduce vascular inflammation and promote glucose tolerance. Could be beneficial as an adjunct therapy in cancer by improving sensitivity to chemotherapeutics.

Safety: Gastrointestinal-related events are the most common side effects at the standard dose. Metabolized in the liver and interacts with other drugs that use cytochrome P450 liver enzymes.

Availability: Rx	**Dose**: 500 □g/day for COPD, oral tablet	**Chemical formula:** $C_{17}H_{14}Cl_2F_2N_2O_3$ **MW**: 403.207 g/mol  Source: Pubchem
Half-life: 17 hours (30 hours for active metabolite)	**BBB**: Penetrant	
Clinical trials: Phase 1 for cognition (n=15, n=27), B cell cancer (n=10). Phase 1 & 2 for Type 2 diabetes (n=205) and cognition (n=20). Several Phase 2 & 3 for COPD.	**Observational studies**: None	

What is it? Roflumilast is a phosphodiesterase (PDE) inhibitor that is highly selective for PDE4 enzymes, and inhibits all four isoforms) of PDE4 (A, B, C, D) [1]. As a PDE4 inhibitor, it prevents the breakdown of cyclic AMP, which in turn affects cell signaling and protein phosphorylation. It has a more favorable therapeutic window than the PDE4 inhibitor rolipram, as it has similar potency in animal models, but a 10x higher concentration is needed to produce significant emetic side effects [2]. It has high oral bioavailability around 80% [3]. It is FDA approved for the treatment of chronic obstructive pulmonary disease (COPD), with efficacy related to its ability to reduce neutrophil mediated inflammation in the lungs. It is marketed under the tradename Daliresp® by AstraZeneca. Since PDE4 inhibition is associated with cognitive enhancement in animal models [4], it has also been tested in small early phase clinical trials for its ability to boost cognitive function in humans.

Neuroprotective Benefit: May boost cognitive function for verbal memory. Neuroprotection may be mediated by induction of neurotrophic factors and reduction of neuroinflammation.

Types of evidence:

- 4 RCT [Phase 1 for cognition: Healthy young adults (n=27), Healthy elderly (n=20), Schizophrenic adults (n=15), Phase 2: Heathy young adults (n=20)]
- 10 laboratory studies

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

PDE4 inhibitors have been demonstrated to have cognitive enhancing effects in rodent preclinical studies. However, they have generally not been clinically viable due to emetic and gastrointestinal related side effects at doses associated with cognitive enhancement [4]. The results from a few small clinical trials suggest that roflumilast may exert cognitive enhancing activity, particularly with respect to verbal memory, at doses below the threshold for gastrointestinal side effects. It is not known whether these effects would provide a sustained benefit that could slow progression of cognitive impairment, or would only offer temporary symptomatic benefits.

Cognitive function: Potential benefit at low dose (100 µg)

The results from RCTs examining the potential cognitive enhancing effects of roflumilast in healthy adults have been mixed, but support a **possible verbal domain specific effect only at low doses**. An RCT assessing the ability of roflumilast to reverse scopolamine-induced cognitive impairments in healthy adults (n=27) alone or in combination with donepezil (10 mg) failed to show significant benefit on performance on immediate or delayed verbal recall tests (NCT02051335). The dose of roflumilast used in this study is unknown, but may be 250 or 500 µg, which are the standard doses in clinical trials for other indications. While roflumilast was able to able to boost cognition in rodents under this paradigm, the effects were dose-dependent, with the greatest effects at intermediate doses, suggesting there is an optimal dosing range [2].

Performance on the verbal word recall test was assessed in healthy young adults (n=20, age 20.9± 2.3 years, 80% female) acutely (1 hour) after roflumilast administration (100, 300, or 1000 µg) (NCT01433666). Word recall was found to be increased by 2-3 words on the third trial [$F(3,57) = 2.868$, $P = .04$] following the 100 µg dose [5]. This was accompanied by an enhanced P600 peak on electroencephalogram (EEG), which is a peak in electrical brain activity associated with language-related tasks ($F(1,39) = 4.493$, $P = 0.048$; Cohen's d: 0.62 for third trial). Sensory gating as measured by EEG was also improved at the 100 µg dose ($Z = -2.01$, $P < 0.05$) [6]. **Improvements were not seen on spatial memory** (object relocation) or attention (Stroop task) domain tests [5]. Significant effects were not seen on any of the measures at the intermediate and high doses (300 and 1000 µg). Similar results were reported for an RCT (ISRCTN96013814) testing roflumilast (100, 250, or 10000 µg) in cognitively normal older adults (age 60-80 years) (n=20) [7]. The 100 µg dose improved verbal word memory (Cohen's d, 0.69), but there were no significant effects at higher doses, or on spatial working memory at any dose.

Roflumilast (100 or 250 µg for 8 days) was also tested for its ability to improve cognitive performance in schizophrenic patients treated with 2nd generation anti-psychotics (n=15, age 40.5 ± 10.5 years) (NCT02079844), as impaired cognitive function is common in this population [8]. In this study, verbal memory, assessed by the Hopkins Verbal Learning Test, improved at the 250 µg dose (Effect size = 0.77 vs placebo), while working memory, assessed by the spatial span test, did not improve. Although, schizophrenic symptoms did not change in this very short study, the mechanism of action based on animal studies suggests it could worsen diseases associated with excessive dopamine.

Dysregulation of dopamine levels can impair the functioning of the prefrontal cortex (PFC). Preclinical studies indicate that roflumilast can **modulate cortico-striatal-thalamic circuitry**, due to dopaminergic modulation by cAMP/PKA signaling [9; 10; 11]. Roflumilast was found to increase levels of dopamine, and due to greater sensitivity for the indirect striatal pathway, is hypothesized to be beneficial for diseases where **less inhibition to the PFC** would be advantageous [9]. In a hyperdopaminergic state, roflumilast was found to exacerbate impulsivity [10]**.** However, roflumilast can also act on the direct pathway [9], which has opposite effects (i.e. would increase inhibition), and this may account for why cognitive enhancement only occurs at low doses, and why the **effective dose may vary based on the baseline level of dopamine.**

Human research to suggest benefits to patients with dementia: None

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

Roflumilast has been shown to protect against cognitive impairment in various preclinical neurodegenerative models, and the benefits appear to be related to the **induction of neurotrophic factors and reduction of inflammation**.

Alzheimer's Disease: Potential benefit (preclinical in rodents)

Roflumilast treatment has been shown to improve performance on learning and memory tasks in transgenic mouse models of Alzheimer's disease (AD) at doses lower than the maximum recommended dose used for COPD (500 µg).

In the APP/PS1 model, roflumilast 0.4 mg/kg (equivalent to approximately 1/3 maximum recommended human dose, about 170 µg) for 3 weeks restored performance on novel object recognition, Morris water maze, and passive avoidance tasks [12]. This was accompanied by increased levels of cAMP and phosphorylated cAMP response element binding protein (p-CREB), the **restoration of levels of brain-derived neurotrophic factor (BDNF) and reduction of pro-inflammatory mediators** (NF-kB, IL-6, TNFα, IL-1β) to levels detected in wild-type animals. Roflumilast also restored performance on novel object

recognition, Morris water maze, and contextual fear conditioning tasks at a sub-efficacious dose (0.01 mg/kg) in combination with a PDE5 inhibitor (vardenafil) for 3 weeks in the APPswe model [13]. The enhancements were maintained for at least 2 months after the cessation of treatment, though it is not clear if combinatorial therapy is necessary to mediate the sustained effects.

Stroke: Potential benefit (preclinical in rodents)

Roflumilast was able to reduce neurological impairments and inflammation in rat stroke models, however, the degree of **benefit was influenced by the severity of neurological injury** and the drug dosage.

In a cerebral hypoperfusion model (4VO/ICA) low dose (0.01 mg/kg, or approximately 1/5 human dose, ~100 µg), but not very low dose (0.003 mg/kg) roflumilast improved survival from 62.5% to 100% ($P<0.01$), and restored spatial memory performance in the aversive radial maze [14]. While levels of Arg+ microglia increased, suggestive of the upregulation of a protective M2-like response, BDNF levels did not increase, and neuronal integrity was not positively affected. High dose roflumilast (3 mg/kg) acutely following subarachnoid hemorrhage, reduced neurological impairment, blood brain barrier (BBB) penetration, brain edema, and levels of proinflammatory cytokines (IL-6, TNFα, IL-1β), but did not improve survival [15]. Moreover, these effects, while statistically significant, were marginal, as the roflumilast treated animals were still significantly impaired relative to sham controls.

Hypertension-related cognitive impairment: Potential benefit (preclinical in rodents)

In rat models of hypertension, roflumilast (0.1, 0.3, or 1 mg/kg) treatment for 10 days improved performance on learning and memory tests, including the novel object recognition task without reducing blood pressure [16; 17]. The cognitive enhancing effects may be related to the concomitant increase in p-CREB, BDNF, and nitric oxide (NO) levels in the brain.

APOE4 interactions: Unknown

Aging and related health concerns: May reduce vascular inflammation and promote glucose tolerance. Could be beneficial as an adjunct therapy in cancer by improving sensitivity to chemotherapeutics.

Types of evidence:

- 7 meta-analyses (Based on 8-12 RCT for COPD)
- 4 clinical trials [Phase 1 RCT: B cell cancers (n=10); Phase 2 RCT: Type 2 diabetes (n=205); Phase 4 RCT Obesity/PCOS (n=31, n=41)]
- 12 laboratory studies

Cardiovascular: Potential benefit

PDE inhibitors, particularly those targeting PDE3 or PDE5, have been shown to affect cardiovascular health, as these enzymes are highly expressed in the heart and/or vascular tissue [18]. Studies in rodents have suggested that PDE4 inhibition could significantly impact cardiac function. However, in humans, PDE4 is only a minor player in the heart due to lower levels of expression relative to other classes of PDE enzymes [19]. Thus, PDE4 inhibition will generally only make a significant contribution to cardiovascular function when the more dominant enzymes are also inhibited, such as with combination therapy.

A meta-analysis of clinical trials (n=14) involving patients (n=12,054) with moderate to severe COPD, which is a population at high risk for cardiovascular disease, indicated a lower composite rate for serious adverse cardiovascular events in patients receiving roflumilast (250 or 500 µg/day) compared to those on placebo (hazard ratio (HR): 0.65 (95% Confidence Interval (CI), 0.45-0.93); P =0.019) [20], suggesting roflumilast **may offer cardioprotective benefits in high risk individuals**. Preclinical models support a protective role for roflumilast through the **reduction of vascular inflammation** by decreasing the adhesion of inflammatory immune cells to vascular endothelial cells [21; 22]. However, decreases in COPD-related disease activity in response to roflumilast treatment may instead account for the decrease in comorbid cardiovascular events. It has not been determined whether roflumilast is cardioprotective in other populations.

Diabetes: Potential benefit

Glucagon-like peptide 1 (GLP-1) is important in glucose regulation, as it promotes insulin secretion in a glucose dependent manner, and GLP-1 agonists are widely used for the management of type 2 diabetes. Since **PDE4 is implicated in the regulation of GLP-1**, PDE4 inhibitors are hypothesized to also be beneficial in diabetes patients [23].

In a Phase 2 RCT (NCT01140542) of patients with newly diagnosed type 2 diabetes without COPD (n=205), roflumilast (500 µg/day) treatment led to a significantly greater **reduction in glycolated hemoglobin (HbA1c)** compared to placebo (least square mean = -0.45%; P < 0.0001) [24]. Based on studies looking at the level of HbA1c reductions associated with clinically meaningful disease mitigation [25], the magnitude of reduction with roflumilast is projected to be clinically relevant. Roflumilast treatment also resulted in significant reductions in glucose (P =0.0082) and glycerol (P =0.0104), and increased C-peptide levels, indicating increased insulin production (P =0.0033). Patients also lost weight, but not significantly more than those in the placebo group (P =0.0584).

Preclinical studies in diabetic rodent models support a role for roflumilast in GLP-1 induction and protection against organ damage-associated with high glucose toxicity. In the rat type 1 diabetes streptozotocin model, roflumilast protected against kidney fibrosis [26] and bladder dysfunction [27] by reducing oxidative stress and inflammation. In the type 2 diabetes (db/db) mouse model, both roflumilast and its active metabolite roflumilast-N-oxide were able to increase GLP-1 in response to a glucose challenge [28]. Chronic administration (3 mg/kg for 28 days) prevented increases in blood glucose, reduced HbA1c levels, and protected against atrophy in the pancreas. Roflumilast (at 500 µg human equivalent dose) also **improved glucose tolerance** and protected against fatty liver disease in a high-fat diet mouse model [29]. The liver protection was associated with increased induction of the cellular respiratory capacity of hepatocytes. This was attributed to the ability of roflumilast to induce mitochondrial biogenesis through the activation of the metabolic regulator peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α).

Obesity: Potential benefit (with comorbid PCOS)

Weight loss is one of the most common side effects associated with roflumilast treatment [30]. While this is likely related, in part, to the increased incidence of gastrointestinal side effects, studies in diabetic models suggest that it may also be attributed to a change in metabolism [29]. Roflumilast (500 µg/day for 12 weeks) was tested in obese women with polycystic ovary syndrome (PCOS) in two RCT (n=31, n=41) for its ability to promote weight loss compared to metformin and/or liraglutide [31; 32] (NCT02037672, NCT02187250). Roflumilast led to significant reductions in weight, body mass index, waist circumference, and visceral adipose tissue; and the weight loss was primarily attributed to a decrease in body fat. Roflumilast was slightly more effective than metformin, but was less effective than liraglutide.

Cancer: Potential benefit (as adjunct therapy for B cell malignancies)

Mature B cell cancers typically involve increased activation of the B cell receptor, leading to aberrant signaling that drives tumor growth [33]. Phosphoinositol-3 kinase (PI3K) is one of the major dysregulated signaling-associated molecules. Effectively targeting PI3K has been challenging due to the toxicity associated with current P13K inhibitors, and many patients become refractory to these treatments.

Roflumilast suppresses P13K signaling by increasing levels of cAMP. In cell culture and mouse xenograft models, roflumilast was found to synergize with the chemotherapeutic PI3K inhibitor, idelalisib, to reduce both PI3K and tumor growth [33]. Roflumilast was also shown to up-regulate glucocorticoid receptor levels on cancerous, but not healthy blood cells, to promote glucocorticoid-mediated apoptosis, which may help overcome resistance to glucocorticoid therapy [34]. PI3K also promotes tumor angiogenesis by inducing VEGF secretion and microvessel formation. Roflumilast can suppress this process in a manner that may promote a tumor microenvironment that increases sensitivity to chemotherapeutic agents [35].

The ability of roflumilast (500 µg/day) to regulate P13K signaling and augment glucocorticoid therapy (prednisone) was tested in a small Phase 1b RCT in patients (n=10) with refractory or relapsed B cell malignancies [36]. Roflumilast was able to **suppress PI3K activity** in 77% of patients, and 66% had a partial response or disease stabilization. The reduction in PI3K was not associated with levels of roflumilast, suggesting the discrepancy may relate to tumor-type sensitivity. This suggests that roflumilast may offer clinical benefit as an adjunct therapy. In an upcoming clinical trial (NCT03458546), roflumilast will be tested as an add-on to standard chemotherapy for patients with diffuse large B cell lymphoma.

The results from preclinical studies suggest that while roflumilast is ineffective as monotherapy for cancer, it may also **synergize with chemotherapeutic agents to overcome resistance** in other cancers. In mouse xenograft models, roflumilast reduced tumor growth by restoring sensitivity to cisplatin in cisplatin-resistant ovarian cancer cells through upregulation of mitochondrial ferratin [37]. Roflumilast also synergized with chemotherapeutic agents (carboplatin or cisplatin) to induce apoptosis in lung cancer cells [38].

COPD: Benefit (for severe disease)

Roflumilast has been demonstrated to significantly reduce lung exacerbations and suppress airway inflammation in COPD patients relative to placebo based on meta-analyses of RCTs [30; 39; 40; 41; 42;

43]. However, compared to other treatment options, roflumilast has a relatively low benefit to side-effect ratio, so it is only recommended for patients with severe COPD [44].

Safety: Gastrointestinal-related events are the most common side effects at the standard dose. Metabolized in the liver and interacts with other drugs that use cytochrome P450 liver enzymes.

Types of evidence:

- 7 meta-analyses (Based on 8-12 RCT for COPD)
- 10 clinical trials [Phase 1 for safety: Healthy volunteers (n=24, n=80); for cognition: Healthy young adults (n=27, n=20), Healthy elderly (n=20), Schizophrenic adults (n=15); B cell cancers (n=10); Phase 2 RCT: Type 2 diabetes (n=205); Phase 4 Obesity/PCOS (n=31, n=41)]
- Numerous laboratory studies

Meta-analyses from RCTs of roflumilast treatment (250 or 500 µg/day) in COPD patients indicate that the most common adverse events were **gastrointestinal-related effects, including nausea and diarrhea** [Odds ratio (OR): 3.13 (95% CI 2.76-3.54)] [30]. Weight loss [Risk ratio (RR): 3.814, (95% CI 3.091~4.707), $P < 0.001$, from 11 RCT] [39] and headache [OR: 2.4 (95% CI 1.83–3.15), from 13 RCTs] [40] were also common and occurred at higher rates than placebo. Roflumilast was generally well-tolerated and a similar side effect profile was found in RCTs with other non-COPD populations, including diabetic patients, obese women, and healthy young adults. The 100 µg dose, which was found to have cognitive benefits in early phase trials, was not associated with an increased incidence of adverse events, including gastrointestinal related events and headache. Increased incidences of serious adverse events were not found in any of the RCTs. Because suicides occurred in a couple of patients on the roflumilast arm in RCTs, the FDA conducted an investigation. They concluded that roflumilast is not associated with increased risk for suicide, but it is associated with **increased risk for psychiatric symptoms**, such as depression [OR: 2.13, (95%CI 1.79-2.54)] [30]. Therefore, roflumilast is not recommended for people with a history of depression.

According to Drugs.com, roflumilast has 273 moderate drug interactions and 10 minor interactions.

Roflumilast is **metabolized in the liver by the cytochrome P450 enzymes** CYP3A4 and CYP1A2. Therefore, roflumilast's metabolism is affected by the presence of other drugs that induce cytochrome P450 enzymes (reduce therapeutic effect), such as rifampicin, or inhibit them (increase systemic exposure) (Rxlist). Correspondingly, roflumilast is also not recommended in people with hepatic impairment.

On Treato.com Daliresp is rated 3.6/5 for overall satisfaction in the treatment of COPD or asthma. The concern level was 2.9/5 with roughly equal positive and negative comments (141 vs 100). The most commonly reported side effects were weight loss, nausea, diarrhea, and insomnia.

Sources and dosing:

Roflumilast is marketed under the tradename Daliresp® by AstraZeneca, who acquired it from Takeda Pharmaceuticals. It is available in oral tablet form by prescription for patients with severe COPD with a recommended dose of 500 µg/day (Drugs.com).

Research underway:

According to Clinicaltrials.gov, there are currently 7 active clinical trials for roflumilast.

Four are for diseases associated with airway inflammation: COPD (NCT02671942) (NCT03762330), Bronchiectasis (NCT03428334), and Asthma (NCT03532490). One is a long-term observational safety study (NCT03381573). Roflumilast is being tested as an adjunct to standard chemotherapy in B cell lymphoma (NCT03458546), and for its ability to delay the onset of AD in a prospective observational study of patients with preclinical AD (NCT02835716).

Search terms:

Pubmed, Google: Roflumilast + neurodegeneration, Alzheimer's, dementia, cognition, aging, cardiovascular, cancer, diabetes, clinical trials, safety, meta-analysis

Websites visited for Roflumilast:

- Clinicaltrials.gov
- Treato.com
- Drugs.com
- WebMD.com
- PubChem
- DrugBank.ca
- Patientslikeme.com

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