



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.

Rolipram

Evidence Summary

Although Rolipram never reached the market, newer PDE4 inhibitors may offer greater promise for neuroprotection without the severe side effects.

Neuroprotective Benefit: Rolipram improves cognitive function in numerous rodent models of AD, diabetes, and chemobrain. PDE4 inhibitors with better safety profiles than rolipram may hold promise for neuroprotection.

Aging and related health concerns: No clinical data exist for preventing or treating age-related diseases. A few rodent studies suggest PDE4 inhibition may be beneficial for peripheral neuropathy.

Safety: Rolipram produces severe side effects including vomiting and headaches. Second generation PDE4 inhibitors may have fewer side effects.



What is it? Rolipram is an inhibitor of phosphodiesterase-4 (PDE4), an enzyme that affects cell signaling. PDE inhibitors increase levels of cyclic AMP, which activates protein kinase A (PKA) and subsequently CREB; CREB promotes transcription of genes related to synaptic plasticity and neurogenesis, like the neurotrophic factor BDNF ([Heckman et al., 2015](#)). Rolipram was originally developed as a potential antidepressant drug in the early 90s, but has since been discontinued due to a narrow therapeutic window with significant gastrointestinal side effects. It is heavily used in preclinical studies as a well-characterized PDE4 inhibitor.

Neuroprotective Benefit: Rolipram improves cognitive function in numerous rodent models of AD, diabetes, and chemobrain. PDE4 inhibitors with better safety profiles than rolipram may hold promise for neuroprotection.

Types of evidence:

- 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: None available.

Mechanisms of action for neuroprotection identified from laboratory and clinical research: Rolipram treatment has been shown to improve cognitive function in rodent models of aging ([Kumar et al., 2017](#)), Alzheimer's disease ([Gong et al., 2004](#); [Comery et al., 2005](#); [Wang et al., 2012](#); [Zhuo et al., 2016](#)), diabetes ([Miao et al., 2015](#); [Zhong et al., 2016](#)), and chemotherapy-induced cognitive impairment ([Callaghan and O'Mara, 2015](#)).

Mechanisms of action for neuroprotection include anti-cholinesterase, anti-amyloid, antioxidative, and anti-inflammatory effects ([Zhuo et al., 2016](#); [Kumar et al., 2017](#)). In an Alzheimer's mouse model, rolipram treatment for 3 weeks improved synaptic transmission and synaptic plasticity while also improving working, reference, and associative memory, an effect that lasted 2 months after treatment ended ([Gong et al., 2004](#)). Also in Alzheimer's mice, rolipram reduced reactive oxygen species and restored glutathione levels and antioxidant enzyme (SOD) activity ([Zhuo et al., 2016](#)). In diabetic rats, rolipram decreased pro-inflammatory TNF α levels, increased anti-inflammatory IL10 levels ([Miao et al.,](#)



2015), and increased levels of the neurotrophic factor BDNF and proteins involved in synaptic plasticity (CREB and Arc) ([Zhong et al., 2016](#)).

Rolipram was one of the 24 compounds identified in a screening platform as modulating NMNAT2, an enzyme that synthesizes NAD⁺ and promotes neuroprotection ([Ali et al., 2017](#)). Thus, aside from the antioxidative, anti-inflammatory, and anti-cholinesterase effects, increasing NMNAT2 activity may be another mechanism of neuroprotective action. The list from the screening included several PDE inhibitors including caffeine, a caffeine analog, and rolipram. Other drugs on the list are not promising for therapy as some were amino acids, others were inhibitors of important cellular functions (microtubule assembly inhibitor, DNA synthesis inhibitor, Golgi function, etc.), and several were toxins (e.g., rotenone and a convulsant).

PDE inhibitors, in general, have been receiving increased attention as possible targets for treating age-related cognitive decline ([Heckman et al., 2015](#)). There are 11 families of PDEs, each with different variants and isoforms such that it is estimated there are over 100 specific human PDEs.

Several subtypes of PDE4s (4D3, 5, 6, 7, and 8) are decreased while PDE4D1 is increased. Rolipram is a non-selective PDE4 inhibitor and thus inhibit all PDE4 (A-D).

Of the 11 families of PDEs, PDE4 and PDE5 have been most extensively tested in preclinical models and appear to be promising targets. In humans, PDE4A, PDE4B, and PDE4D are expressed in the hippocampus—PDE4B is the most highly expressed PDE4 type in human CNS.

APOE4 interactions: Unknown.

Aging and related health concerns: No clinical data exist for preventing or treating age-related diseases. A few rodent studies suggest PDE4 inhibition may be beneficial for peripheral neuropathy.

Types of evidence:

- 5 laboratory studies

Peripheral neuropathy: BENEFIT IN RODENTS. In rodent studies, rolipram alleviated symptoms (pain and pain sensitization) of peripheral neuropathy in three different rat models: alcoholic neuropathy ([Han et al., 2012](#)), chemotherapy-induced neuropathy ([Kim et al., 2015](#)), and neuropathy from spinal nerve



ligation ([Kim et al., 2011](#)). In the spinal nerve ligation study, rolipram treatment also improved nerve conduction velocity ([Kim et al., 2011](#)). PDE4 inhibitors have not been tested in people with peripheral neuropathy.

Cholesterol: A cell culture study has shown that rolipram and cilomilast, another PDE4 inhibitor, increased apoA-I-mediated cholesterol efflux ([Lin and Bornfeldt, 2002](#)). Thus PDE4 inhibitors may improve cardiovascular disease by mobilizing cholesterol from atherosclerotic lesions. These very early preclinical studies have not yet been followed up.

Safety: Rolipram produces severe side effects including vomiting and headaches. Second generation PDE4 inhibitors may have fewer side effects.

Types of evidence:

- 2 clinical trials
- Numerous laboratory studies

Although the first clinical trial in 58 people with major depressive disorder showed some anti-depressant response with rolipram and good tolerance to the drug ([Fleischhacker et al., 1992](#)), subsequent studies showed that rolipram produces severe dose-limiting side effects including vomiting, headache, and excessive gastric acid secretion ([Heckman et al., 2015](#)). Interestingly, severe side effects of rolipram such as vomiting are not apparent in rodents ([Kim et al., 2011](#); [Heckman et al., 2015](#)).

A small open-label study in 8 multiple sclerosis patients was terminated prematurely because rolipram was poorly tolerated ([Bielekova et al., 2009](#)). Side effects included severe insomnia and gastroesophageal reflux. There were also safety concerns with rolipram treatment as there was an increase in brain inflammatory activity, as measured by contrast-enhanced lesions on the MRI. The number of infections also increased from 0.73 per year (baseline) to 1.97 per year during rolipram therapy, though the data are based on 8 patients receiving treatment for 8 months. Despite these issues, all patients remained stable or slightly improved during the treatment.

Sources and dosing: Rolipram is used extensively in preclinical studies as a well-characterized PDE4 inhibitor. Rolipram never reached the market due to severe dose-limiting side effects. There are “second generation” PDE4 inhibitors currently being developed or tested (discussed below) that are predicted to have less side effects such as nausea, vomiting, and headaches. PDE4 inhibitors were initially considered for treating depressive disorders, but are now considered for other indications including Alzheimer’s

disease, autoimmune diseases, and respiratory diseases (e.g., asthma, chronic obstructive pulmonary disease).

Research underway: There are currently no ongoing clinical trials testing rolipram for dementia or age-related diseases due to its narrow therapeutic window. It continues to be used extensively in preclinical studies as a well-characterized PDE4 inhibitor.

There are a few other PDE4 inhibitors that are currently being tested in clinical trials. A randomized double-blind controlled trial is testing if BND14770 reverses drug (scopolamine)-induced cognitive impairment in healthy volunteers ([NCT03030105](#)). Also, an open-label trial is testing whether Roflumilast improves blood sugar and insulin levels in prediabetic overweight or obese people ([NCT01862029](#)). Roflumilast is approved as an anti-inflammatory drug for the treatment of chronic obstructive pulmonary disease. Results of a clinical trial testing Roflumilast on cognitive function was completed in 2013 but its results have not been published ([NCT01433666](#)). A phase II study testing MK0952 in patients with mild-to-moderate Alzheimer's disease was terminated ([NCT00362024](#)).

Conclusion: Rolipram itself is not viable due to severe side effects. Based on PDE expression patterns, PDE1, 2, 4, and 8 appear to be good targets for improving memory as they have high expression in the hippocampus and cortex and lower peripheral levels ([Heckman et al., 2015](#)). However, studies from animal models of aging or Alzheimer's disease suggest therapeutic profiles of PDE5 inhibition is most promising, but this is partly due to the relative lack of studies/inhibitors for other PDE families.

Search terms:

Pubmed, Google: Rolipram

- + cognitive, + clinical trials, + safety, + neuropathy, + lifespan

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