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.

Roluperidone (MIN-101)

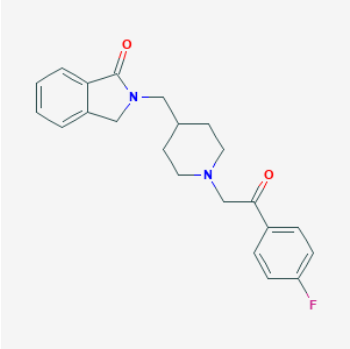
Evidence Summary

The evidence for roluperidone is limited to a single randomized controlled trial in schizophrenia patients. Roluperidone may interact with medications that inhibit CYP2D6.

Neuroprotective Benefit: Roluperidone improved several cognitive scores in schizophrenia patients, but it is not known whether it would benefit age-related cognitive decline or dementia.

Aging and related health concerns: No studies have tested roluperidone for age-related conditions.

Safety: Common adverse events with roluperidone included headache and anxiety based on a study in schizophrenia patients, though a few serious adverse events were also observed (vomiting, syncope, bradycardia). May interact with CYP2D6 inhibitors.

Availability: Not available; in clinical trials	**Dose:** The clinical trial in schizophrenia patients tested two oral doses: 32 mg/day and 64 mg/day.	**Chemical formula:** $C_{22}H_{23}FN_2O_2$ **MW:** 366.4  Source: PubChem
Half life: Not documented	**BBB:** Not documented	
Clinical trials: A phase 2b study in schizophrenia patients included 244 patients.	**Observational studies:** N/A	

What is it? Roluperidone, also known as MIN-101, is an antagonist for sigma2, 5-HT_{2A}, and α1-adrenergic receptors, and is under development by Minerva Neurosciences to target negative symptoms (e.g., blunted affect, poverty of speech/thought, apathy, anhedonia, lack of interest) and cognitive dysfunction in schizophrenia patients (Krogmann et al., 2019). The majority of schizophrenia patients demonstrate cognitive impairment that is severe across multiple domains, including learning and memory, attention/vigilance, executive functioning, verbal fluency, and speed of processing (Keefe et al., 2018). The magnitude of cognitive impairment is on average 2 standard deviations below the healthy control mean, and the severity of impairment is more predictive of functional outcomes than are positive and negative symptoms. Roluperidone has low affinity for dopaminergic, muscarinic, cholinergic, and histaminergic receptors. Though at high doses, roluperidone increased dopamine turnover and slightly elevated prolactin, suggesting a weak antagonistic effect at dopamine D2 receptor (original data not published but discussed in Keefe et al., 2018). It is currently being tested in a phase 3 double-blind randomized controlled trial (dose, 32 mg and 64 mg per day) in patients with negative symptoms of schizophrenia (NCT03397134).

Neuroprotective Benefit: Roluperidone improved several cognitive scores in schizophrenia patients, but it is not known whether it would benefit age-related cognitive decline or dementia.

Types of evidence:

- 1 clinical trial (results of which have been published across multiple papers)
- A few laboratory studies

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

No studies have evaluated roluperidone for prevention of dementia or age-related cognitive decline.

In a double-blind randomized controlled trial of 244 schizophrenia patients, roluperidone treatment (32 mg/day or 64 mg/day) for 12 weeks improved several cognitive scores on the Brief Assessment of Cognition in Schizophrenia (BACS) battery (Keefe et al., 2018). BACS is a tool for measuring cognitive function in participants with schizophrenia that consists of 6 domains: verbal memory (list learning), working memory (digit sequencing task), motor speed (token motor task), verbal fluency (category instances, letter fluency), attention and processing speed (symbol coding), and executive function (Tower of London test).

Patients on the 32 mg/day dose of roluperidone significantly improved on the BACS motor ($p=0.04$), verbal fluency ($p=0.01$), and composite z scores ($p=0.05$) when compared to patients on placebo (Keefe et al., 2018). Treatment with the 64-mg dose did not show significant difference from placebo on the composite score or any subscales and in general was associated with lower levels of improvement. Although the patients on the 64-mg dose did not show significant cognitive improvement compared to the placebo group, improvement in the negative symptoms of schizophrenia significantly correlated with improvements in the cognitive composite score. This correlation was not observed in the 32-mg dose group.

The primary outcome for this clinical trial was negative symptoms, measured by the Positive and Negative Syndrome Scale (PANSS) factor score. At the end of 12 weeks, there was a statistically significant reduction in PANSS negative symptom pentagonal structure factor score for the 32 mg-dose and 64 mg-dose groups compared with the placebo group ($p\leq0.024$, $d=0.45$, and $p\leq0.004$, $d=0.57$, respectively; Davidson et al., 2017). Similar findings were observed on the PANSS negative "classic" scale and PANSS total score. The effect on negative symptoms remained after controlling for depression, which suggests the effect was not due strictly to improvement in mood.

Subsequent analyses of negative symptoms from the same clinical trial revealed that both doses of roluperidone (32 mg and 64 mg/day) were superior to placebo on "reduced experience" and "reduced expression" (Harvey et al., 2019). Roluperidone treatment at the higher 64 mg dose also improved exploratory outcomes including "personal and social relationships" (p=0.013), "self-care" (p=0.021), "socially useful activities" (p=0.013), and "disturbing and aggressive behaviors" (p=0.006)(Rabinowitz et al., 2019).

Human research to suggest benefits to patients with dementia: None available.

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

Rodent studies: In rodents, roluperidone treatment improved phencyclidine-induced impairment in social interaction as well as drug (MK-801)-induced impairment of spontaneous alternation behavior (original data not published but discussed in Davidson et al., 2017). These results are suggestive of potential therapeutic benefit on negative symptoms. Roluperidone also showed benefit on the conditioned avoidance response test, without reducing the percentage of escapes, consistent with the finding that roluperidone does not have sedative effects.

Cell culture studies: Based on a press release, a preclinical study showed that roluperidone administration for 3 days increased the release of the neurotrophic factor BDNF in cultured brain hippocampal neurons in a dose dependent manner (Minerva Neurosciences press release). The increase in BDNF was by approximately 20%, comparable to the effect shown by pridopidine, a sigma-1 receptor agonist and reference molecule used in the study. Pridopidine is currently under development for Huntington disease.

Mechanisms of action: Roluperidone has high affinities for sigma-2 and 5HT-2A receptors, and also for α1-adrenergic receptors. It is possible that sigma-2 receptors modulate dopamine and glutamatergic pathways, as well as calcium (Davidson et al., 2017). Recent research also suggests new binding sites on sigma receptors, including the progesterone receptor membrane component 1 (PGRMC1).

APOE4 interactions: Unknown.

Aging and related health concerns: No studies have tested roluperidone for age-related conditions.

Types of evidence:

- None

No studies have tested roluperidone for age-related health conditions. Antagonists of 5-HT2A receptors have mostly been developed for treating psychosis (Sommer, 2010). Antagonists of sigma-2 receptors have also been studied for their antipsychotic and antidepressant activities. Sigma-2 receptors are overexpressed in tumor cells and therefore they may be good biomarkers or therapeutic targets (Waarde et al., 2015), but roluperidone has not been pursued for these indications.

Safety: Common adverse events with roluperidone included headache and anxiety based on a study in schizophrenia patients, though a few serious adverse events were also observed (vomiting, syncope, bradycardia). May interact with CYP2D6 inhibitors.

Types of evidence:

- 1 clinical trial
- 1 review article of therapies for schizophrenia

In a double-blind randomized controlled trial of 244 schizophrenia patients, roluperidone treatment (32 mg/day or 64 mg/day) for 12 weeks was not associated with clinically significant changes in vital signs, routine laboratory values, weight, metabolic indices, and Abnormal Involuntary Movement Scale score (Davidson et al., 2017). The 3 groups had similar decreases in plasma levels of prolactin. Eight patients experienced serious adverse events (2 in the placebo group and 6 in the roluperidone groups), of whom 6 were hospitalized for worsening of schizophrenia symptoms (2 in the placebo group and 4 in the roluperidone 32 mg/day group). The 2 remaining serious adverse events occurred in the roluperidone 64 mg/day group: vomiting and abdominal pain in one patient and syncope and bradycardia in the other. The most commonly reported adverse events for patients in the roluperidone groups were headache (3.6% in the placebo group, 7.5% in the roluperidone groups), anxiety (6.0% in the placebo group, 6.8% in the roluperidone groups), insomnia (9.6% in the placebo group, 5.6% in the roluperidone groups), schizophrenia symptoms (10.8% in the placebo group, 5.6% in the roluperidone groups), asthenia (physical weakness; 2.4% in the placebo group, 5.6% in the roluperidone groups), nausea (3.6% in the placebo group, 3.7% in the roluperidone groups), and somnolence (0% in the placebo group, 3.7% in the roluperidone groups).

Drug interactions: Drug interactions have not been documented. Based on the enrollment criteria for the phase 2b study in schizophrenia patients with negative symptoms, poor or intermediate metabolizers for P450 CYP2D6 were excluded from this study (Davidson et al., 2017). Also, in the ongoing phase 3 trial, patients requiring medications that inhibit CYP2D6 or CYP3A4 are excluded (NCT03397134). Thus, medications that inhibit CYP2D6 (see list here) or CYP3A4 may need to be avoided when taking roluperizone.

Sources and dosing: Roluperidone is under clinical development by Minerva Neurosciences, Inc., a clinical-stage biopharmaceutical company focused on the development of treatments for central nervous system diseases, including schizophrenia, insomnia and mood disorders, major depressive disorder, and Parkinson's disease. The dose used in the clinical trial in schizophrenia patients were 32 mg/day and 64 mg/day (Davidson et al., 2017).

Research underway: There is currently one phase 3 double-blind randomized controlled trial testing the efficacy of roluperidone (32 mg and 64 mg) in patients with negative symptoms of schizophrenia (NCT03397134). This study is a 12-week study followed by a 40-week open-label extension. It is scheduled to be completed in March 2020.

Search terms:
Pubmed, Google:

- Roluperidone, MIN-101

Websites visited for Roluperidone, MIN-101:

- Clinicaltrials.gov
- Examine.com (0)
- DrugAge (0)
- Geroprotectors (0)
- Drugs.com (0)
- WebMD.com (0)
- PubChem
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- Labdoor.com (0)
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