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.

PRX-03140

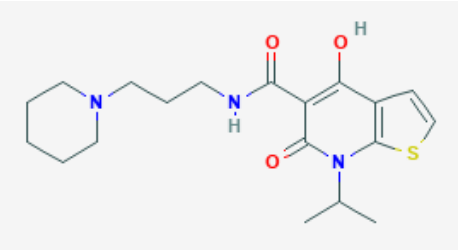
Evidence Summary

Appears to improve cognitive functions while increasing acetylcholine levels, but clinical trial results are unpublished, and there are some mixed findings in rodent studies. Safety data are also unpublished.

Neuroprotective Benefit: Improved cognitive functions in Alzheimer's patients, but the data are unpublished. Rodent data are mixed but improved cognitive functions, increased acetylcholine release, and increased hippocampal theta oscillation power.

Aging and related health concerns: PRX-03140 has not been evaluated for age-related health concerns.

Safety: Although 2 clinical trials have tested PRX-03140, no data have been published. 5-HT4 agonists have been associated with cardiovascular adverse events, but a newer 5-HT4 agonist prucalopride was not, due to its high selectivity and affinity for the receptor.

Availability: in clinical trials	**Dose**: not established	**Chemical formula**: $C_{19}H_{27}N_3O_3S$ **MW**: 377.503 g/mol  Source: PubChem
Half life: unknown	**BBB**: penetrant in rats	
Clinical trials: 2 trials have been completed, one in Alzheimer's patients (n=80) and the other in patients with post-traumatic stress disorder (n=7).	**Observational studies**: none	

What is it? PRX-03140 is a highly selective serotonin 4 (5-HT4) receptor partial agonist (intrinsic activity of 18% compared to serotonin)(Shen et al., 2011). It was developed by Predix Pharmaceuticals Inc and was under clinical development by EPIX Pharmaceuticals Inc (AlzForum). In 2006, EPIX Pharmaceuticals and GlaxoSmithKline entered a multi-target strategic collaboration for novel drug development targeting G-protein coupled receptors, including PRX-03140, for the treatment of Alzheimer's disease (Informa). EPIX was responsible for development up to clinical proof of concept, at which point GSK had an exclusive option to license and further develop the drug(s). A phase 2 trial in Alzheimer's was completed in 2008 (NCT00384423) and a pilot study in post-traumatic stress disorder was completed in 2014 (NCT01492699).

Neuroprotective Benefit: Improved cognitive functions in Alzheimer's patients, but the data are unpublished. Rodent data are mixed but improved cognitive functions, increased acetylcholine release, and increased hippocampal theta oscillation power.

Types of evidence:

- 1 clinical trial in Alzheimer's patients
- 3 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:
A randomized double-blind placebo-controlled phase 2a study assessed the short-term effects of PRX-03140 alone and in combination with donepezil in 80 patients with mild Alzheimer's disease (NCT00384423). Treatment duration was 14 days. Primary outcome measures included safety and tolerability during treatment and EEG changes. Secondary outcome measures included changes in cognition after 2 weeks and blood concentrations of PRX-03140 and donepezil. This study sponsored by Epix Pharmaceuticals, Inc. was completed in 2008 but the study results have not been uploaded to ClinicalTrials.gov or published in a peer-reviewed journal article. However, results are described in a rodent study publication (Shen et al., 2011), which cited an abstract from the International Conference on Alzheimer's Disease (HT-01-07, abstract, Megerian, JT Kmssua, 2008. *Results of a Phase 2A study of a novel 5HT4 agonist for the treatment of Alzheimer's Disease*). Based on this abstract, PRX-03140 treatment in patients with mild to moderate Alzheimer's was associated with a statistically significant, 3.6-point improvement in the Alzheimer's Disease Assessment Scale - cognitive subscale (ADAS-cog) score versus a 0.9-point worsening for placebo, after two weeks of therapy.

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

In a study in rats, a single injection of PRX-03140 (1, 5, and 10 mg/kg) significantly enhanced memory (measured by delayed spontaneous alternation performance)(Mohler et al., 2007). PRX-03140 (1 and 5 mg/kg) concomitantly enhanced hippocampal acetylcholine output and delayed spontaneous alternation scores compared to that of vehicle controls but had no effect on hippocampal acetylcholine release under a resting condition. Also, a combination of subtherapeutic doses of PRX-03140 and the acetylcholinesterase inhibitor galanthamine enhanced memory. PRX-03140 also regulated amyloid precursor protein (APP) metabolism by inducing a concentration-dependent increase in the non-amyloidogenic soluble form of APP (sAPPα) with an EC_{50} of approximately 1-10 nM.

In another study in rats, PRX-03140 bound to native rat brain 5-HT4 receptors with Ki values of 110 nM and increased cAMP production in a cell culture (HEK-293 cells) expressing recombinant rat 5-HT4 receptors (Johnson et al., 2012). *In vivo* receptor occupancy studies established that PRX-03140 penetrated the blood-brain barrier and bound to 5-HT4 receptors in the rat brain, achieving 50% receptor occupancy at free brain exposures of 330 nM. Rat microdialysis studies showed that PRX-03140 significantly increased cortical histamine levels at 50 mg/kg but failed to affect acetylcholine release at doses lower than 150 mg/kg. In combination therapy studies, donepezil-induced increases in cortical acetylcholine levels were potentiated by PRX-03140 at a dose that did not increase acetylcholine when given alone (50 mg/kg, s.c.). Also, electrophysiological studies in rats demonstrated

that PRX-03140 increased the power (but not the frequency) of brainstem-stimulated hippocampal theta (θ) oscillations at 5.6 mg/kg. These results suggest that PRX-03140 may exert effects on brain activity at doses below those required for improving cognitive test scores.

In this study, PRX-03140 was compared with prucalopride, a high affinity 5-HT4 receptor agonist that was recently FDA-approved (for the treatment of constipation). PRX-03140 was 3.5-fold less potent in binding to 5-HT4 receptors compared to prucalopride (Ki value of 110 nM compared to 30 nM). Prucalopride increased acetylcholine and histamine levels in the prefrontal cortex at much lower doses (5 and 10 mg/kg, respectively) compared to PRX-03140 (50 mg/kg and 150 mg/kg, respectively). However, both drugs at a subtherapeutic dose (5.6 mg/kg) had the ability to increase hippocampal theta oscillations.

In contrast to some positive findings with PRX-03140, a different study in rats reported that PRX-03140 treatment (0.03-1.0 mg/kg) had "relatively low" brain penetration and failed to significantly reverse spatial learning deficit induced by scopolamine (Shen et al., 2011). Although this may be due to the low doses tested, they observed an inverted U-shaped dose response, and 1.0 mg/kg dose of PRX-03140 exhibited the same magnitude of learning deficit as the scopolamine alone group. PRX-03140 did, however, produce a concentration-dependent increase in the secretion of non-amyloidogenic soluble APP (sAPPα), consistent with the study described above (Mohler et al., 2007).

APOE4 interactions: Unknown.

Aging and related health concerns: ***Rated N/A for potential and N/A for evidence.*** PRX-03140 has not been evaluated for age-related health concerns.

Types of evidence:

- None

No studies have examined the potential of PRX-03140 in treating or preventing age-related health conditions. Other drugs in development that target the 5-HT4 receptor are going after gastrointestinal indications such as constipation and irritable bowel syndrome. Serotonin is produced by specialized enterochromaffin cells in the mucosa of the gut and plays an important role in the motility and secretory functions of the intestine (NIH LiverTox). Activation of 5-HT4 receptors present in the intestinal mucosa increases peristalsis and intestinal tone.

Safety: ***Rated C for potential and D for evidence.*** Although 2 clinical trials have tested PRX-03140, no data have been published. 5-HT4 agonists have been associated with cardiovascular adverse events, but a newer 5-HT4 agonist prucalopride was not, due to its high selectivity and affinity for the receptor.

Types of evidence:

- Several reviews on the safety of 5-HT4 agonists
- 1 laboratory study

PRX-03140: CLINICAL DATA UNPUBLISHED.
Although 2 clinical trials have been completed with PRX-03140, none of the data has been posted on ClinicalTrials.gov or published in peer-reviewed journals. In preclinical studies, PRX-03140 had no effect on contractile properties in guinea pig ileum or colon preparations and a single dose of PRX-03140 (up to 10 mg/kg) in rats did not alter intestinal transit (Mohler et al., 2007). Although a 5-HT4 agonist is expected to increase peristalsis and intestinal movement, in a study in guinea pig colon tissue, PRX-03140 had negligible 5-HT4 agonist activity (Shen et al., 2011).

Other 5-HT4 agonists

Cisapride and Tegaserod: ASSOCIATED WITH CARDIOVASCULAR ADVERSE EVENTS.
Two 5-HT4 receptor agonists (cisapride and tegaserod) have been developed and were approved in the US, but both were associated with significant adverse effects; cisapride was withdrawn in 2000 and tegaserod was withdrawn in 2007 but gained reapproval in 2019 (NIH LiverTox)(DrugBank). The FDA has noted a relationship between tegaserod use and increased risks of heart attack or stroke. These findings dampened the enthusiasm for pursuing 5-HT4 as a target.

Prucalopride: HEADACHE, DIARRHEA, NAUSEA.
Prucalopride, one of the newer generation of highly selective 5-HT4 receptor agonists, was approved by the European Medical Agency in 2009 (and by the FDA in December 2018) for the treatment of chronic constipation in adults who have failed to respond to standard laxative therapy (Shin 2016). Unlike older 5-HT4 agonists, prucalopride has not been associated with adverse cardiovascular side effects or QT prolongation due to its high selectivity and affinity for the 5-HT4 receptor without significant cross-reactivity at the human ether-à-go-go-related gene (hERG) potassium channel or other 5-HT receptor subtypes that have been implicated in cardiovascular events and arrhythmias (Shin 2016). Prucalopride has high affinity only for the 5-HT4b and 5-HT4a receptors (Ki values of 8 nM and 2.5 nM, respectively) and at least a 290-fold selectivity for the 5-HT4 receptor. The most commonly reported adverse events

include headache, diarrhea, nausea, and abdominal pain with no major cardiovascular safety concerns. There were no significant differences in incidence of prolonged QT between treatment groups. No clinically significant cardiac events occurred with the exception of one patient with a preexisting history of mitral valve prolapse and supraventricular tachycardia who experienced that condition while receiving prucalopride.

A more recent 2018 review also stated that "second generation" 5-HT4 receptor agonists such as prucalopride and velusetrag display greater 5-HT4 selectivity, minimal affinity for hERG/Kv11.1 potassium channels, and substantially reduced cardiovascular liability in comparison to their predecessors (Guidicessi et al., 2018).

Drug interactions: Drug interactions for PRX-03140 have not been investigated. Cisapride, another 5-HT4 agonist, has 325 major drug interactions and 154 moderate drug interactions (Drugs.com).

Sources and dosing: PRX-03140 was developed by Predix Pharmaceuticals Inc and was under clinical development by EPIX Pharmaceuticals Inc (AlzForum). It has been tested in phase II studies in Alzheimer's patients and a small safety study in patients with post-traumatic stress disorder (see below). In the safety study in 7 patients with post-traumatic stress disorder, the initial dose for PRX-03140 was 50 mg once daily for 2 weeks, then the dose was increased to 100 mg once daily for 10 weeks (NCT01492699).

Research underway: There are no currently ongoing clinical trials testing PRX-03140. On ClinicalTrials.gov, 2 trials have been completed, one phase 2 trial in Alzheimer's patients (NCT00384423) and one pilot study in patients with post-traumatic stress disorder (NCT01492699). There have been 2 other trials which have been terminated (NCT00693004; NCT00672945). The reasons for the terminations are not indicated.

Search terms:
Pubmed, Google:

- PRX-3140, PRX-03140, NTC-942, VRX-03011

Websites visited for PRX-3140, PRX-03140, NTC-942, VRX-03011:

- Clinicaltrials.gov
- AlzForum
- DrugAge (0)

- Geroprotectors (o)
- Drugs.com (o)
- WebMD.com (o)
- PubChem
- DrugBank.ca
- Cafepharma (o)
- Pharmapro.com (o)

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