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.

Centrophenoxine (Meclofenoxate)

Evidence Summary
Centrophenoxine increases lifespan in mice and may improve a few aspects of cognitive function in humans, but the DMAE component may be associated with adverse effects. Most studies are very old.

- **Neuroprotective Benefit**: The studies are old and some are of suboptimal quality, but centrophenoxine may benefit a few aspects of cognitive function.
- **Aging and related health concerns**: Although only preclinical data exist, centrophenoxine increases lifespan in mice.
- **Safety**: Although most clinical trials suggested that centrophenoxine is safe with no toxic side effects, a study with DMAE reported a few serious adverse events. It may also have teratogenic effects, so should be avoided by women of child-bearing age.
What is it? Centrophenoxine, also known as meclofenoxate, is a cholinergic nootropic used as a dietary supplement to alleviate cognitive symptoms of dementia. Centrophenoxine is an ester of dimethylaminoethanol (DMAE) and an absorption enhancer (4-chlorophenoxyacetic acid), the former of which is the active cholinergic component. It is sold under several brand names including Lucidril and can be obtained over-the-counter or online. In younger people without dementia, centrophenoxine is best known for its potential memory-boosting abilities. It is also thought to reduce lipofuscin, which are age-associated granules composed of oxidatively damaged proteins and membrane lipids [1].

Neuroprotective Benefit: The studies are old and some are of suboptimal quality, but centrophenoxine may benefit a few aspects of cognitive function.

Types of evidence:
• 6 randomized controlled trials, 3 in dementia patients, 2 in elderly, and 1 in head trauma patients
• Numerous laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?
Most clinical studies of centrophenoxine are old and some are of suboptimal quality. The largest and most well-carried out study was a double-blind randomized control trial of 74 healthy elderly that examined the effects of a 9-month centrophenoxine treatment (600 mg, twice daily) on cognitive functions [2]. The centrophenoxine group performed significantly better than placebo in delayed free-recall, suggesting that the treatment may improve consolidation of new information into long-term memory. They found no treatment effects on other measures of memory, such as immediate free-recall, digit-span, recognition memory, past events, or prose passage. Thus, centrophenoxine does not appear to affect memory that is already in storage. The subjects in the centrophenoxine group reported "increased alertness" and "feeling of well-being" to describe some subjective changes.

In contrast, a smaller double-blind crossover study in 28 people with memory deficits reported that 3 weeks of centrophenoxine treatment (300 mg, 4 times daily) did not show any statistically significant effects on 8 tests of memory or mental concentration [3]. They found greater differences between pre- vs post-treatment than between treatment and placebo. Authors noted that the subjects may have been too confused or demented to show improvement; it is possible that the subjects recruited were heterogeneous and some may have had dementia.
The other randomized controlled cross-over trial was in 51 patients with head trauma [4]. Patients received centrophenoxine (900 mg/day) for 2 weeks and placebo for 2 weeks. Although centrophenoxine significantly reduced dizziness compared to placebo, it was not effective in reducing headaches from the head injury. Because not enough subjects experienced memory disturbances, no significant treatment effects emerged.

*Human research to suggest benefits to patients with dementia:*

Clinical trials in dementia patients have been carried out but the studies are of suboptimal quality and the results are inconclusive.

A double-blind randomized controlled trial of 50 dementia patients examined the effects of 8 weeks of centrophenoxine treatment (2 g/day) [5]. There was a high variability in cognitive performance and only intra-individual analyses could be performed; 48% of the centrophenoxine group (10/21) displayed improvements in memory functions while only 28% (7/25) of the placebo group showed improvement. But more people on the centrophenoxine group (5) significantly worsened compared to the placebo group (1). The authors concluded that centrophenoxine may be a useful and safe drug in treating dementia, but these claims are not supported by statistics, which were not carried out rigorously.

Another double-blind randomized trial of 63 mild-to-moderate Alzheimer’s patients compared the effects of centrophenoxine (1560 mg/day for 3 months) with a combination treatment (Antagonic-Stress®) that included centrophenoxine (1560 mg/day), methionine (900 mg/day), aspartic acid-Mg (540 mg/day), fructose (60 mg/day), vitamin B1 (48 mg/day), vitamin B6 (66 mg/day), nicotinic acid (60 mg/day), and zinc sulfate (63 mg/day) [6]. There was no placebo control, but both treatments were able to improve cognitive functions compared to baseline, and the Antagonic-Stress® treatment was significantly superior to centrophenoxine alone in attention, memory, intelligence IQ, verbal IQ, performance IQ, and full IQ. However, it is impossible to tease apart the “practice effect” from this trial in the absence of a placebo control.

More recently, a double-blind randomized controlled trial of 242 prodromal Alzheimer’s patients tested the effects of DMAE pyroglutamate (V0191; 1500 mg/day for 24 weeks) on cognitive functions [7]. DMAE is the active cholinergic component of centrophenoxine. The study found no statistically significant differences in memory, executive function, or attention between V0191 and placebo though some trends emerged at week 12 that favored the V0191 treatment. There were also no significant differences in pre- versus post-treatment on any of the neuropsychological test variables. Authors noted
that there was likely insufficient power to assess changes in cognition over time and the treatment duration was short.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:
Numerous old studies have shown that centrophenoxine improves learning and memory in aged rats [8] and in rodent models of memory impairment induced by scopolamine [9], clonidine [10], aluminum [11], and chronic cerebral ischemia [12]. Likely mechanisms of neuroprotective action include centrophenoxine’s ability to decrease pro-inflammatory mediators (TXB2, 6-keto-PGF1α) [12], hydroxyl radicals [13], lipid peroxidation [14], and brain levels of lipofuscin, the age-associated granules composed of oxidatively damaged proteins and membrane lipids [1]. Interestingly, the process of lipofuscin removal (likely mediated by microglia) appears to continue after cessation of centrophenoxine [1]. The study reported that even 30 mg/kg per day (i.m.), the lowest dose tested in aged guinea pigs, was sufficient to initiate and sustain lipofuscin clearance. While an intriguing study, the article was written in German and the full text was not accessible.

APOE4 interactions: Unknown.

Aging and related health concerns: Although only preclinical data exist, centrophenoxine increases lifespan in mice.

Types of evidence:
- 6 laboratory studies

Lifespan: POTENTIAL BENEFIT IN PRECLINICAL MODELS. In male mice, centrophenoxine treatment (approximately 60 mg/kg/day in drinking water) for 10 months significantly increased mean (by 27.3% or 2.66 months), median (by 29.5% or 2.8 months), and maximum lifespan (by 26.5% or 6.9 months).[15]. The mechanisms of lifespan extension were not examined, but the group receiving centrophenoxine had lower body weights at the end of the study. It is unclear whether they ate less or they had increased metabolism.

Parkinson’s disease: POTENTIAL BENEFIT IN PRECLINICAL MODELS. In a rodent model of Parkinson’s, centrophenoxine treatment (100 mg/kg, i.p.) for 35 days significantly attenuated motor dysfunction, changes in dopamine levels, and lipid peroxidation [16].
Cardiovascular: UNKNOWN. Two studies, one in rats and another in aged guinea pigs, reported that centrophenoxine treatment (80mg/kg/day in guinea pigs and 100 mg/kg/day in the rats) decreased lipofuscin size and levels in the myocardium [17; 18]. Both studies suggested that centrophenoxine treatment resulted in facilitation of removal of lipofuscin via the capillaries. However, it is unclear how the decreased lipofuscin levels in the myocardium may contribute to heart function or cardiovascular diseases. In a retrospective analysis of 201 endomyocardial biopsies in adolescents and young adults, higher lipofuscin levels were correlated with the patient age and with improved cardiac compensation (better ejection fraction) [19]. Thus, even though lipofuscin levels are increased with aging, higher lipofuscin levels may be beneficial for heart function in this age group and patient population (heart failure or other conditions).

Safety: Although most clinical trials suggested that centrophenoxine is safe with no toxic side effects, a study with DMAE reported a few serious adverse events. It may also have teratogenic effects, so should be avoided by women of child-bearing age.

Types of evidence:
- 4 randomized controlled clinical trials with centrophenoxine
- 1 randomized controlled trial with DMAE
- 1 systematic review of randomized controlled trials testing cholinergic drugs in patients with tardive dyskinesia
- A few laboratory studies

Side effects with centrophenoxine are often mild and include nausea, headache, dizziness, gastrointestinal issues, and mild stimulant effects, which may disrupt sleep if taken late in the day.

There have been several double-blind randomized controlled trials that examined the effects of centrophenoxine. One in 63 mild-to-moderate Alzheimer’s patients noted that toxicity was “very low”, though no details were provided in the number of patients who experienced adverse events and their nature [6]. Another trial in 50 moderate Alzheimer’s disease patients reported that there were no signs of toxic side effects encountered during the trial and 3 dropouts were due to comorbidities that were not related to the treatment [5]. In a trial with head trauma patients, 8 out of 63 subjects experienced mild side effects: 2 thirst, 2 blurred vision, 1 nausea, 1 heartburn, 1 diarrhea, and 1 insomnia, though it is unclear whether these were related to the head injury or to centrophenoxine [4]. No abnormal changes were observed in laboratory tests, blood pressure, or pulse.
There was also a systematic review of 11 randomized controlled trials (total of 261 patients) testing various cholinergic treatments in patients with tardive dyskinesia [20]. They reported that there were no statistically significant differences between groups on leaving the study early; however, no details were provided on the types of adverse events reported or differences between drug and placebo groups. Only 1 randomized controlled trial examined centrophenoxine and the other 10 looked at choline, galantamine, donepezil, rivastigmine, and others. No deaths were reported in any of the trials.

**DMAE: POTENTIAL HARM.** Centrophenoxine is an ester of dimethylaminoethanol (DMAE) and an absorption enhancer. A double-blind randomized controlled trial of 242 prodromal Alzheimer’s patients reported that DMAE pyroglutamate treatment (V0191; 1,500 mg/day) for 24 weeks was associated with adverse events in 43.5% of people on the drug and 29.6% of people on placebo [7]. And 8.1% of people in the V0191 group and 4.8% in the placebo group had adverse events leading to discontinuation of the study drug. Most frequent adverse events were bronchitis (higher in placebo; 1.6% in V0191 and 4.0% in placebo), UTI, headache, and diarrhea. There were 3 serious adverse events: cardiorespiratory arrest, cardiac failure with fatal outcome, and grand mal convulsion in the V0191 group. They could not exclude the relationship between the events and V0191.

**Teratogenicity: POTENTIAL HARM.** Females of child-bearing age should avoid centrophenoxine as DMAE has been shown to produce neural tube defects in mouse embryos grown in vitro [21]. Embryos were unable to convert choline into phosphatidylcholine, which is critical for neural tube formation.

**Drug interactions:** Unknown. No entries were found in Drugs.com or WebMD.com. Centrophenoxine is contraindicated in people with severely high blood pressure [22].

**Sources and dosing:** Centrophenoxine is available as a supplement in capsules that contain 200-300 mg each. Clinical trials that tested the effects of centrophenoxine on cognitive functions have used daily doses of 1,200 mg in healthy elderly and doses of up to 2,000 mg in dementia patients [2; 3; 5; 6; 7].

Centrophenoxine has been marketed under the brand names Amipolen, Analux, Brenal, Cellative, Centrophenoxin, Cerebron, Cerutil, Closeste, Helfergin, Licidril, Lucidryl, Lutiaron, Marucotol, Proserout, Proseryl, and Ropoxyl. Centrophenoxine is also a component of Antagonic-Stress®, a combination therapy patented internationally for purported effects on managing stress, aging, and age-related diseases; the formulation also includes methionine, aspartate, fructose, vitamin B1, vitamin B6, nicotinic acid, magnesium, zinc, and sulfate [23]. Several reports were published between 1994 and 2004.
Research underway: Many studies of centrophenoxine were carried out in the 60s and 70s. There are no ongoing clinical trials with centrophenoxine in the US or Europe.

Search terms:
Pubmed, Google: centrophenoxine, meclofenoxate, Lucidril
- + cognitive, + memory, + Alzheimer’s, + ApoE, + clinical trial, + meta-analysis, + systematic review, + lifespan, + longevity, + anti-aging, + cardiovascular, + safety

Centrophenoxine, meclofenoxate, Lucidril:
- clinicaltrials.gov (0)
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- WebMD.com (0)
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