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.

Sodium phenylbutyrate (Buphenyl, 4-phenylbutyrate)

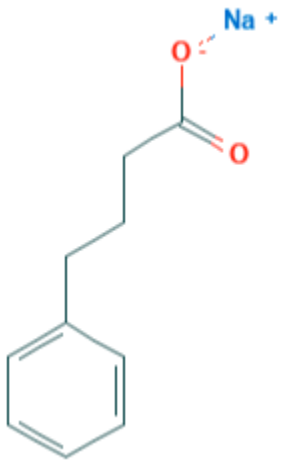
Evidence Summary

Sodium phenylbutyrate has shown efficacy in several animal studies, but potential side effects may limit its use for Alzheimer's patients.

Neuroprotective Benefit: Multiple preclinical studies suggest cognitive benefits, but evidence for changes in pathology are inconsistent.

Aging and related health concerns: Some evidence for benefits in preclinical models, but it is not convincing that it would be more beneficial than currently available drugs.

Safety: Sodium phenylbutyrate is associated with a number of mild side effects at doses used for neurodegenerative diseases, but larger studies are needed.

Availability: Oral drug as a prescription, Buphenyl	**Dose**: 9-13g/day used in clinical trials for neurodegenerative diseases	**Chemical formula**: $C_{10}H_{11}NaO_2$ **Molecular weight:** 186.2 g/mol  **Source:** PubChem
Half life: 45 minutes (1.3 hours for metabolite phenylacetate)	**BBB**: Possibly (Yes in animals, still unclear in humans)	
Clinical trials: One combination (with TUDCA) ongoing in ALS and one combination (with TUDCA) in Alzheimer's disease	**Observational studies**: None	

What is it?

Sodium phenylbutyrate is an oral medication approved for the treatment of hyperammonemia (it can act as an ammonia scavenger). It is metabolized in the liver and kidneys to produce phenylacetate, the bioactive form of the drug (Corbett et al, 2013). In addition to its ammonia scavenger activity, it has been reported to be a weak HDAC class I inhibitor and a small molecular chaperone (Wiley et al, 2010).

There are four classes of histone deacetylases (HDACs): class 1 (HDAC 1, 2, 3, and 8), class II (HDAC 4, 5, 6, 7, 9, and 10), class IV (HDAC 11), and class III (the sirtuins, 1-7). Class 1 HDACs are expressed ubiquitously and primarily located in the nucleus where they can remove acetyl groups off histones and silence gene transcription (Yoon and Eom, 2016; Govindaraajan et al, 2012). It is hypothesized that increased HDAC expression and/or activity with aging and in Alzheimer's disease may repress protein translation required for memory formation. Therefore, a class 1 HDAC inhibitor, such as sodium phenylbutyrate, may prevent the silencing of gene transcription.

Sodium phenylbutyrate has also been investigated as a chemical chaperone that can prevent misfolded protein aggregation and reduce endoplasmic reticulum (ER) stress. When misfolded proteins accumulate in the ER, the unfolded protein response (UPR) is activated. The UPR is a mechanism whereby the cell reduces global protein translation while increasing the translation of proteins that improve protein folding and degrade misfolded proteins. In situations where there is chronic UPR activation, the UPR may initiate apoptotic programs. Thus, sodium phenylbutyrate may be beneficial in conditions of chronic ER stress (Kolb et al, 2015).

Neuroprotective Benefit: Multiple preclinical studies suggest cognitive benefits, but evidence for changes in pathology are inconsistent.

Types of evidence:

- 4 preclinical Alzheimer's mouse studies
- One open-label clinical trial in ALS patients
- One preclinical ALS mouse study
- One preclinical stroke study

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?
None

Human research to suggest benefits to patients with dementia:
None

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

Alzheimer's
In vitro studies suggest that sodium phenylbutyrate increases the expression of BDNF and neurotrophin-3 (NT-3) in astrocytes via the protein kinase C (PKC)-cAMP-response element-binding protein (CREB) pathway, increases the expression synaptic proteins, such as the AMPA receptor subunit GluA1 and PSD-95, and decreases the production of pro-inflammatory cytokines (Roy et al, 2012; Corbett et al, 2013). *In vivo* studies in an Alzheimer's mouse model confirm increased expression of BDNF (Corbett et al, 2013).

Early treatment

Phenylbutyric acid given before the onset of pathology decreased amyloid plaque pathology in the cortex (but not the hippocampus) but did not change levels of Aβ42 or synaptic proteins PSD95 or synaptotagmin 1. It also increased alpha secretases (ADAM10 and TACE), upregulated glutamate receptor levels, and improved cognition (Wiley et al, 2011). In another animal model, treatment at the beginning of the accumulation of amyloid pathology (5 weeks, 200mg/kg/day) increased synaptic spine density (Ricobaraz et al, 2012).

Late treatment

Sodium phenylbutyrate, given after the initiation of amyloid plaque pathology, was shown to improve cognition but not alter astrocyte inflammation, in an Alzheimer's animal model (100mg/kg/day for 30 days) (Corbett et al, 2013). Another study reported improvements in cognition, a reduction in ptau, an increase in synaptic spine density, an increase in synaptic proteins (including PSD95 and GluA1), and a reduction in proteins indicative of ER stress, but no change in amyloid levels (Ricobaraz et al, 2009; Ricobaraz et al, 2012).

The brain penetrance of sodium phenylbutyrate in humans is unclear. Two patients with adrenoeukodystrophy were given sodium phenylbutyrate (20g/day) for 11 days. Sodium phenylbutyrate could only be detected in the CSF and brain (using in vivo MRS) in only one of the patients at concentrations that corresponded to 0.25 and 0.57mM in the white matter and CSF, respectively (Barker et al, 2000). However, a primate study in three animals reported that after an infusion of phenylbutyrate (130mg/kg), phenylbutyrate was found in the CSF with a CSF:plasma ratio of 41% (Berg et al, 2000).

Stroke

In a diabetic rat model of ischemia, treatment with sodium phenylbutyrate decreased infarct volume, reduced cell death and improved functional recovery, presumably due to a reduction in ER stress (Srinivasan and Sharma, 2011).

ALS

Sodium phenylbutyrate combined with riluzole increase lifespan in an ALS mouse model by 21.5%, which was better that either drug alone (riluzole 7.5%; sodium phenylbutyrate 12.8%) (Del Signore et al, 2009). In an open label, phase 2 clinical study in patients with ALS, 40 individuals were treated with doses of sodium phenylbutyrate from 9g/day up to 21g/day. 26 patients completed the dose escalation. The adverse events that led to drop-outs were considered to be unrelated or possibly related to the study treatment. Adverse events including falls, dizziness, diarrhea, edema, dry mouth, nausea, and rash

were higher than a placebo cohort (no information on where the placebo cohort came from). There were no increases in laboratory values, EKGs or vital signs. The greatest increase in histone acetylation occurred at the lowest dose (9g/day) but did not reach the levels of normal individuals – the authors were unclear why an increase in histone acetylation was highest at the lowest dose, though they mention an inverse dose response in gene expression in a previous Huntington's disease trial (12g/day) (Cudkowicz et al, 2009; Horgarth et al, 2007).

APOE4 interactions:
None reported

Aging and related health concerns: Some evidence for benefits in preclinical models, but it is not convincing that it would be more beneficial than currently available drugs.

Types of evidence:

- One drosophila lifespan study
- Three preclinical cardiovascular studies
- One clinical study in diabetic patients
- One review of cancer studies

Lifespan
Sodium phenylbutyrate increased mean and maximum lifespan in drosophila by 36% and 52%, respectively. Also, brief treatment for the first 12 days of life or after the first 12 days of life also increase mean and maximum lifespan (Kang et al, 2002).

Cardiovascular disease
In a mouse model of myocardial ischemia/reperfusion injury, acute sodium phenylbutyrate treatment (200mg/kg) reduced cardiac cell death, reduced infarct volume, reduced markers of the unfolded protein response (UPR), and improved cardiac function 21 days after injury (Takatori et al, 2017). In an animal model of pulmonary arterial hypertension, sodium phenylbutyrate, given in either a preventative or treatment manner, reduced pulmonary arterial pressure, reduced vascular remodeling, and reduced markers of the UPR (Wu et al, 2016). However, these effects may be context dependent. In a mouse model of cardiac dysfunction due to pressure overload (transverse aortic constriction, resulting in blood pressure ~225/90), sodium phenylbutyrate (100mg/kg over 6 weeks) increased mortality, increased pulmonary congestion, exacerbated cardiac remodeling, and reduced cardiac function (Ma et al, 2016).

Diabetes

In a small study of 8 overweight non-diabetic men, 2 week treatment with sodium phenylbutyrate (7.5g/day) partially ameliorated lipid-infusion induction of insulin resistance and partially prevented lipid-induced B-cell dysfunction (Xiao et al, 2011).

Cancer

Sodium phenylbutyrate has been investigated as a potential anti-cancer drug in a variety of *in vivo* cancer models and *in vitro* cancer studies (Iannitti and Palmieri, 2011). Some early phase safety clinical trials were conducted in different malignancies, but there are no ongoing clinical trials. HDAC inhibitors as a class are used for lymphomas and myelomas with five currently approved drugs on the market (vorinostat, romidepsin, chidamide, panobinostat, belinostat).

Safety: Sodium phenylbutyrate is associated with a number of mild side effects at doses used for neurodegenerative diseases, but larger studies are needed. It is unclear whether lower doses would be beneficial for Alzheimer's disease.

Types of evidence:

- Two open label studies, one in ALS and one in Huntington's disease

In an open label, phase 2 clinical study in patients with ALS, 40 individuals were treated with doses of sodium phenylbutyrate from 9g/day up to 21g/day. Adverse events including falls, dizziness, diarrhea, edema, dry mouth, nausea, and rash were higher than a placebo cohort (no information on where the placebo cohort came from). There were no increases in laboratory values, EKGs or vital signs (Cudkowicz et al, 2009). In a dose escalating study in 24 patients with Huntington's disease, 15g/d was reported to be the maximum tolerated dose, with side effects including vomiting, lightheadedness, confusion, and gate instability (Horgarth et al, 2007).

Given the gastrointestinal side effects and increased risk of falls seen in these studies, it is not clear whether it is appropriate for an Alzheimer's population at these doses.

Other side effects on drugs.com include change in the frequency of breathing, irregular menstruation (up to 23% of individuals), decreased appetite (4%) lower back or stomach pain, mood changes, muscle pain, nausea, nervousness, edema, unpleasant taste, and unusual tiredness (see list here). It is reported

that sodium phenylbutyrate should be taken along with a low-protein diet, but it is not clear if this is only for its intended population (children with hyperammonemia).

***Drug interactions*:**
Sodium phenylbutyrate may interact with other HDAC 1 inhibitors, such as vorinostat, valproic acid, or sodium butyrate. Other major interactions on drugs.com include ampicillin and colchicine. See full list (here). A potential interaction on drugs.com is mentioned for neuropathy though these are seen in less than 2% of patients (here and here).

Sources and dosing:
Sodium phenylbutyrate is available as an oral medication (Buphenyl) with a prescription from Horizon Pharma. It has been reported to taste very bitter. Maximum tolerated doses used in adult humans with neurodegenerative disease were reported from 9-15g/day. Recommended doses for individuals weighing over 20kg is 9.9-13 g/m2/day (~22-28g/day for 90kg person who is 6'8'')

Research underway:
A combination trial of sodium phenylbutyrate and TUDCA are currently ongoing in ALS and Alzheimer's disease. ADDF is currently funding the Alzheimer's trials. It is also being investigated for cystic fibrosis.

Search terms:

Pubmed
sodium phenylbutyrate +
alzheimer + longevity +
cardiovascular + atherosclerosis +
safety

sodium phenylbutyrate (title)
sodium phenylbutyrate [clinical
trials]

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If you have suggestions for drugs, drugs-in-development, supplements, nutraceuticals, or food/drink with neuroprotective properties that warrant in-depth reviews by ADDF's Aging and Alzheimer's Prevention Program, please contact INFO@alzdiscovery.org. To view our official ratings, visit Cognitive Vitality's Rating page.