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.

Vorinostat (Zolinza)

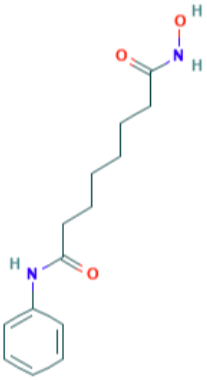
Evidence Summary

Vorinostat is an HDAC inhibitor currently used for cutaneous T-cell lymphoma. Although epigenetic drugs are of potential interest for Alzheimer's disease, vorinostat's side effects may prohibit its use in this population.

Neuroprotective Benefit: Vorinostat has shown efficacy in animal models, but probably will not be beneficial at safe doses for humans.

Aging and related health concerns: Vorinostat is beneficial for cutaneous T-cell lymphoma and possibly other hematological cancers, but has not been tested for other age-related indications.

Safety: Vorinostat at current doses is associated with side effects such as diarrhea, thrombocytopenia, and neutropenia.

Availability: As a prescription for cutaneous T-cell lymphoma	**Dose**: For cancer: 300-400mg/day usually in an on-off format (e.g. 3 days on, 7 days off or 14 out of 21 days – dosing varies depending on trial). 200 to 400 mg on a 3 day on/4 day off schedule for Niemann-Pick disease type C. Currently in a maximum tolerated dose study for Alzheimer's disease.	**Chemical formula**: $C_{14}H_{20}N_2O_3$ **MW**: 264.32 g/mol  **Source:** Pubchem
Half life: 2 hours	**BBB**: Penetrant in animals, but possibly with low efficiency	
Clinical trials: 110 completed phase 1 or 2 trials in various cancers; 3 completed phase 3 trials in cancer; 1 completed phase 1/2 study in Niemann-Pick Disease. 70 ongoing clinical trials – most for cancer; 1 phase 1 trial for Alzheimer's; 1 phase 1 trial for schizophrenia	**Observational studies**: 0	

What is it?

There are four classes of histone deacetylases (HDACs): class I (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. Class II HDACs are expressed in a tissue-specific manner and shuttle from the nucleus to the cytoplasm (Yoon and Eom, 2016). Class 1 HDACs modify histones by removing acetyl groups, while class II HDACs modify other substrates (Govindaraajan et al, 2012).

Histone acetytransferases (HATs) add an acetyl group to lysine residues on histones causing the chromatin structure to relax and allowing gene transcription to occur. This process is reversed by class 1 HDACs which remove the acetyl group and silence gene transcription. Vorinostat is a drug approved for patients with treatment-resistant advanced cutaneous T-cell lymphoma (CTCL). It is an inhibitor of class I HDACs (HDAC 1, 2, 3, 8), and a class IIb HDAC (HDAC 6). Gene transcription is important for memory formation, and class I HDAC inhibitors, such as vorinostat, are being investigated for Alzheimer's disease. A major substrate of HDAC 6 is a-tubulin, and it has been implicated in the regulation of cytoskeleton stability, intracellular transport and cell motility.

Neuroprotective Benefit: Vorinostat has shown efficacy in animal models, but probably will not be beneficial at safe doses for humans.

Types of evidence:

- 2 studies of HDAC expression in Alzheimer's patients
- 4 preclinical studies of vorinostat in Alzheimer's animal models
- 5 other preclinical animal studies

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

Human research to suggest benefits to patients with dementia:
Graff et al (2012) reported increased levels of HDAC2, but not HDAC1 or HDAC3, in post-mortem Alzheimer's tissue. On the other hand, Mastroeni et al (2010) reported a decrease in HDAC2 positive neurons in the entorhinal cortex of Alzheimer's patients (from 92% in controls to 13% in Alzheimer's patients).

Mechanisms of action for neuroprotection identified from laboratory and clinical research:
Treatment for 2-3 weeks with three different HDAC inhibitors (sodium valproate, sodium butyrate, and vorinostat) reversed fear memory deficits in an Alzheimer's mouse model (Kilgore et al, 2010). Another study in an Alzheimer's mouse model reported a decrease in expression of genes related to synaptic plasticity which was partially restored after treatment with vorinostat. Vorinostat improved cognition in the Alzheimer's mice but did not change plaque load (Benito et al, 2015). In contrast, aged animals were associated with an increase in expression of inflammatory genes and a decrease in expression of

metabolic and "learning-related" genes. Again, treatment with vorinostat partially restored gene expression, long-term potentiation, and improved cognition (Peleg et al, 2010; Benito et al, 2015)

On the other hand, Hanson et al (2013) reported that although vorinostat increased long-term potentiation (LTP) in vitro (while impairing long-term depression, LTD), it failed to rescue memory dysfunction in an Alzheimer's animal model. Furthermore, they reported low brain concentrations of vorinostat, and that it was a substrate for the brain efflux transporters Pgp and Bcrp1. Notably, Hanson et al (2013) and Kilgore et a (2010) gave intraperitoneal injections of vorinostat while Peleg et al (2010) gave intracerebral injections and Benito et al (2015) dissolved it in B-cyclodextrin, a molecule that increases solubility and bioavailability.

Vorinostat also improved cognition and improved insulin resistance in high-fat diet fed mice (Sharma and Taliyan, 2016).

In a genetic Alzheimer's model crossed with an HDAC 6 knockout line, Govindarajan et al (2012) reported that plaque load did not change but cognition improved. They reported that eliminating HDAC 6 made neurons resistant to beta-amyloid-mediated impairment of mitochondrial trafficking. On the other hand, Guan et al (2009) reported no cognitive improvement with an HDAC 6 specific inhibitor.

HDAC inhibitors as a class have shown benefits in a number of Alzheimer's and aged animal models (Graff and Tsai, 2013). Sodium butyrate and sodium phenylbutyrate are class 1 HDAC inhibitors while vorinostat inhibits class I HDACs and HDAC 6.

Since chronic pan-HDAC inhibition may cause side-effects, another strategy being pursued is to combine low-dose vorinostat with tadalafil since they may have complementary effects (PDE5 inhibitors increase cellular cGMP which can activate genes important for synapse formation). Cuadrado-Tejedor et al (2015) tested low-dose tadalafil and low-dose vorinostat in an Alzheimer's animal model. *In vitro* studies suggested that the combination increased histone acetylation more than each drug individually, and that combination treatment increased LTP in Alzheimer's animal hippocampal slices more than individual treatments alone. In an Alzheimer's animal model, 2 weeks of low-dose combination treatment (tadalafil 1mg/kg; vorinostat 12.5mg/kg) improved hippocampal memory, increased hippocampal spine density, reduced beta-amyloid levels, and decreased ptau levels more than each treatment alone. Both drugs crossed the blood brain barrier, with brain/plasma ratios of 11% (tadalafil) and 5.5% (vorinostat) which corresponded to effective brain concentration of 30 and 345.5nmol/kg,

respectively. Similar results were reported from the same group with a novel dual PDE5/HDAC inhibitor (Cuadrado-Tejedor et al, 2017).

However, other groups think that developing HDAC 2-specific inhibitors may be beneficial in Alzheimer's disease without the side-effects of pan-HDAC inhibitors. siRNA-mediated downregulation of HDAC 2 in an Alzheimer's animal model restored cognition (Graff et al, 2012), and vorinostat failed to further improve cognition in HDAC 2 knockout mice (Fischer et al, 2014; Guan et al (2009)). This suggests that inhibiting HDAC 2 alone may provide memory benefits in Alzheimer's disease without the side effects associated with vorinostat.

APOE4 interactions: None reported

Aging and related health concerns: Vorinostat is beneficial for cutaneous T-cell lymphoma and possibly other hematological cancers, but has not been tested for other age-related indications.

Types of evidence:

- 1 study in drosophila on lifespan
- 1 in-vitro study in human chondrocytes
- Many clinical studies in cancer, approved for cutaneous T-cell lymphoma

In a drosophila model, sodium butyrate (an HDAC 1 inhibitor) decreased lifespan when given throughout life but increased it when given later in life (during the senescence stage). Vorinostat slightly increased lifespan when given later in life (it was never given throughout lifespan). The authors speculate that use earlier in life could negatively affect normal epigenetic modifications but may be beneficial later in life when there are detrimental epigenetic modifications (McDonald et al, 2013). One study reported that vorinostat blocked IL-1B-induced expression of MMP-13 and TNFα in human chondrocytes, suggesting a potential benefit for osteoarthritis – though further research is needed (Makki and Haggi, 2016).

Cancer:
Vorinostat is currently approved for treatment-resistant cutaneous T-cell lymphoma. It is currently in clinical trials for several other cancers – mostly hematological.

Safety: Vorinostat at current doses is associated with side effects such as diarrhea, thrombocytopenia, and neutropenia.

Types of evidence:

- 1 review of clinical trial evidence
- 1 report of long-term use

Vorinostat is associated with several side effects in patients with CTCL or hematologic malignancies. It is commonly given intermittently (e.g. 3 days on, 4 days off; 14 days on, 7 days off). Common treatment-related adverse events in clinical studies of patients with hematologic malignancies given the normal dose of vorinostat (400mg/day) include diarrhea (75%), nausea (61%), fatigue (60%), thrombocytopenia (48%), hyperglycemia (40%), vomiting (38%), anorexia (36%), anemia (32%), neutropenia (31%) among others (Duvic and Dimopoulos, 2016).

The only long-term study followed 6 patients over 2 years and reported common adverse events diarrhea (100%), nausea (83%), fatigue (67%), and alopecia (50%). Serious adverse events included anorexia, increased creatinine phosphokinase, pulmonary embolism, rash, and thrombocytopenia (all 17% or 1/6 of patients) (Duvic et al, 2009). It is not clear what the safety profile would be of low-dose vorinostat or in non-cancer patients.

One open-label study in Niemann Pick's disease type C (results at clinicaltrials.gov) treated patients for 3 months at 200mg and 3 months at 400mg. All patients tolerated it. Serious adverse events included vomiting (1/12), infections (2/12), CSF leakage (2/12), increased liver tests (1/12), pneumonia (1/12). Other adverse events included gastrointestinal disorders (9/12), fatigue (4/12), infections (8/12), nervous system disorders (14/12 – some patients had more than 1), among others. Note that this was not placebo controlled, so it is not clear which effects were due to vorinostat or NPC.

Other potential side effects are discussed at drugs.com.

Drug interactions:
Major drug interactions from drugs.com include valproic acid (another HDAC inhibitor) and thalidomide (drugs.com). Presumably there would be interactions with other HDAC inhibitors such as sodium butyrate, sodium phenylbutyrate, and trichostatin A.

There are a number of other potential moderate interactions including metformin, insulin, and vitamin E (drugs.com).

Sources and dosing:
For cancer: 300-400mg/day usually in an on-off format (e.g. 3 days on, 7 days off or 14 out of 21 days – varies depending on trial). 200 and 400 mg on a 3 day on/4 day off schedule for Niemann-Pick disease type C.

Research underway:
There is maximum tolerated dose study in Alzheimer's patients (NCT03056495). It is also being tested in ~65 cancer studies (link).

Search terms:
Pubmed:
vorinostat + alzheimer, aging, cardiovascular
HDAC + alzheimer, cognitive aging
suberoylanilide hydroxamic acid + alzheimer
vorinostat + safety

Clinicaltrials.gov:
- vorinostat