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.

Nitazoxanide

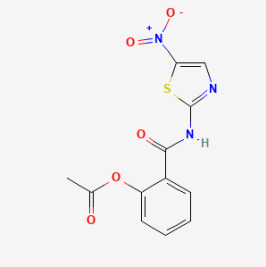
Evidence Summary

Nitazoxanide is an effective antiparasitic and may have broad-spectrum antipathogenic actions. Initial preclinical data suggest potential use as autophagy, inflammation, or mitochondrial modulator.

Neuroprotective Benefit: Nitazoxanide may stimulate autophagy and/or modulate mitochondrial function and has been tested in some AD animal models. However, nitazoxanide has not been investigated in humans for any neuroprotective role.

Aging and related health concerns: Nitazoxanide has been trialed in humans for treatment of infectious diseases that are particularly dangerous in older adults. However, these trials have not found clear efficacy of nitazoxanide treatment.

Safety: Trials of nitazoxanide often find no increase in adverse events or increases only in gastrointestinal complaints. It is often termed 'safe and tolerable', but published data on large trials or observational studies, especially in healthy populations, is lacking.

Availability: Rx	**Dose**: For parasitic infection, 500 mg of nitazoxanide is taken by mouth twice a day for 3 days.	**Chemical formula:** $C_{12}H_9N_3O_5S$ **MW**: 307.28 g/mol  Source: PubChem
Half-life: 6 minutes; active metabolites have variable half life of approximately 1-7 hours based on food intake and whether it is a single or repeated dose	**BBB**: Poor penetrance	
Clinical trials: Largest meta-analysis included 1,514 participants in RCTs	**Observational studies**: Few observational studies were identified; most were open label prospective trials of up to approximately 100 subjects	

What is it?

Nitazoxanide is a synthetic broad-spectrum anti-parasitic thiazolide. Upon oral administration, nitazoxanide is rapidly converted to tizoxanide, its active metabolite. Nitazoxanide is a first line treatment for protozoal infections such as cryptosporidiosis and giardiasis. It has been investigated for several other infectious diseases. Clinical trials have indicated potential efficacy for other infections such as parasitic worms, bacterial infections such as *C. diff* and *H. pylori*, and viral infections like influenza, among others (PubChem; Rossignol, 2014).

There are several different mechanisms by which nitazoxanide may exert its anti-parasitic effects. The most accepted is that it inhibits a crucial metabolic enzyme, pyruvate/ferredoxin oxoreductase (PFOR) in anaerobic organisms such as certain protists. PFOR is necessary for metabolism in these species. Other potential mechanisms with at least some preclinical evidence include inhibition of viral replication,

disruption of viral infectivity factors, mitochondrial perturbations, and modulating host immunity, such as by stimulation of macrophage autophagy or induction of type I interferon responses (Shakya et al., 2018, Jasenosky et al., 2019).

Nitazoxanide has been investigated for use outside of infectious indications, and studies looking to repurpose drugs have identified nitazoxanide as a potential treatment for other conditions. Nitazoxanide has been suggested to be a PPARγ agonist and thus a potential treatment for type 2 diabetes (T2D); preclinical work in rats has suggested the nitazoxanide may help improve blood glucose levels and insulin sensitivity (Kovacs et al., 2013). The immunomodulatory effects of nitazoxanide in peripheral blood cells from patients with T2D have also been explored in one study (Castillo-Salazar et al., 2021). A few screens of FDA-approved compounds have also identified nitazoxanide as a potential treatment for other conditions such as stroke, AD, and Parkinson's disease (PD) through its potential autophagy-stimulating and mitochondrial-modulating properties (Ma et al., 2023, Lam et al., 2012, Fan et al., 2019, Amireddy et al., 2017, Haneczok et al., 2023).

Neuroprotective Benefit: Nitazoxanide may stimulate autophagy and/or modulate mitochondrial function and has been tested in some AD animal models. However, nitazoxanide has not been investigated in humans for any neuroprotective role.

Types of evidence:

- 9 laboratory studies

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

No studies have evaluated the effects of nitazoxanide on cognition or on potential prevention of dementia or decline.

Human research to suggest benefits to patients with dementia:

No studies have evaluated the potential use of nitazoxanide in patients with dementia.

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

Nitazoxanide has not been tested for efficacy in prevention or treatment of dementia in humans, and it is in early preclinical stages. The drug has been identified in several papers as an autophagy stimulator.

A 2012 paper exploring novel treatments for tuberculosis examined the effect of nitazoxanide on autophagy, after an earlier report had found that a chemically similar drug had stimulated autophagy in a cell-based screen (Balgi et al., 2009). The authors of the 2012 paper found that nitazoxanide inhibits NQO1 and mTORC1 signaling, thereby stimulating autophagy, in cell culture models (Lam et al., 2012). Separately, a 2019 paper also independently identified nitazoxanide in a cell-based screen of FDA-approved library to find autophagy stimulators. This group found that nitazoxanide treatment promoted clearance of secreted Aβ40 and Aβ42 in culture and reduced plaque burden in a mouse model of AD, as well as reduced tau hyperphosphorylation in cell and animal models. Their experiments indicated that nitazoxanide stimulated autophagy in cell and animal models by inhibiting P13K / AKT / mTOR and potentially through inhibition of NQO1 / mTOR signaling. Treatment with nitazoxanide improved learning and memory impairments in a mouse model of AD (Fan et al., 2019).

Another preclinical paper also found that nitazoxanide treatment in cell culture increased autophagy through activation of the AMPK/JNK pathway (Amireddy et al., 2023). A companion paper from the same group synthesized and investigated nitazoxanide-based derivatives that might have increased potency and/or improved blood-brain barrier (BBB) penetrance, as their experiments indicated that nitazoxanide had poor BBB permeability (Li et al., 2019).

Another potential mechanism of action is through mitochondrial modulation. Nitazoxanide treatment may have a mild uncoupling effect in mitochondria, and may be able to mitigate the effects of mitochondrial toxins on markers of mitochondrial health and function such as ATP and ROS production and membrane potential, as well as cell death in cell and animal models of Parkinson's disease (PD) (Amireddy et al., 2017). A 2023 paper utilized machine learning to screen FDA-approved compounds for their potential for increasing the expression of PINK1, an important mitochondrial quality control protein that is mutated in certain familial forms of PD. The machine learning model identified nitazoxanide as a top drug candidate for enhancing PINK1 expression (Haneczok et al., 2023).

APOE4 interactions:

It is not known whether nitazoxanide has any differential effects based on APOE status.

Aging and related health concerns: Nitazoxanide has been trialed in humans for treatment of infectious diseases that are particularly dangerous in older adults. However, these trials have not found clear efficacy of nitazoxanide treatment.

Types of evidence:

- 2 systematic reviews and meta-analyses
- 2 randomized controlled clinical trials
- 1 open label study
- 2 reviews
- 3 laboratory studies

Nitazoxanide is primarily used for parasitic infections that infect people of all ages, but it has also been trialed for efficacy against age-related infectious diseases such as influenza and COVID-19.

COVID19: NO PROVEN CLINICAL BENEFIT

Due in part to its proposed pan-antiviral mechanisms of action, such as suppressing viral replication, interference with viral protein production / maturation, and modulating host interferon responses, nitazoxanide was investigated for efficacy against COVID-19. Two systematic reviews and meta-analyses were published in 2022, both looking at the efficacy and safety of nitazoxanide as a treatment for COVID-19.

Abuelazm et al., 2022 included 6 RCTs comparing nitazoxanide to placebo in their meta-analysis, comprising 1,412 participants with COVID-19. Doses ranged from 1,200 mg to 3,000 mg per day, for 5 to 14 days. The authors found that compared to placebo, treatment with nitazoxanide was associated with increased viral clearance (RR=1.30; 95% CI 1.08 to 1.56, p = 0.006) and decreased oxygen requirements (RR=0.48; 95% CI 0.39 to 0.59, p = 0.00001). However, they did not detect a difference in clinical resolution, ICU admission, or mortality between placebo and nitazoxanide. They include several limitations of their work, including low-quality evidence as assessed by GRADE.

Weng et al., 2022 analyzed 5 RCTs and included 1,351 participants with COVID-19; the RCTs they included were all also included by Abuelazm and colleagues. Like Abuelazm et al., Weng and colleagues also did not find a statistically significant difference in clinical response mortality but did find that nitazoxanide was associated with higher viral eradication rate than placebo (risk difference=0.09; 95% CI 0.01 to 0.17; p=0.03).

Influenza POTENTIAL SYMPOMATIC BENEFIT

A randomized double-blinded Phase 2b/3 trial of nitazoxanide safety and efficacy in 624 participants with acute uncomplicated influenza was published in 2014. Participants were 12-65 years of age and received either placebo, 300 mg of nitazoxanide twice a day, or 600 mg of nitazoxanide twice a day, all for 5 days, and then followed for 28 days. The primary endpoint was time from first dose to alleviation of symptoms in patients with confirmed influenza. Of the 624 participants, 257 had confirmed influenza. Given that the medication was to be given within 48 hours of symptom onset, it was necessary to treat participants before confirmation of underlying viral pathogen.

The authors report that the median duration of symptoms in the confirmed influenza cases was 116.7 hours (95% CI 108.1 to 122.1, n=89) for the placebo group, 109.1 hours (95% CI 96.1 to 129.5, p=0.52, n=89) for the 300 mg group, and 95.5 hours (95% CI 84.0 to 108.0; p=0.0084, n=79) for those receiving 600 mg nitazoxanide. When they included all treated participants, there was a significant decrease in time from first dose to alleviation of symptoms in the 600 mg nitazoxanide group (94.9, 95% CI 86.1 to 106.3, p=0.0052) compared to placebo (108.2 hours, 95% CI 104.3 to 119.0) (Haffizulla et al., 2014).

A follow-up Phase 3 study of 1,941 patients to compare the efficacy of nitazoxanide and/or oseltamivir in comparison to placebo in treating acute uncomplicated influenza was completed in 2015. However, the results have not been published.

Safety: Trials of nitazoxanide often find no increase in adverse events or increases only in gastrointestinal complaints and is often termed 'safe and tolerable'. However, published data on large trials or observational studies, especially in healthy populations, is lacking.

Types of evidence:

- 1 systematic review
- 4 randomized controlled clinical trials
- 1 open label study
- 6 reviews
- 3 laboratory studies

It is estimated that nitazoxanide has been used to treat millions of people worldwide in the more than 2 decades since nitazoxanide was introduced (Rossignol, 2014), though published safety data appears limited to multiple clinical trials on the order of dozens to a thousand or so participants. While largely not collected into meta-analyses, the repeated finding in many is no significantly increased rate of adverse events with nitazoxanide compared to placebo or active comparator, besides for potentially increased rate of gastrointestinal disturbances. Some examples include but are not limited to: Gamino-Arroyo et al., 2019 (257 participants taking nitazoxanide or placebo for flu-like symptoms in the hospital); Haffizulla et al., 2014 (624 participants taking placebo or one of two doses of nitazoxanide for flu); Rossignol et al., 2006 (55 participants taking placebo or nitazoxanide for treatment of cryptosporidiosis); Sokhela et al., 2022 (828 healthy participants with no treatment, nitazoxanide treatment, or sofosbuvir/daclatasvir treatment for potential prevention of COVID-19);

A review of safety data from trials of nitazoxanide for treatment of acute infections included 9 studies and 1,514 subjects. Approximately 2/3 of those participants were in placebo-controlled studies, and 1/3 were in studies comparing nitazoxanide to an active comparator. The authors did not find any significant difference in proportion of adverse events or serious adverse events. They saw a trend towards increase of GI adverse events in those treated with nitazoxanide compared to placebo, but this did not reach statistical significance. One included ascending dose study reported an increase with GI adverse events with increasing dose (Pepperrell et al., 2020).

A 2022 meta-analysis from Abuelazm and colleagues assessed the efficacy and safety of nitazoxanide in treating COVID-19. They reported that only incidence of vomiting was significantly associated with nitazoxanide treatment; the incidence of at least one adverse event was also not statistically significantly different between nitazoxanide and placebo. They include several limitations of their work, including low-quality evidence as assessed by GRADE (Abuelazm et al., 2022). A meta-analysis of many of the same studies similarly found similar risk of any adverse event (Weng et al., 2022).

A small open-label study tested a high dose of nitazoxanide of 1,500 mg twice daily for 7 days in 14 healthy adults. Gastrointestinal disturbances were the most common adverse events; all were mild or moderate, and resolved upon discontinuation of the drug (Walker et al., 2021).

Studies have reported chromaturia (yellow discoloration of urine) in subjects receiving nitazoxanide. Yellow discoloration of the sclera was also observed. There was no clinically significant elevation of bilirubin reported (Pepperrell et al., 2020; Walker et al., 2021).

Other less common side effects (reported in less than 1% of trial participants) may include headache, dizziness, rash, changes in appetite, dry mouth, fever, enlarged salivary glands, fatigue, skin itching, sweating, elevated creatinine levels, and elevated ALT levels, among others (Fox & Saravoltz, 2005).

Drug interactions:

Nitazoxanide is known to interact with 22 drugs through competition for plasma protein binding sites. These drugs include warfarin, valproic acid, diazepam, and lorazepam. Nitazoxanide is thought to increase blood levels and therefore effects of the drugs with which it interacts (Drugs.com).

Alinia oral suspension contains enough sugar content to be considered when administered to diabetic patients. Nitazoxanide has also not been studied in patients with impaired renal and/or hepatic function, and should be used with caution in these populations (Drugs.com). While nitazoxanide is not thought to be unsafe in immunocompromised individuals, it is also unclear whether it is effective in immunocompromised patients. Nitazoxanide is also not approved for infants under 1 year of age (CDC).

Research underway:

There are 18 studies registered on ClinicalTrials.gov that are investigating nitazoxanide. Almost all are testing nitazoxanide for use in different infectious disease contexts.

One study, NCT05894954, is investigating whether a precision medicine approach can mitigate the decline of cognitive function in patients with mild cognitive impairment or early dementia. The 9-month long study aims to enroll 72 patients who will be randomized to standard of care or to the personalized medicine approach. The personalized medicine approach will involve a battery of testing to create a personalized treatment plan including diet, sleep habits, stress management, and mental and physical exercise. One of the many potential treatments in the intervention group is treatment with nitazoxanide, if applicable. The study is scheduled to start recruitment in the near future.

Search terms:

Pubmed, Google: nitazoxanide, tizoxanide

- Dementia, Alzheimer's, APOE4, safety, mitochondria, diabetes, stroke, inflammation, observational

Websites visited for nitazoxanide:

- Clinicaltrials.gov
- Drugs.com
- WebMD.com
- PubChem
- DrugBank.ca
- Cafepharma

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