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.

BISPHOSPHONATES

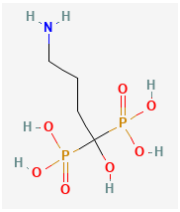
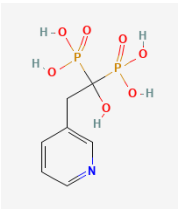
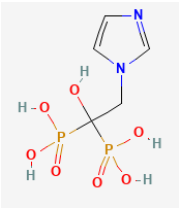
Bisphosphonate Evidence Summary

Bisphosphonates improve outcomes only for specific populations of patients, such as those with osteoporosis or cancers that metastasize to bone. Serious side effects include osteonecrosis of the jaw.

Neuroprotective Benefit: Observational research has suggested a lower dementia risk in osteoporosis patients treated with bisphosphonates. There is currently no direct evidence that bisphosphonates are neuroprotective in healthy populations.

Aging and related health concerns: Bisphosphonates decrease risk of fracture in osteoporosis patients and patients with Paget's disease of the bone. They also reduce bone metastases and provide survival benefit for cancer subtypes that spread to the bone.

Safety: Serious side effects are rare but can be more common at higher doses or long-term treatment and include osteonecrosis of the jaw, atrial fibrillation, hypocalcemia, severe musculoskeletal pain, atypical stress fractures of the femur, and eye inflammation.

Availability: Rx	**Dose**: Alendronate (oral): 10 mg/day or 70 mg/week Risedronate (oral): 5 mg/ day or 35 mg/week or 150 mg/month Zoledronate (oral): 5 mg/year *these doses are for osteoporosis	**Chemical formula and MW**: Alendronate: $C_4H_{13}NO_7P_2$; 249.10  Risedronate $C_7H_{11}NO_7P_2$ 283.11  Zoledronate $C_5H_{10}N_2O_7P_2$ 272.09  Source: PubChem
Half-life: Terminal elimination half-life can range from 37 hours to 10.5 years based on specific drug and patient, as bone releases drug during bone remodeling	**BBB**: Mixed evidence. Animal biodistribution studies (rats, rabbits, dogs) indicate very little to no BBB permeability. However, certain prediction tools indicate bisphosphonates may be able to cross the BBB.	
Clinical trials: Largest meta-analysis has 43,000 patients using bisphosphonates.	**Observational studies**: Many observational studies totaling tens of thousands of patients.	

What is it?

Bisphosphonates were originally developed to treat age-related loss of bone density (osteoporosis) and is used as first-line treatments for osteoporosis. Bisphosphonates selectively bind to bone, particularly areas of active bone remodeling (Drake et al., 2008). There are two classes of bisphosphonates, both of which kill osteoclasts, the cells responsible for bone resorption. Non-nitrogenous bisphosphates such as etidronate and clodronate induce osteoclast death by being incorporated into ATP and rendering that ATP unusable (Drake et al., 2008). Nitrogenous (amino) bisphosphonates such as alendronate, risedronate, and zoledronate, on the other hand, prevent prenyl group production by inhibiting enzymes necessary for prenyl group synthesis (Drake et al., 2008; Itzstein et al., 2011). Prenyl groups are added to

proteins to target them to the cell membrane for proper functioning. The inhibition of prenyl group production by nitrogenous bisphosphonates disrupts membrane protein trafficking and cytoskeletal dynamics in osteoclasts and ultimately inhibits the HMG-CoA reductase pathway, resulting in cell death.

The non-nitrogenous bisphosphonates are far less potent with more side effects, and so are not commonly prescribed or studied. This report will therefore focus on nitrogenous bisphosphonates unless otherwise noted.

Neuroprotective Benefit: Observational research has suggested a lower dementia risk in osteoporosis patients treated with bisphosphonates. There is currently no direct evidence that bisphosphonates are neuroprotective in healthy populations.

Types of evidence:

- 1 retrospective cohort study
- 2 prospective single treatment arm studies
- Numerous laboratory studies

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

Osteoporosis and dementia share several risk factors, and osteoporosis may itself be a risk factor for dementia. A retrospective cohort analysis from Taiwan using national electronic medical records examined records from 71,520 patients (23,941 with osteoporosis, the rest age and sex matched) and found a 1.46-fold and 1.39-fold higher risk of dementia (95 % CI = 1.37–1.56) and Alzheimer's disease (95 % CI = 0.95–2.02), respectively, compared with the matched non-osteoporosis patients (Chang et al., 2014). They found osteoporosis patients who were treated with bisphosphonates had an adjusted HR of 0.73 (0.63–0.84) of dementia diagnosis as compared to patients who received no treatment. However, as this is a retrospective study, there are potential confounders, such as clinicians prescribing medications to healthier patients.

Two prospective studies in Turkey, totaling 165 patients, treated men and women with osteoporosis with bisphosphonates for 1 year, and assessed cognition through MMSE (Safer et al., 2016; Tasci et al

2016). The studies were not placebo controlled; instead, they looked at change in MMSE score at baseline and at 12 months. They did not find any change in cognition due to bisphosphonate treatment.

Human research to suggest benefits to patients with dementia:

Unavailable.

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

There are several routes by which bisphosphonates could have a neuroprotective effect. Some are indirect effects. Bisphosphonates reduce risk of fractures, and fractures are in and of themselves mortality risk factors. Reducing fractures can also indirectly facilitate lifestyle protective factors such as exercise or socialization. Improving bone health could also mediate changes in brain health, potentially through osteocalcin.

There are also hypotheses on how bisphosphonates could more directly provide neuroprotection. Bisphosphonates act in the mevalonate pathway, which is involved in a number of key cellular events, including cholesterol synthesis and protein prenylation. It is possible that bisphosphonates decrease cholesterol synthesis. However, bisphosphonates are better studied for their more direct role in reducing levels of a protein modification called prenylation. Prenylated proteins are involved in various diseases, including Hutchinson-Guilford progeria syndrome (HGPS) and Alzheimer's disease (AD). A preclinical study in mouse models of progeria showed a survival benefit when the mice were treated with bisphosphonates and statins. Unfortunately, clinical trials of this medication combination in children with HGPS showed no benefit of bisphosphonate treatment (discussed in detail below, under the "Aging and related health concerns" section).

One preclinical study in rodents reported acetylcholinesterase inhibitor properties of one bisphosphonate (Cibickova et al., 2007), and a study using brain extract from deceased AD and healthy control patients reported that bisphosphonates could protect certain acetylcholine receptors from oxidative stress (Fawcett et al., 2002). These have led to hypotheses that bisphosphonates can act directly on neuronal receptors relevant to AD. However, these two preclinical studies were not replicated in more physiological conditions.

Moreover, there are mixed reports of whether bisphosphonates can even cross the blood brain barrier (BBB). Chemical compound prediction algorithms like ADMET indicate that bisphosphonates could cross the BBB. However, in animal studies using radiolabeled bisphosphonates, there was little to no radiotracer signal in the brain. This indicates that bisphosphonates do not cross the intact blood brain barriers in rats, rabbits, or canines (Weiss et al., 2008, Luurila et al., 1998). Radiolabeled medronate, the smallest bisphosphonate, is used for bone scans in humans. These scans very rarely show cerebral uptake of the compound (less than 0.2% of patients) (Mackie 2003).

Intracerebral calcifications are a rare disorder characterized by build ups of calcium in the brain that can cause neurodegeneration. Bisphosphonates bind to and chelate this kind of calcium. Three small studies with a total of 10 patients examined whether bisphosphonate treatment could be used to treat this disorder. The results were inconclusive, with some patients showing symptom improvement and others remaining stable or deteriorating. These studies have been cited as proof that bisphosphonates cross the blood brain barrier, but brain calcification can be associated with BBB impairment. The studies did not show direct evidence of bisphosphonates entering the brain (Loeb 1998, Loeb et al., 2006, Oliveira & Oliveira 2017).

APOE4 interactions:

The APOE4 allele (especially APOE4/APOE4) has been hypothesized to increase risk of fractures and/or osteoporosis in women, though studies have had varied results (Souza et al., 2018, Long et al., 2004). The association may be due to common risk factors rather than causality. Still, it may be particularly important to monitor for and manage osteoporosis in patients carrying APOE4 mutations, particularly those who are homozygous for APOE4.

Aging and related health concerns: Bisphosphonates decrease risk of fracture in osteoporosis patients and patients with Paget's disease of the bone. They also reduce bone metastases and provide survival benefit for cancer subtypes that spread to the bone.

Types of evidence:

- 1 systematic review for Endocrine Society Clinical Guidelines
- 4 Cochrane meta-analyses (1 for fracture risk, 1 for multiple myeloma, 1 for breast cancer, 1 for advanced prostate cancer)
- 2 meta-analysis (1 for association with mortality, 1 for cardiovascular disease)
- 1 single-arm treatment clinical trial in patients with progeria
- 1 observational study with a systematic review of other observational studies

Osteoporosis: BENEFIT; USED AS FIRST-LINE TREATMENT

In 2019, The Endocrine Society published clinical guidelines for the treatment of osteoporosis in postmenopausal women based on systematic reviews. For postmenopausal women with a high risk of fracture, particularly those who have had a recent fracture, the Society recommends initial treatment with one of the bisphosphonate medications (alendronate, risedronate, zoledronate, or ibandronate), with a re-evaluation of fracture risk after 3-5 years. If the patient is still high risk, they should continue treatment. The systematic review included 107 RCTs that enrolled 193,987 women with postmenopausal osteoporosis. Significant reduction in vertebral, hip, and non-vertebral fractures was seen with alendronate, risedronate, and zoledronate treatment (Eastell et al., 2019).

A Cochrane meta-analysis of 11 RCTs that enrolled just over 12,000 postmenopausal women found that alendronate significantly decreases risk of vertebral, hip, and non-vertebral fractures (Wells et al., 2008).

Several RCTs found survival benefits after bisphosphonate treatment in various groups, including osteoporosis, osteopenia, and those with hip fractures. A 2019 meta-analysis explicitly sought to determine whether there was an overall mortality decrease with use of bisphosphonates to explore whether these drugs should be prescribed to all older adults regardless of their fracture risk. The meta-analysis included 38 RCTs with a total of 101,642 patients. These studies were all placebo-controlled, examined drugs with proven anti-fracture efficacy at doses for osteoporosis patients, and were at least 1 year long. Twenty-one of these trials, comprising 42,867 patients, involved bisphosphonates. The authors found no association between bisphosphonate treatment and overall mortality (RR=0.95; 95%

CI, 0.86-1.04; P = 0.17), with no evidence for heterogeneity (I2 = 0%). When the authors looked only at zoledronate (5 mg every 12 to 18 months) they similarly found no increase in survival for those who received bisphosphonates (RR=0.88; 95% CI, 0.68-1.13; P = 0.31). However, for the zoledronate analysis, there was evidence of heterogeneity (I2 = 48.2%) (Cummings et al., 2019).

Many observational studies do find survival benefits for osteoporosis patients treated with bisphosphonates, including a systematic review and population based retrospective cohort study published in May 2022. Using the national health care record system in Taiwan to find patients with osteoporosis who were hospitalized with a major fracture, the authors identified 24,390 bisphosphonate users and 76,725 non-users. They found bisphosphonate users had a reduced mortality rate (RR=0.90; 95% CI, 0.88 - 0.93). They found zoledronate had the strongest effect (RR=0.77, 95% CI 0.73 - 0.82), and that treatment for three years or more was more associated with survival benefit than treatment for less than 3 years. Their systematic review included 11 studies using population-based databases. Eight of the 11 papers found an association between bisphosphonate use and reduced mortality (Hsu et al., 2022).

***Cancer*: BENEFIT FOR CERTAIN SUBTYPES**

Multiple Myeloma:

A 2017 Cochrane network meta-analysis of 24 RCTs (20 placebo or no treatment controlled, 4 with a bisphosphonate comparator) including a total of 7293 multiple myeloma patients found that bisphosphonates significantly reduced vertebral fractures and skeletal-related events. There may be a survival benefit, particularly with zoledronate, but there was significant heterogeneity in the results (Mhaskar et al., 2017).

Breast Cancer:

A Cochrane meta-analysis from 2017 included 44 RCTs with a total of 37,302 patients with either early breast cancer (EBC), advanced breast cancer without bone metastases (ABC), and metastatic breast cancer with bone metastases (BCBM). The meta-analysis found that in women with EBC, bisphosphonate treatment reduced risk of bone metastases and increased survival when compared to placebo or no treatment. Bisphosphonate treatment also reduced the risk of skeletal-related events,

and may reduce bone pain in patients with BCBM as compared to those who received placebo or no treatment. (O'Carrigan et al., 2017).

Advanced Prostate Cancer:

A Cochrane meta-analysis from 2017 of 4843 men with advanced prostate cancer with bone metastases showed that treatment with bisphosphonates resulted in a probable reduction in skeletal related events and disease progression. (Macherey et al., 2017).

Cardiovascular disease: NO CHANGE

A meta-analysis in 2015 looked at 14 RCTs involving bisphosphonate treatment that included cardiovascular event data. There were 5,822 treated patients and 3,564 controls. They did not find any effect of bisphosphonate treatment on total cardiovascular events, atrial fibrillation, myocardial infarction, stroke, and cardiovascular death (Kim et al., 2015).

Critically Ill Patients: POTENTIAL BENEFIT

A 2016 paper from Australia examined hospital records of 7830 patients admitted to the intensive care unit. Of these patients, 245 had bisphosphonate treatment in the past 5 years. The authors compared the mortality of these patients to bisphosphonate-naïve patients who were matched for characteristics like age, sex, and co-morbidity. They found that while bisphosphonate users were older and had greater mortality risk based on co-morbid conditions, that they had reduced mortality in hospital compared to non-users (5.2% in the bisphosphonate user group compared to 9.1% in the bisphosphonate non-user matched controls). A small substudy of 37 bisphosphonate users and 74 matched controls showed that while bisphosphonate users had a lower baseline bone density, bone loss in this group was significantly attenuated as compared to matched controls (−3% ± 13% per week in the bisphosphonate user group as compared to −15% ± 14% per week in the bisphosphonate naïve group). The data suggested that the mortality risk reduction was greatest in the most fragile and vulnerable patients (Lee et al., 2016).

Progeria: POTENTIAL HARM

Nitrogenous bisphosphonates have been tested in Hutchinson-Guilford Progeria Syndrome (HGPS), a disease of premature aging caused by abnormal protein prenylation of lamin A, resulting in a

dysfunctional protein called progerin. Statins, bisphosphonates, and farnesyltransferase inhibitors (FTI) all act in the protein prenylation pathway, and thus have been explored as potential treatment options. A preclinical study in a mouse model of HGPS found that combined use of statins and bisphosphonate extended the lifespan of mice that mimic HGPS (Verela et al., 2008). An early phase single arm treatment trial of FTIs alone in patients with progeria showed improvements in weight gain and cardiovascular readouts, and a second trial showed survival benefits (Gordon et al., 2012, Gordon et al., 2014).

It was thought that combining FTIs, statins, and bisphosphonates could lead to greater clinical improvements, as the three drug classes all act at different points in the protein prenylation pathway. The single arm treatment trial enrolled 37 patients with progeria. The combination therapy improved measures of bone health such as bone density and size, but otherwise did not improve upon single treatment of FTI. The rates of atherosclerotic plaques increased in the triple therapy as compared to single therapy, potentially indicating that triple treatment including a bisphosphonate increased rate of disease progression (Gordon et al., 2016).

Safety: Serious side effects are rare but can be more common at higher doses or long-term treatment and include osteonecrosis of the jaw, atrial fibrillation, hypocalcemia, severe musculoskeletal pain, atypical stress fractures of the femur, and eye inflammation.

Types of evidence:

- 1 Cochrane meta-analysis in multiple myeloma patients
- 1 meta-analysis of bisphosphonate treatment and cardiovascular events
- 1 retrospective analysis of post-marketing adverse event databases
- 1 observational study
- 1 Mayo Clinic Clinical Practice Guideline

In the 2017 Cochrane network meta-analysis of 24 RCTs including a total of 7293 multiple myeloma patients, the authors found some evidence of increased risk of osteonecrosis of the jaw with bisphosphonate treatment (Mhaskar et al., 2017). A position paper from the American Association of Oral and Maxillofacial Surgeons found that incidence risk of ONJ in case series, case-controlled studies, and cohort studies ranged from 0.8% to 12% (Ruggiero et al., 2009).

The 2015 meta-analysis of 14 RCTs of 9.386 patients (5,822 treated patients and 3,564 controls) involving bisphosphonate treatment and cardiovascular event data performed a subgroup analysis of 6 trials using zoledronate. The authors did see an increase in risk of atrial fibrillation, with little evidence of heterogeneity (RR 1.24, 95% CI 0.96–1.61; I2 = 0.0%). (Kim et al., 2015).

A 2021 paper examined adverse events reported to the Food and Drug Administration Adverse Events Reporting System (FAERS) and the World Health Organization's (WHO) global database for adverse drug reactions, VigiAccess. The authors specifically looked for adverse events related to depression and anxiety in patients with osteoporosis taking a single osteoporosis medication. They found that alendronate was associated with significantly increased risk of depression and anxiety compared to other, non-bisphosphonate first-line osteoporosis treatment options (Keshishi et al., 2021).
A 2020 paper followed 196,129 patients treated with bisphosphonates in the Kaiser Permanente Southern California health care system for 10 years. They found that bisphosphonate users had an atypical femur fracture rate of 1.74 fractures per 10,000 patient-years as compared to patients who never took bisphosphonates (0.10 per 10,000 person-years). The rates of atypical fractures increased with age, duration of bisphosphonate treatment, and were higher in Asian women than white women (Black et al., 2020).

Severe musculoskeletal pain, eye inflammation, hypocalcemia, and renal impairment are all rare but have been reported after bisphosphonate use, as reviewed in a 2008 Mayo Clinic Proceedings paper (Drake et al., 2008)

Other Adverse Reactions: Gastrointestinal side effects (nausea, heartburn, stomach pain) are often seen with oral formulations such as alendronate and risedronate, though these can be mitigated by adhering to dosing instructions. Acute inflammatory responses that present as flu-like symptoms (fever, body aches, headache, fatigue) are common with IV formulations such as zoledronate.

Drug interactions:

There are 26 major and 88 moderate known drug interactions with zoledronate, and 2 major and 99 moderate drug interactions with alendronate and risedronate. Some examples include: calcium supplements or calcium-mimic drugs, as these can block absorption of bisphosphonates; aminoglycoside antibiotics such as gentamicin, kanamycin, neomycin, paromomycin, streptomycin, and tobramycin, as these can cause kidney dysfunction or hypocalcemia; aspirin and other nonsteroidal anti-inflammatory

drugs (NSAIDs) such as ibuprofen and naproxen, as these can increase risk of GI side effects; cancer chemotherapy medications; and diuretics such as bumetanide, ethacrynic acid, and furosemide (Lasix), as these can affect blood calcium levels (Drugs.com).

Research underway:

There are 107 currently ongoing clinical trials in the US and the EU, and 99 active studies in NIH Reporter that involve bisphosphonates. One study is in a dementia population, but examines fracture risks. There are no studies examining the use of bisphosphonates and effect on cognition, and no ongoing studies assessing bisphosphonate use and mortality.

Search terms:

Pubmed, Google:

- +cognitive, +neurodegeneration, +dementia, +mortality, +cardiovascular, +cancer, +Cochrane, +ApoE4

Websites visited for bisphosphonates, including: alendronate, risedronate, zoledronate

- Clinicaltrials.gov
- NIH RePORTER
- Drugs.com (alendronate, risedronate, zoledronate – brand names Reclast in the US)
- WebMD.com (alendronate, risedronate, zoledronate)
- PubChem (alendronate, risedronate, zoledronate)
- DrugBank.ca (alendronate, risedronate, zoledronate)

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