



*Cognitive Vitality Reports<sup>®</sup> 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.*

## Bumetanide

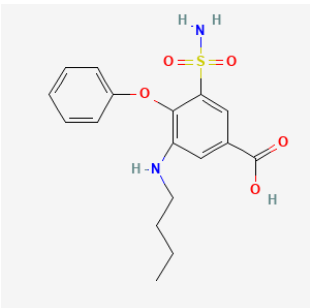
### Evidence Summary

Some studies suggest bumetanide may protect against AD, particularly in APOE4 carriers, but no clinical trials have validated these findings. Orthostatic hypotension and hypokalemia are common side effects.

**Neuroprotective Benefit:** Based on observational and preclinical studies, bumetanide may protect against AD, particularly in APOE4 carriers. But no clinical trials have validated these findings and low brain penetrance may preclude benefit.

**Aging and related health concerns:** Bumetanide is used to treat fluid retention in people with congestive heart failure, liver disease, and kidney disease, but it is not known to treat or prevent the underlying pathologies.

**Safety:** Bumetanide is a potent diuretic that can lead to water and electrolyte depletion. Orthostatic hypotension and hypokalemia are common. Bumetanide also interacts with many drugs.

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| <p><b>Availability:</b> Rx</p>   | <p><b>Dose:</b> Adult doses for ascites, edema, or pulmonary edema are 0.5-2.0 mg once daily orally or 0.5-1.0 mg once via intravenous or intramuscular injection.</p> | <p><b>Chemical formula:</b> C<sub>17</sub>H<sub>20</sub>N<sub>2</sub>O<sub>5</sub>S</p> <p><b>MW:</b> 364.4</p>  <p>Source: <a href="#">PubChem</a></p> |
| <p><b>Half-life:</b> 1-1.5 hours</p>   | <p><b>BBB:</b> poorly penetrant</p>  |  |
| <p><b>Clinical trials:</b> A meta-analysis of autism spectrum disorder included a total of 496 children.</p> | <p><b>Observational studies:</b> Studies of electronic health records have included thousands of patients using bumetanide.</p>  |  |

### What is it?

Bumetanide is a loop diuretic that is used to treat fluid retention in people with congestive heart failure, liver disease, and kidney disease. Bumetanide increases urinary excretion of water, sodium, and chloride by inhibiting the reabsorption of sodium and chloride at the ascending loop of Henle in the kidney through inhibition of the sodium-potassium-chloride cotransporter 1 and 2 (NKCC1 and NKCC2)([DrugBank](#)).

While NKCC2 is expressed only in the kidney, NKCC1 is also expressed in the central nervous system ([Kharod et al., 2019](#); [Virtanen et al., 2020](#)). GABA, typically known as an inhibitory neurotransmitter, can act as an excitatory neurotransmitter in the early stages of brain development because of accumulation of chloride ions inside the cells (reversed chloride gradient)([Mollajani et al., 2019](#)). In neonates, bumetanide may prevent seizures by blocking the NKCC1 to inhibit chloride uptake and thus decreasing the chloride concentration in neurons, shifting GABA from excitation to inhibition ([PubChem](#)).

Bumetanide has also been studied in patients with temporal lobe epilepsy, autism spectrum disorders, Parkinson's disease, and schizophrenia ([Kharod et al., 2019](#)). Bumetanide was also identified as a top drug for treating APOE4-related Alzheimer's disease through a computational drug screen ([Taubes et al., 2021](#)).



**Neuroprotective Benefit:** Based on observational and preclinical studies, bumetanide may protect against AD, particularly in APOE4 carriers. But no clinical trials have validated these findings and low brain penetrance may preclude benefit.

*Types of evidence:*

- 1 meta-analysis in autism spectrum disorders
- 3 observational studies (2 on Alzheimer's risk and 1 on epilepsy patients)
- 1 case report in Parkinson's patients
- Numerous laboratory studies

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

No clinical trials have tested the efficacy of bumetanide in the prevention of dementia or cognitive decline.

Two electron health record databases were used to analyze whether bumetanide is associated with Alzheimer's disease risk and found that bumetanide use is associated with a significantly lower Alzheimer's prevalence in people over the age of 65 ([Taubes et al., 2021](#)). One database from the University of California at San Francisco (UCSF), which contains complete medical records for 1.3 million patients. The other database was from the Mount Sinai Health System (MSHS), which covers 3.9 million patients. There were 1,850 and 1,901 patients over the age of 65 who used bumetanide in the UCSF and MSHS electron health record database, respectively. Because bumetanide is prescribed in people with hypertension and edema, control cohorts were matched using a propensity score based on age, race, sex, hypertension diagnosis, and edema diagnosis, who were not exposed to bumetanide. Ten permutations of iterative matching of the control group showed that bumetanide treatment was associated with a 35-75% lower prevalence of Alzheimer's disease compared to unexposed controls across both databases. To further control for hypertension, a risk factor for dementia, another control group was formed based on hypertension or edema diagnosis and use of a non-bumetanide non-loop diuretics. Ten permutations of iterative matching of the control group showed a significantly lower Alzheimer's disease prevalence (40-70% lower) with bumetanide use compared to non-bumetanide-exposed people in 8 out of 10 permutations in the UCSF database and 10 out of 10 permutations in the MSHS database.



In a case-control study of 5,839 Alzheimer's patients and 116,103 matched controls, exposure history of bumetanide and furosemide (another loop diuretic) were compared with regards to risk of developing Alzheimer's disease ([Graber-Naidich et al., 2023 preprint](#)). The Alzheimer's case was matched with a control cohort (1:20 case:control) based on sex, race, ethnicity, and hypertension; 5,839 Alzheimer's cases and 116,103 matched controls were included. A total of 1,759 patients (54 cases and 1,705 controls) were exposed to bumetanide. After adjusting for congestive heart failure, socioeconomic status (bumetanide is more expensive than furosemide), and other confounders, those who had taken bumetanide had a significantly lower risk of Alzheimer's disease compared to unexposed people (OR=0.50; 95% CI, 0.37 to 0.68,  $p=9.9\times 10^{-6}$ ). The unadjusted odds ratio for Alzheimer's diagnosis in those exposed to bumetanide was 0.63 (95% CI, 0.48 to 0.82;  $p=7.6\times 10^{-4}$ ). In a sensitivity analysis where the cohort was restricted to patients with insurance and income data, 1.06% (45 out of 4238) of Alzheimer's cases and 1.8% (1,321 out of 73,450) matched control cases were exposed to bumetanide. The OR was 0.59 (95% CI, 0.43 to 0.79;  $p=4.5\times 10^{-4}$ ). Exposure to the most common loop diuretic, furosemide, was not associated with lower Alzheimer's risk (unadjusted OR=1.11; 95% CI, 1.03 to 1.18;  $p=0.003$ ). In fact, the risk was higher, though after adjusting for congestive heart failure, this effect disappeared. The authors speculated that there may be unique effects of bumetanide that is not observed with furosemide, including the greater potency and inhibition of the chloride cotransporter NKCC1 in the brain.

Because all studies related to Alzheimer's disease have been observational studies, a prospective, randomized, double-blind, placebo-controlled clinical trial is warranted to validate the potential neuroprotective effects of bumetanide.

A meta-analysis of 6 randomized controlled trials including a total of 496 children with autism spectrum disorder reported that bumetanide treatment (0.5 to 2.0 mg, twice daily, orally) for 3 months significantly improved the severity of autism symptoms (measured by CARS and SRS) and Clinical Global Impressions of Efficacy (CGI-E) compared to the control group ([Wang et al., 2021](#)). There was also evidence that bumetanide treatment had a positive effect on social affect and restricted/repetitive behavior. Bumetanide had no significant effect on sensory symptoms. There were 2 studies that measured the concentration of neurotransmitters using magnetic resonance spectroscopy ([Dai et al., 2020](#); [Zhang et al., 2020](#)). Both studies found that bumetanide significantly decreased GABA levels in the insular cortex compared to the control, and this reduction correlated with symptom/clinical improvement. In a secondary analysis of neurocognitive function in a trial included in the meta-analysis, bumetanide treatment (titrated to a maximum of 1.0 mg twice daily, orally) for 3 months failed to show a superior effect over placebo on any of the cognitive domains ([van Andel et al., 2023](#)). The test battery

measured information processing and control, memory imprinting, visual memory, verbal memory, visual working memory, verbal working memory, attentional flexibility, and motor inhibition. The mechanism underlying bumetanide's effects in autism likely includes correction of dysfunctional GABAergic transmission and the imbalance in excitatory and inhibitory neurotransmission ([Mollajani et al., 2019](#)). During development, GABA acts as an excitatory neurotransmitter, which leads to increased chloride ions inside the cell. Bumetanide, through antagonism of the NKCC1 chloride cotransporter, can reduce the intracellular chloride ion concentration and shift GABA from excitatory to inhibitory. Long-term effects of bumetanide needs to be determined in larger, longer-term trials.

In a longitudinal study of 12 patients with refractory epilepsy, bumetanide treatment (2 mg/day, as adjuvant therapy to regular antiepileptic drugs) for 6 months significantly reduced seizure frequency in 8 patients and this was accompanied by white matter reconstruction and improved cognitive function ([Gharaylou et al., 2019](#)). Percent errors in the spatial memory test was significantly reduced and spatial memory was significantly enhanced. Of the 8 patients, 2 patients became close to seizure-free with greater than 90% reduction in seizures. Brain connectivity, measured by fractional anisotropy, increased in the cingulum-cingulate gyrus, anterior thalamic radiation, and temporal part of the superior longitudinal fasciculus; microstructural changes in the superior longitudinal fasciculus and anterior thalamic radiation correlated a reduction in the error rate in the spatial memory test.

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

No clinical trials have tested the efficacy of bumetanide in patients with dementia.

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

In a study using a computational drug repurposing algorithm to treat APOE4-related Alzheimer's disease, bumetanide was identified as a top drug out of over 1,300 existing drugs ([Taubes et al., 2021](#)). This study was based on the hypothesis that drugs that reverse differentially expressed genes in a disease state back towards normal expression may be promising therapies for repurposing. First, transcriptomic signatures of APOE4-related Alzheimer's disease were established using a publicly-available human brain database. Then they queried these signatures against the Connectivity Map database including transcriptomic characters of 1,300+ existing drugs. Of the top 5 compounds identified as potential therapeutics, they performed a literature-based search of potential mechanism of action and selected bumetanide for further evaluation. Bumetanide reversed the expression of both up- and down-regulated genes in human APOE4/E4 transcriptomic signature of Alzheimer's disease. Transcriptomics



effects of bumetanide showed a preference for E4/E4, with a weaker Connectivity Map score against E3/E4 and E3/E3 Alzheimer's disease, though it may also work against non-E4 Alzheimer's disease to some extent. In APOE4-knock-in (APOE4-KI) mice, bumetanide was in the 7-8<sup>th</sup> percentile of drugs predicted to reverse the transcriptomic signature of brain aging (reversing transcriptomic changes in 12 and 24-month-old APOE4-KI mice compared to 3-month-old APOE4-KI mice). In bumetanide-treated cells in the Connectivity Map database, genes upregulated in aged APOE4-KI mice were downregulated, and those downregulated in aged APOE4-KI mice were upregulated.

These findings were further confirmed *in vivo*. In 16-month-old female APOE4-KI mice, treatment with bumetanide (0.2 mg/kg, daily, i.p.) for 8 weeks reversed neuronal hyperexcitability in the hippocampal CA1 region and fully restored synaptic plasticity, measured by long-term potentiation, which is important for memory formation ([Taubes et al., 2021](#)). In 22-month-old female APOE4-KI mice, bumetanide treatment (0.2 mg/kg, daily, i.p.) for 8 weeks significantly improved learning, measured by the Morris water maze, to levels comparable to APOE3-KI mice. Bumetanide treatment did not have a significant effect on learning in APOE3-KI or wild-type mice. In fact, bumetanide treatment appeared to worsen memory performance of APOE3-KI mice.

Disease-related gene expression changes were reversed with bumetanide in APOE4-KI mice in 12 out of 18 cell types, including excitatory and mixed neuronal clusters and some interneurons; however, this reversal was not seen in inhibitory neuron subtypes and non-neuronal cells, including astrocytes and oligodendrocytes in the hippocampus of APOE4-KI mice ([Taubes et al., 2021](#)). Thus, bumetanide may exert cell type-selective effects.

Next, the effects of bumetanide were examined in APOE4-KI mice expressing mutant human APP (J20 mice). In J20/E4-KI and J20/E3-KI mice at 10 months of age, bumetanide treatment (0.2 mg/kg, daily, i.p.) for 12 weeks rescued hippocampal CA1 neuronal hyperexcitability, specifically in J20/E4-KI mice, and restored long-term potentiation deficit in both J20/E4-KI and J20/E3-KI mice ([Taubes et al., 2021](#)). Bumetanide treatment also significantly reduced A $\beta$  plaque numbers and covered areas in both the hippocampus and the cortex of J20/E4-KI mice. Together, bumetanide treatment restored normal neuronal excitability and synaptic plasticity, while reducing A $\beta$  plaque loads in J20/E4-KI mice

In APOE4/E4-iPSC-derived human neurons, bumetanide treatment (10  $\mu$ M) for 6 hours upregulated genes that were shifted downward in APOE4/E4 Alzheimer's disease and downregulated those that were shifted upward ([Taubes et al., 2021](#)). Pathway analysis of the differentially expressed genes whose expression was affected by bumetanide in APOE4/E4-iPSC-derived human neurons identified 19



pathways that were significantly perturbed. After combining data from APOE4-KI mice, J20/E4-KI mice, and E4/E4-iPSC-derived human neurons, 3 pathways were common: GABAergic synapse, circadian entrainment, and morphine addiction. These pathways may be related to bumetanide's mechanism of action for preventing Alzheimer's disease in APOE4 carriers. In other words, bumetanide may correct deficits in GABAergic interneurons and circadian-related impairments, including sleep deficit. While morphine addiction has not been described as a characteristic of Alzheimer's disease, morphine addiction pathway affects both GABAergic function and circadian rhythms ([Listos et al., 2019](#); [Eckert and Yaggi, 2022](#)).

In a case report of 4 patients with [Parkinson's disease](#), bumetanide treatment (5 mg/day, orally) added to anti-Parkinson medications for 2 months improved motor symptoms in all 4 patients and improved gait and freezing in 2 of the patients ([Damier et al., 2016](#)). Cognitive benefits were not assessed as only 1 of the patients had cognitive impairment at baseline. In Parkinson's disease, GABAergic medium spiny neurons in the striatum generate aberrant currents ([Dehorter et al., 2009](#)). Bumetanide, through inhibition of the chloride cotransporter NKCC, may restore physiological levels of intracellular chloride and normalize GABAergic actions. A larger, randomized, controlled study is needed to validate the potential benefits of bumetanide in Parkinson's disease patients.

In a rat model of cerebral ischemia (induced by injection of endothelin-1 in the left cortical motor area and left corpus striatum), bumetanide treatment (200 µg/kg/day, injected into the lateral ventricle with mini-osmotic pump) for 21 days promoted neural precursor cell regeneration, lengthened dendrites in the hippocampal dentate gyrus, and restored cognitive function, measured by the Morris water maze ([Xu et al., 2016](#)). However, bumetanide treatment did not reduce the infarct size.

In a mouse model of brain trauma (controlled cortical impact), bumetanide treatment (2 mg/kg, i.p., twice daily) during the first week after injury inhibited the appearance of depressive-like behavior, while rescuing secondary neurogenesis ([Goubert et al., 2019](#)).

Although some promising findings have been observed with bumetanide, it is important to note that it has a short half-life (between 90 minutes to 3 hours) and is poorly blood-brain-barrier penetrant ([Mollajani et al., 2019](#)). Multiple active efflux transport, mediated by Oat3, Oatp1a4, and multidrug resistance protein 4, limit accumulation of bumetanide in the mammalian brain ([Romermann et al., 2017](#)). Thus, systemic administration of bumetanide leads to brain levels that are typically below those needed to inhibit NKCC1. Higher doses of bumetanide would likely lead to significant safety concerns.



To overcome these challenges, prodrugs with lipophilic/uncharged esters and alcohol/amide analogs, which convert to bumetanide after entering the brain, are under development ([Kharod et al., 2019](#)). For example, an ester prodrug, BUM5, showed higher concentration in the mouse brain compared to bumetanide when infused intravenously at equimolar doses ([Tollner et al., 2014](#)). In a mouse model of epilepsy (induced by pilocarpine), BUM5 treatment was more effective than bumetanide in altering seizure thresholds.

**APOE4 interactions:** In a study using a computational drug repurposing algorithm to treat APOE4-related Alzheimer's disease, bumetanide was identified as a top drug out of over 1,300 existing drugs ([Taubes et al., 2021](#)). *In vitro* and *in vivo* studies suggest that bumetanide may be beneficial for APOE4 and APOE3 carriers, with a higher efficacy in APOE4 carriers. However, bumetanide has not yet been tested in patients with Alzheimer's disease.

**Aging and related health concerns:** Bumetanide is used to treat fluid retention in people with congestive heart failure, liver disease, and kidney disease, but it is not known to treat or prevent the underlying pathologies.

*Types of evidence:*

- 1 meta-analysis
- Numerous laboratory studies

Patients with chronic heart failure with symptoms of congestion and fluid retention often receive long-term treatment with loop diuretics ([Heindenreich et al., 2022](#)). In a network meta-analysis of 34 randomized controlled trials including 2,647 patients with chronic heart failure, there were no significant differences across different loop diuretics with regards to all-cause mortality, cardiovascular mortality, or hypokalemia ([Tager et al., 2019](#)). Loop diuretics in the network meta-analysis included bumetanide, azosemide, furosemide, and torasemide; comparators included placebo, standard medical care, or other active treatments. Torasemide ranked highest in terms of heart failure hospitalization, and there was a trend towards benefit with torasemide with regards to occurrence of acute renal failure.

Bumetanide is also used to treat fluid retention in people with liver disease and kidney disease ([Drugs.com](#)).





**Safety:** Bumetanide is a potent diuretic that can lead to water and electrolyte depletion. Orthostatic hypotension and hypokalemia are common. Bumetanide also interacts with many drugs.

*Types of evidence:*

- 3 meta-analyses
- 1 review

**US Boxed Warning:** Bumetanide is a potent diuretic and if given in excessive amounts, can lead to a profound diuresis with water and electrolyte depletion ([Drugs.com](#)). Careful medical supervision is needed, and dose/dosage schedule have to be adjusted to the individual.

In patients with chronic heart failure, clinicians may prefer torasemide over other loop diuretics such as bumetanide, as torasemide is superior in terms of heart failure-related hospitalizations and a trend towards fewer renal complications, based on a network meta-analysis of 34 randomized controlled trials including 2,647 patients ([Tager et al., 2019](#)).

In a meta-analysis of 3 observational studies with 94 patients with heart failure, acute kidney injury, or volume overload, bumetanide infusion (mean dose of  $1.08 \pm 0.43$  mg/hour with a mean treatment duration of  $45.09 \pm 10.12$  hours) led to a 24.7% incidence of acute kidney injury ([Hansrivijit et al., 2020](#)). Increasing doses of bumetanide was correlated with increased urine output ( $p=0.026$ ) and increased incidence of acute kidney injury ( $p<0.01$ ).

In a meta-analysis of 6 randomized controlled trials including a total of 496 children with autism spectrum disorder, a meta-analysis of adverse events with bumetanide could not be performed due to insufficient data ([Wang et al., 2021](#)). In the double-blind randomized controlled phase 2 trial (BAMBI) of 92 children with autism spectrum disorder, bumetanide treatment (maximum of 1.0 mg twice daily, orally) led to diuretic effects (orthostatic hypotension in 36% of bumetanide-treated versus 11% of placebo;  $p=0.007$ ) and hypokalemia (51% of bumetanide-treated vs 0% of placebo;  $p<0.0001$ ) ([Sprenger et al., 2021](#)). Hypokalemia did not occur before day 14 of treatment, and potassium levels did not drop below 3.0 mM/L. There were 3 serious adverse events: syncope after venipuncture (bumetanide arm), extended hospitalization after a Kieselbach coagulation (placebo arm), and acute appendicitis requiring appendectomy (bumetanide arm). These severe adverse events were determined to be probably unrelated to treatment with the study medication, except for syncope, which was possibly related. Other studies reported diuretic effects (polyuria, dehydration), hypokalemia, mild hyperuricemia

(elevated uric acid in the blood), loss of appetite, constipation, nausea, vomiting, asthenia (weakness or lack of energy), and sleeping problems ([Wang et al., 2021](#)).

**Drug interactions:** Bumetanide interacts with 437 drugs, of which 24 are major interactions, 389 are moderate, and 24 are minor ([Drugs.com](#)). Drugs with major interactions are amikacin, aminolevulinic acid, amiodarone, arsenic trioxide, cisapride, desmopressin, dofetilide, dolasetron, dronedarone, droperidol, etelcalcetide, gentamicin, kanamycin, levomethadyl acetate, lithium, neomycin, netilmicin, pimozone, plazomicin, streptomycin, tizanidine, tobramycin, and ziprasidone. Bumetanide also has 7 disease interactions: anuria, cirrhosis, electrolyte losses, ototoxicity, renal dysfunction, diabetes, and hyperuricemia ([Drugs.com](#)).

#### Sources and dosing:

Bumetanide is marketed as Bumex (Validus Pharmaceuticals) and Burinex (Zuellig Pharma) and is available by prescription to treat fluid retention in people with congestive heart failure, liver disease, and kidney disease. Adult doses for ascites, edema, or pulmonary edema are 0.5-2.0 mg once daily orally or 0.5-1.0 mg once via intravenous or intramuscular injection ([Drugs.com](#)).

#### Research underway:

There are 7 clinical trials currently ongoing testing bumetanide ([ClinicalTrials.gov](#)). Four trials are in heart failure patients, 1 study is in chronic kidney disease, 1 study is in autism, and 1 study is in unresectable hepatocellular carcinoma.

To overcome the low brain penetrance of bumetanide, prodrugs with lipophilic/uncharged esters and alcohol/amide analogs are under development ([Kharod et al., 2019](#)).



**Search terms:**

Pubmed, Google: Bumetanide

- + Alzheimer, + meta-analysis, + cognitive, + APOE

Websites visited for Bumetanide:

- [Clinicaltrials.gov](https://clinicaltrials.gov)
- [NIH RePORTER](https://reporter.nih.gov)
- DrugAge (0)
- Geroprotectors (0)
- [Drugs.com](https://drugs.com)
- [WebMD.com](https://www.webmd.com)
- [PubChem](https://pubchem.ncbi.nlm.nih.gov)
- [DrugBank.ca](https://drugbank.ca)
- [Cafepharma](https://www.cafepharma.com)

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