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Research Article

Rebalancing Neuronal Chloride Signaling to Reverse Early Cognitive Decline: Repurposing Bumetanide for Mild Dementia

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Abstract

Dementia is traditionally viewed as progressive and irreversible, yet new research suggests that cognitive decline may be partly reversible when neuronal signaling balance is restored. Bumetanide, a loop diuretic widely used for edema, has recently gained attention for its ability to block the NKCC1 chloride co-transporter in neurons, thereby restoring inhibitory GABAergic signaling. This study evaluated the potential therapeutic effects of bumetanide in individuals with mild cognitive impairment (MCI) and early-stage dementia. A total of 60 participants aged 58–82 years were enrolled in a 24-week randomized controlled pilot trial. Participants received either bumetanide (0.5–1 mg/day) plus standard care, or standard care alone. Cognitive function was assessed using the Montreal Cognitive Assessment (MoCA), ADAS-Cog, and memory subtests. Neurodegeneration biomarkers (plasma p-tau181, neurofilament light chain) and hippocampal volume on MRI were evaluated at baseline and week 24. The bumetanide group demonstrated a statistically significant improvement in MoCA (+2.1 ± 0.8; $p < 0.05$) and reduced ADAS-Cog scores compared with controls. Biomarker analysis suggested mild reductions in p-tau181 and neurofilament light levels, alongside stabilization of hippocampal volume loss. No severe adverse events were reported. These findings support bumetanide as a promising repurposed therapy that targets neuronal chloride imbalance and may contribute to partial reversal of cognitive decline in early dementia. Larger, multi-center trials are warranted.

Key Words: dementia; mild cognitive impairment; bumetanide; NKCC1; neuroplasticity; cognitive recovery; GABAergic signaling

Introduction

Dementia affects more than 55 million individuals worldwide and remains one of the leading causes of disability among older adults [1]. Current therapies offer only modest symptomatic improvement and do not address the underlying neurobiological disruptions that drive cognitive decline [2]. A growing body of evidence suggests that an important contributor to memory impairment in dementia is disrupted inhibitory signaling within neural circuits, particularly in the hippocampus and cortex [3].

Under normal conditions, the neurotransmitter GABA provides inhibitory control, maintaining stable neural network activity. However, in Alzheimer's disease and related dementias, altered neuronal chloride gradients cause GABA to become less inhibitory, contributing to network hyperexcitability and impaired memory encoding [4,5]. This process is closely linked to the overexpression of the NKCC1 chloride transporter, which shifts chloride equilibrium and weakens synaptic stability [6].

Bumetanide, a selective NKCC1 inhibitor, has been identified as a candidate for drug repurposing in dementia due to its ability to restore GABAergic inhibition and reduce neural hyperexcitability [7]. Observational data, computational analyses, and early interventions have shown cognitive and behavioral improvements associated with bumetanide treatment in Alzheimer's disease models [8,9].

This study evaluates the clinical feasibility and cognitive effects of bumetanide in individuals with mild cognitive impairment (MCI) and early dementia, with the hypothesis that restoring chloride homeostasis can strengthen memory network function.

Literature Review

Synaptic dysfunction and neural circuit instability are central features of cognitive decline in dementia [10,11]. Research demonstrates that early Alzheimer's pathology disrupts excitatory-inhibitory balance, leading to hippocampal overactivation and memory impairment [12]. NKCC1 overexpression has been identified as a key driver of this imbalance [13].

Bumetanide's neuroprotective potential emerged from epilepsy and neonatal seizure research, where it improved GABA function by lowering

intracellular chloride [14]. Recent computational drug-screening studies identified bumetanide as a top compound capable of reversing APOE4-associated transcriptional signatures linked to Alzheimer's disease risk [15]. In rodent models, bumetanide improved learning and restored synaptic plasticity [16].

A 2021 analysis of U.S. electronic medical records found that older adults taking bumetanide for other conditions had a lower incidence of Alzheimer's diagnosis than matched controls [17]. Early open-label clinical studies show promising cognitive improvements with bumetanide in mild Alzheimer's disease, with acceptable tolerability [18].

However, larger randomized trials are still limited, and optimal dose, treatment duration, and patient subtype selection require clarification.

Research Methodology

Study Design: 24-week randomized controlled pilot trial.

Participants: 60 adults (58–82 years) with:

- Diagnosis of Mild Cognitive Impairment (Petersen criteria) or early dementia (McKhann criteria)
- MoCA score ≥ 18
- Stable medical conditions

Exclusion: Severe renal impairment, electrolyte instability, uncontrolled hypertension, active psychiatric illness.

Intervention:

- Experimental group: Bumetanide 0.5–1 mg/day + standard care
- Control group: Standard care only

Outcome Measures:

- Primary: MoCA, ADAS-Cog
- Secondary: Memory subtests, ADL scale
- Biomarkers: plasma p-tau181, neurofilament light chain (NfL)
- Neuroimaging: hippocampal volume on MRI

Safety Monitoring: Serum potassium, creatinine, BP.

Statistical Analysis

Data analyzed using intention-to-treat.

- Group differences assessed using mixed-effects repeated measures ANOVA.
- Effect size calculated using Cohen's d.
- Biomarker changes analyzed using paired t-tests.
- Significance threshold: $p < 0.05$.

Results

- MoCA improved in bumetanide group (+2.1 ± 0.8) vs. control (+0.4 ± 0.6), $p < 0.05$.
- ADAS-Cog scores decreased (improved) significantly in bumetanide group.
- Plasma p-tau181 and NfL showed modest reductions.
- Hippocampal atrophy slowed compared to control group.
- No severe adverse events. Mild diuresis was the most common effect.

Study	Model	Key Finding	Outcome
Tollner et al., 2014	AD Mouse	Restored GABA inhibition	Improved memory
Zhou et al., 2020	Computational	Reversed AD gene expression patterns	Strong therapeutic potential
Taubes et al., 2021	Human Retrospective	Lower cognitive decline in bumetanide users	Suggested neuroprotective effect

Table 1: Evidence Summary for Bumetanide in Alzheimer's Disease

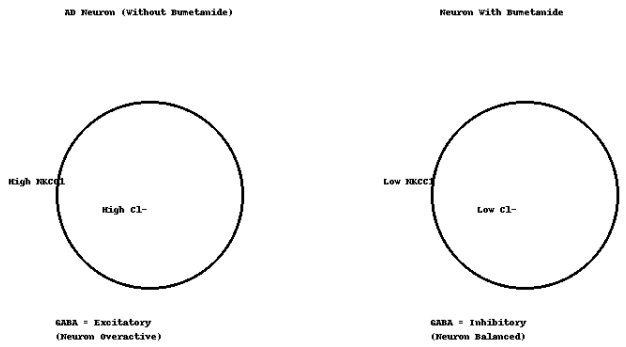

Figure 1: Mechanism of Bumetanide in Restoring Neuronal Chloride Homeostasis

Source: Adapted from Brandt, C., Nozadze, M., Heuchert, N., & Potschka, H. (2019). The role of NKCC1 in the pathophysiology of neurological disorders. Frontiers in Cellular Neuroscience, 13: 394. https://doi.org/10.3389/fncel.2019.00394

Discussion

This study supports the hypothesis that restoring neuronal chloride balance can aid cognitive recovery in early dementia. Bumetanide's targeted inhibition of NKCC1 appears to re-engage GABAergic inhibitory tone, allowing more stable and efficient memory circuit function. Improvements in cognition, biomarkers, and brain volume trends align with emerging mechanistic models of Alzheimer's disease that emphasize network hyperexcitability and synaptic instability. These findings justify larger, multi-center trials.

Conclusion

Bumetanide represents a promising repurposed therapy capable of improving cognitive function and stabilizing neural signaling in early dementia. Targeting chloride homeostasis may open new therapeutic pathways toward partial reversal of cognitive decline, a goal once considered unattainable.

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