Repurposing verapamil for prevention of cognitive decline in sporadic Alzheimer's disease

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Dementia is currently the only leading cause of death that is still on the rise, with its overall costs already surpassing those of cancer and heart disease combined, it has developed into a worldwide crisis. In response to its serious and far-reaching effects, the US government has established the "National Alzheimer's Project Act" (Public Law 111-375), which aims to prevent and successfully manage Alzheimer's disease (AD), the most common cause of dementia, by 2025. Unfortunately, the incidence of this rapidly progressive, irreversible neurodegenerative cerebral disorder is expected to increase further in coming years, given its close connection with advanced age, yet there are no satisfactory therapies. All the available agents, currently approved by the Food and Drug Administration (FDA) for managing AD are merely palliative, their efficacy decreases over time and they are frequently associated with undesirable side effects. Moreover, efforts to develop new and more efficacious treatments have been futile, despite all the time taken (nearly 20 years) and billions of dollars spent in the rigorous process of drug design, research, development, formulation, and testing.

This has resulted in a move geared towards the repurposing of existing mediations, licensed for other therapeutic indications, for their potential application in AD and related cognitive disorders. Such practice of "medication repurposing" aims to maximize use of resources and reduce unnecessary expenditure. A repurposed medication has already passed the initial steps required for primary approval, a laborious process, which includes everything from *in vitro* and preclinical screening, chemical optimization, toxicological studies to bulk manufacturing and formulation. The safety and efficacy profile has hence already been established so it is quick to advance to the market, for the proposed indication (Ahmed and Ishrat, 2020).

Indeed, medication repurposing aka medication repositioning has shown therapeutic success in many other areas including cancer and cardiovascular disease (Corbett et al., 2012; Ahmed and Ishrat, 2020). As for the choice of medication, a substantial body of clinical and experimental evidence indicates that Ca^{2+} channel blocking drugs, especially verapamil can potentially be repurposed, for prevention of neurodegeneration and dementia in patients at high risk or in the early stages of disease. This is because verapamil, a highly efficacious phenylalkylamine Ca^{2+} channel blocking, with antioxidant, anti-inflammatory and nonspecific TXNIP inhibiting properties, effectively targets the main factors involved in the pathophysiology of dementia. Verapamil is currently approved by the FDA for treatment of various cardiovascular conditions including angina, hypertension and arrhythmias. It is also used first line in prevention of cluster headaches (Petersen et al., 2019). Furthermore, multiple pre-clinical studies indicate a positive effect of verapamil in ameliorating cognitive deficits and diminishing AD-like pathology in various animal models (Melone et al., 2018; Ponne et al., 2020; Popovic et al., 2020; Ahmed et al., 2021). These include models of familial "early-onset" AD (Melone et al., 2018), which account for only 5% of AD patients in addition to the more prevalent, late onset sporadic AD (sAD) (Chen et al., 2013; Kamat, 2015; Ahmed et al., 2021). The former is mostly associated with rare genetic mutations to amyloid precursor protein, presenilin-1, and presenilin-2, that cause initial symptoms to occur as early as the person's thirties, whereas the latter, which comprises over 95% of cases, typically occurs in subjects of advanced age (Ahmed and Ishrat, 2020). This form was modeled in our most recent study, given its much higher prevalence. In brief, we conducted a long-term study, for which we utilized a well-established model of clinical sAD in aged animals. This was obtained by intracerebroventricular administration of streptozotocin, a glucosamine-nitrosourea compound known to induce sAD like pathology. This model shares many biochemical and pathological features with clinical sAD, including acute neuroinflammation, impaired cerebral glucose metabolism, defective brain insulin signaling and central insulin resistance in addition to disturbed synaptic plasticity (Chen et al., 2013; Kamat, 2015; Ahmed et al., 2021). Moreover, the intracerebroventricular streptozotocin model of sporadic AD is reportedly associated with amyloid β plaques and hyperphosphorylated tau tangles in the later stages of disease (Chen et al., 2013).

In order to assess neurotherapeutic efficacy, we employed functional (cognitive/behavioral) and molecular outcomes. Our main focus was centered on preclinical functional measures, using tests established to simulate those implemented in the clinic. We believe that it is critical to target functional outcomes in any study assessing potential treatments for AD. This is because AD is fundamentally a clinical diagnosis, with cognitive and neurobehavioral outcomes serving as the primary criteria (cornerstone for diagnosis) in clinical practice (McKhann et al., 2011; Ahmed and Ishrat, 2020). Moreover, the large clinical studies currently focus primarily on behavioral and functional outcomes as the main measure of therapeutic success (Ahmed and Ishrat, 2020).

We determined that long-term, low dose verapamil treatment effectively prevents cognitive decline and sustains synaptic plasticity in this valid animal model of age related sAD (Ahmed et al., 2021). The results of our investigation were in accordance with earlier findings supporting the beneficial effects of verapamil in other models (Kumar et al., 2016; Melone et al., 2018; Ponne et al., 2020; Popovic et al., 2020; Ahmed et al., 2021). We also discovered the minimum effective dose of verapamil for cognitive support to be 1 mg/kg per day, which is much lower than that approved by the FDA for reduction of blood pressure. In fact, the dose used in our study is equivalent to a clinical dose of 80 mg/day, which is only 1/3 of the minimum clinical daily dose of verapamil (240 mg), calculated based on the average weight of an adult male ≈ 80 kg (176 pounds). Such a low dose, may effectively sustain cognitive function without affecting blood pressure, rendering it useful even for normotensive individuals. These findings indicate that long-term treatment with low dose verapamil may delay progression of sporadic AD in susceptible subjects of advanced age.

Although, the exact molecular mechanisms leading to such effect are not entirely understood, they are likely a result of not one but, a combination of favorable actions (**Figure 1**). Verapamil primarily functions to regulate Ca^{2+} and maintain homeostasis. This is essential since Ca^{2+} imbalance is known to be a critical factor in the pathogenesis of many neurodegenerative conditions and most notably AD. This Ca^{2+} imbalance leads to mitochondrial dysfunction, increases production of reactive oxygen species, impairs synaptic plasticity and mediates apoptosis. Verapamil also possesses acute anti-inflammatory activity, partly due to its early-stage downregulation of TXNIP and associated inhibition of the NLRP3 inflammasome pathway (Ahmed et al., 2021).

It is intuitive that complex, progressive conditions like AD would require a systematic approach for screening of patients in the early stages and initiating appropriate therapy, within a suitable time window of efficacy. Future trials should

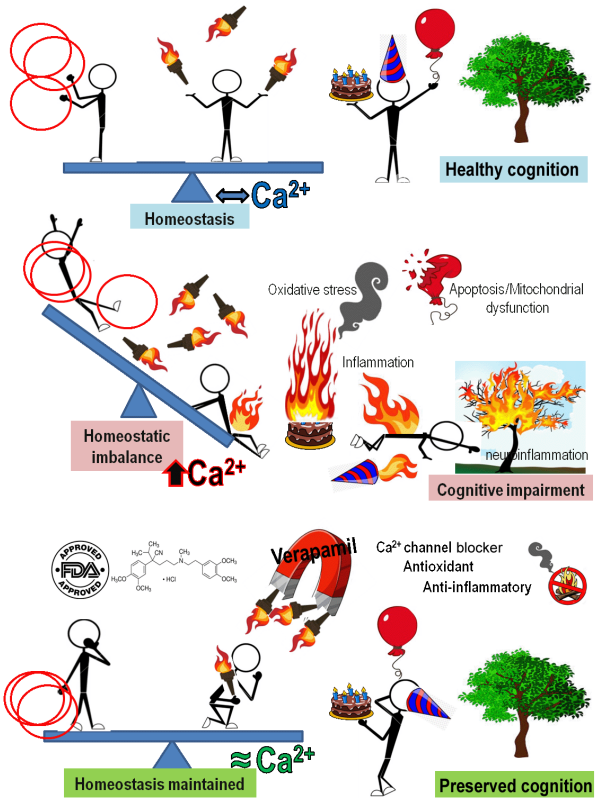

Figure 1 | **A mechanistic analogy of how verapamil works to preserve cognition.**
A simple analogy describing what sets off Alzheimer's disease in the brain is that of a birthday party gone awry because of a torch juggler's fatal attempt at breaking his own record, leading to disastrous consequences. In the healthy state, all is well and the performer juggles the metal fire torches (representing Ca^{2+}) skillfully and effortlessly, hence entertaining the audience and serving his purpose. The problems arise once he tries to juggle more than he can handle. The torches are not only heavy, causing an obvious "imbalance" but the juggler becomes overwhelmed and starts dropping them everywhere, starting with the candle studded birthday cake which catches fire (inflammation) and results in formation of smoke (oxidative stress). The excessive heat causes expansion of an air filled balloon in the vicinity (mitochondrial dysfunction) resulting in its rupture (Ca^{2+} mediated apoptosis/cell death), neuroinflammation (burning tree), neurodegeneration and cognitive impairment. Verapamil, a phenylalkylamine approved by the Food and Drug Administration, is represented by the magnet, which blocks the excess Ca^{2+} (metal torches) to maintain homeostasis. It also possesses additional anti-inflammatory and antioxidant activity.

hence focus on identifying patients in the very early pre-symptomatic stages, using relatively simple albeit effective diagnostic techniques. This is because there is often a delay in the development of symptomatic cognitive decline. This "preclinical phase" is likely the optimal stage for application of interventions to preserve cognition, as it would target their therapeutic time window of efficacy. While verapamil alone may not "cure" AD, there is reasonably consistent evidence supporting its benefit and potential application in prevention of dementia. Its ease of administration (oral availability, desirable pharmacodynamic characteristics), great tolerability, favorable side-effect profile, reasonable cost and extensive use are amongst the criteria that make verapamil particularly attractive. Typically, a specialized treatment regimen must be established, as part of a complete set of clinical guidelines and recommendations, for therapeutic management of patients in the various stages of disease. These should be periodically revised and updated as necessary to account for the most recent clinical findings. We believe that verapamil can potentially be repurposed for AD as part of a comprehensive therapeutic plan/regimen.

Further investigations using different models designed to explore the mechanism in greater depth would be useful. Nevertheless, irrespective of the complete mechanism, it is clear that verapamil appears to be a promising agent that may potentially be repurposed for prevention of cognitive decline and dementia in older adults who may be at risk.

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