Alzheimer’s disease (AD) is a neurodegenerative disorder that has affected millions of people worldwide. However, currently, there is no treatment to cure the disease. The AD drugs available in the market only manage the disease symptomatically and the effects are usually short-term. Thus, there is a need to look at alternatives AD therapies. This literature review aims to shed some light on the potential of repurposing antihypertensives to treat AD. Mid-life hypertension has not only been recognised as a risk factor for AD, but its relation with AD has also been well established. Hence, antihypertensives were postulated to be beneficial in managing AD. Four classes of antihypertensives, as well as their potential limitations and prospects in being utilised as AD therapeutics, were discussed in this review.

Keywords: Drug repurposing, alzheimer’s disease, anti-hypertensive, calcium channel blockers, ACE inhibitors, AT1 inhibitors, beta-blockers.

1. INTRODUCTION

Alzheimer’s disease (AD) is a neurodegenerative disorder, which is characterised by a progressive decline in cognitive and non-cognitive functions, affecting the patient’s memory and language skills [1]. The worldwide healthcare and personal costs that have exceeded hundreds of billions USD per year impose an undue burden on the caregivers [2]. Nearly 50 million people worldwide have been diagnosed with AD and related dementias, such as vascular dementia (VaD), frontotemporal dementia (FTD) and dementia with Lewy bodies (DBL) [3]. By the year 2050, the number is expected to increase to 131 million [4, 5]. AD is the most common type of dementia, covering two-thirds of the overall incidence of dementia and is the main focus of this review [6].

1.1. Current Medication for AD in the Market

The current treatments for AD, which are either cholinesterase inhibitors (CIs) or N-methyl-D-aspartate (NMDA) receptor antagonist, worked by balancing the disturbed neurotransmitter levels. CIs, including donepezil, rivastigmine and galantamine are used to treat mild-to-moderate AD by suppressing the activity of cholinesterase, thereby increasing acetylcholine (ACh) concentration at the synapses [4]. On the other hand, memantine, which is an NMDA receptor agonist, blocks the toxic amount of calcium through the NMDA receptor channel and is commonly used to treat moderate-to-severe AD [7, 8]. However, the success of these drugs in treating AD is limited as they do not work for every AD patient. Additionally, they fail to halt or reverse AD progression as they provide only short-term symptomatic benefits to the patients. Currently, no treatment can successfully treat the long-term progression and ongoing deterioration of dementia patients, including the acetylcholinesterase (AChE) inhibitors and others. Thus, more effective therapies are urgently needed to treat or delay the onset of disease.

1.2. Shortcomings of the Current Anti-AD Therapeutic Strategies

Over the last decade, researchers have been focusing on developing disease-modifying therapies (DMTs) including anti-amyloids which target the amyloid-beta (Aβ) peptide. β-site amyloid precursor protein cleavage
enzyme-1 (BACE1) inhibitor is one of the anti-
amyloids that aims to delay cognitive decline by reduc-
ing the generation of Aβ and subsequently formation of 
its oligomers. Studies conducted in vivo and on mild-
to-moderate AD patients have demonstrated a dose-
dependent reduction of Aβ levels in the cerebrospinal 
fluid (CSF) upon treatment with BACE1 inhibitors. However, these studies showed little to no cognitive 
benefit causing 17 of the BACE1 inhibitors to fail in placebo-controlled clinical trials. In fact, some of the 
trials were halted due to toxicity or safety concerns and 
cognitive worsening in the patients as compared to pla-
cebo [9].

Another anti-amyloid approach is monoclonal anti-
odies (mAbs), an immunotherapy strategy to lower 
Aβ oligomers in the CSF. No mAb has yet to produce 
significant clinical benefits in the patients despite being 
able to effectively abate the oligomeric forms of Aβ. 
One of the few mAbs, crenezumab has recently failed 
two phase III trials in AD patients due to lack of effi-
cacy [10]. Failure of the current efforts in managing 
AD suggests that strategies involving a single therapeu-
tic target at any stage might be insufficient to stop the 
progression of AD, considering the simultaneous in-
volvement of multiple pathological events [11].

1.3. Drug Repurposing

Drug repurposing or drug repositioning is an effec-
tive approach to drug discovery. It involves the explo-
ration of new applications for existing drugs that have 
already been licenced for the use of other indications 
[2, 12]. The conventional method of drug development is 
not only time-consuming, but it is also often met 
with limited success. The average success rate of a 
drug candidate reaching the market is only 2.01%, with 
many of them failing at various stages of clinical trials 
[13].

In drug repurposing, new indications will be built 
on the established safety profiles hence reducing the 
 risk of failure and shorten the time frame for drug de-
velopment [14, 15]. Besides, the cost of developing a 
new drug could be brought down significantly with this 
approach. Drug development via this approach costs 
only $1.6 billion as compared to $12 billion needed if 
the drug was developed from scratch [13]. The benefits 
ofered by this approach have led to numerous suc-
cesses in developing new indications using existing 
therapeutics. A few of the well-known examples in-
clude repurposing of minoxidil (initially developed to 
treat ulcer) to treat hypertension and anti-hypertensive 
sildenafil to treat erectile dysfunction [15]. Other ex-
amples of drugs that have been successfully repurposed 
recently are aspirin (anti-inflammatory) for myocardial 
infarction and topiramate (anti-epileptic) for obesity 
[16].

Drug repurposing could turn out to be a wise ap-
proach in the search for new AD therapeutics. Not a 
single AD drug has been pushed out to the market de-
spite billions of dollars spent on developing new AD 
drugs in the last two decades. Much of this is due to the 
complexity of the disease itself. The etiology of AD 
has yet to be completely understood. Thus, investing a 
huge sum of money, time and effort to develop an AD 
drug without clearly understanding the cause of the 
disease is a considerable risk. As a fit-for-all AD ther-
apy has so far failed, a shift in paradigm where targeted 
treatment is developed for specific AD patients that 
share distinct genetic or pathological similarities is a 
viable strategy.

1.4. The Relation between Hypertension and Alz-
heimer’s Disease

The link between mid-life hypertension and onset of 
AD is well-studied. Mid-life hypertension is not only 
recognised as a risk factor for AD but atherosclerosis as 
well [17, 18]. Atherosclerosis initiates re-modeling of 
cerebral arteries and narrows the arterial lumen. The 
resulting impairment of cerebral autoregulation leads to 
cerebral hypoperfusion, which limits blood flow and 
oxygenation in the white matter of the central nervous 
system [19]. White matter, which consists of mainly 
myelin-producing oligodendrocytes and axons enclosed 
by myelin, plays a role in signal transmission between 
different regions of the brain [20]. Reduced blood flow 
and delivery of oxygen to the tissues cause ischemic 
and hypoxic damages, respectively. Ischemic periven-
tricular white matter induces oligodendrocyte cell 
death, forming white matter lesions (WMLs) following 
demyelination of the cells in affected areas. WMLs 
have been shown to be present in parallel with amyloid 
and tau abnormalities in the cerebrospinal fluid (CSF) 
of AD patients [19], suggesting that they contribute to 
the formation of senile plaques and neurofibrillary tan-
gles (NFTs) [21-23].

Two of the mechanisms underlying both oligoden-
drocyte cell death and demyelination are oxidative 
stress and inflammation [20]. Previous studies have 
reported that oxidative stress can be induced by ische-
mia due to over-production of reactive oxygen species 
(ROS) [20]. In addition to ischemia, angiotensin II (ang 
II) also tends to amplify the production of ROS by 
stimulating the activation of NADPH oxidase, which
promotes oxidative stress. Ang II is found at high levels in people with hypertension. It was previously reported that oxidative stress accelerates the deposition of Aβ and aids the formation of NFT [24, 25]. Moreover, it was also shown to activate NF-κB, a transcription factor that initiates the inflammation cascade, which plays a role in the progression of AD [26].

Having established a clear correlation between hypertension and AD (Fig. 1), it was hypothesized that antihypertensives (AHTs) might be beneficial in combating AD. Considering the need and urgency to find new AD therapeutics which have seen many failed trials in the past decade, the proposition of utilising AHTs in AD is indeed of great interest. Hence, this review aims to provide an insight into the current status of repurposing several classes of AHTs for the treatment of AD. The limitations as well as future prospects of AHTs in being used as AD therapeutics will also be discussed in this review.

2. ANTIHYPERTENSIVE DRUGS

AHTs are compounds that aid in the prevention, control and treatment of hypertension. There is a wide range of AHTs which can be separated into various classes, as they differ in terms of their structures and mechanisms of action [27]. In this review, four classes of the most common AHTs are reviewed to evaluate their potential for the management of AD (Fig. 2) (Table 2). They are calcium channel blockers (CCBs), angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs) and beta-blockers (BBs).

2.1. Calcium Channel Blockers

Calcium ions are important for memory formation as they control synaptic plasticity. However, increased intracellular calcium levels at the L-type calcium channel (LTCC) is undesirable [4]. At high intracellular calcium levels, modulation of APP processing will be affected. This, in turn, facilitates Aβ formation through the action of β-secretase. Furthermore, elevated levels of intracellular calcium will also promote the hyper-phosphorylation of tau protein, which eventually leads to NFT formation [28]. Besides, this rampant increase in calcium further triggers the overexpression of Ca v1.2, exacerbating calcium influx to a greater extent [29].

Findings from in vitro and in vivo studies supported the use of CCBs to treat AD. CCBs are efficient in curbing intracellular calcium levels, thus reducing glutamate-induced cell death. CCBs help in reducing production, oligomerization and accumulation of Aβ as well, which subsequently prevent Aβ-induced neurotoxicity [2]. Furthermore, in vivo CCB treatment has been demonstrated to improve the clearance of toxic Aβ1-42 from the brain due to a significant increase in transcytosis across blood-brain barrier (BBB) [29]. Some of the current CCB which have been evaluated as potential AD therapeutics are further discussed.

2.1.1. Isradipine

Isradipine is a dihydropyridine CCB which selectively binds to Ca v1.2. Apart from being able to attenuate the level of hyperphosphorylated tau [30, 31], it has been shown to provide neuroprotective effects downstream of senile plaques formation [31]. Anekonda and Quinn have reported the attenuation of tau burden and Aβ oligomer toxicity in both in vivo as well as in vitro studies. These effects were conferred following the suppression of Ca v1.2 expression and calcium influx by depreciating the function of over-activated Ca v1.2 [28]. Additionally, the reduction of the neurotoxic effect caused by Aβ accumulation in AD models was reported by Copenhaver et al. [32]. Isradipine has also shown to attenuate apoptotic cell death induced by oxidative stress in hypoxic rat models, which contributed towards the protection of memory function [28].

2.1.2. Nilvadipine

Nilvadipine is a dihydropyridine CCB that is being used to treat hypertension and chronic significant cerebral artery occlusion. In the AD context, it provides benefits by preventing further cognitive decline in mild cognitive impairment (MCI) of hypertensive patients [33]. Its mechanism of action has been probed and it is postulated to hasten Aβ clearance. Administration of nilvadipine in AD animal models was shown to reduce Aβ levels significantly in the AD brain and further boosting learning and memory. Lowered Aβ levels also restored the cerebral blood flow (CBF) in in vivo studies and early-stage AD patients [30, 31, 34].

Paris et al. reported an increase in CBF of AD animal models following a complete antagonism of the vasoactivity of Aβ after a short-term nilvadipine treatment of two weeks [35]. Restored CBF is vital to allow optimal delivery of both nutrients and oxygen to the glial cells and neurons, besides removing metabolic wastes and neurotoxins effectively from the brain [35, 36]. Low dosage of nilvadipine was found to be neuroprotective by preventing spatial memory and neuronal apoptosis [37]. Nilvadipine has also been shown to reduce hyperphosphorylation of tau and inflammation in AD mouse models, besides facilitating Aβ clearance,
which is possibly attributed to the restoration of CBF [38].

Although phase II trial demonstrated that nilvadipine was safe and well-tolerated in AD patients [12], it failed a phase III trial. It was reported to fail to slow down cognitive decline in AD patients despite showing a reduction in Aβ production, inflammation, tau activity and restoration of regional CBF [39, 40].

2.1.3. Nimodipine

Nimodipine is another AHT drug that belongs to the dihydropyridine class of CCB. Tan et al. reported a significant drop in apoptosis of neuronal cells and tau hyperphosphorylation with the administration of nimodipine [41]. Improvement of memory and learning abilities was demonstrated owing to the decline in tau hyperphosphorylation. The miR-132/GSK-3β pathway was hypothesized to be responsible for the attenuation of both cell apoptosis and tau hyperphosphorylation. miR-132 regulates synaptic plasticity and is involved in learning and memory. It is also believed to take part in the prevention of neuronal apoptosis. In the AD brain, miR-132 is down-regulated. In order to regulate its expression, it targets the tau protein mRNA. GSK-3β on the other hand is an enzyme that helps in regulating cellular processes in neurodegenerative disorders. Over-activation of GSK-3β is linked to neuronal dysfunction. Nimodipine exerts its neuroprotective effects by up-regulating the expression of miR-132 while down-regulating GSK-3β [41].

In a phase IV trial, nimodipine failed to prevent cognitive decline in patients with vascular MCI and acute ischemic stroke despite demonstrating moderate cognitive improvement in terms of the patient’s memory domain [42]. The limited clinical efficacy could be due to its low oral bioavailability as it is poorly water-soluble [43]. For this purpose, Moreno et al. have recently come up with a strategy to overcome the low bioavailability of nimodipine [44]. They developed pegylated nanoparticles as oral carriers of nimodipine and reported a significant improvement of the oral bioavailability approximately 7-fold higher than control drug in solution [44]. The results in the actual trial remain to be seen.

2.2. Renin-Angiotensin System (RAS) Inhibitors

RAS is an enzyme cascade system that not only regulates the blood pressure, but is also vital in regulating cognitive function [45]. Juxtaglomerular cells in the kidney are stimulated by a drop in arterial blood pressure to release renin, a proteolytic enzyme that acts on angiotensinogen to form angiotensin (ang) I. ACE then hydrolyses ang I into ang II. Ang II exerts its physiological effects by binding to either one of its two receptors, namely the ang II receptor type 1 (AT1) and ang II receptor type 2 (AT2). A continual RAS activation has been reported to be associated with impaired cognitive functions [46].

Ang II develops neuroinflammation, which is one of the underlying AD pathophysiology [47] and this may be attributed to the role of ang II in releasing inflammatory mediators. Besides, ang II inhibits ACh release at the synapse, contributing to the cholinergic hypothesis [2]. The binding of ang II to AT1 also results in an increase in oxidative stress and APP mRNA, cerebral hypoperfusion and remodeling of tissue, which disrupts memory consolidation and retrieval [48]. The two types of RAS inhibitors are ACE inhibitors and ARBs.

2.2.1. Angiotensin-Converting Enzyme (ACE) Inhibitor

ACE inhibitors are prescribed to impede the conversion of ang I to ang II, thus reducing both the level of ang II and activation of AT1. The use of ACE inhibitors in AD has demonstrated restoration of cerebral hypoperfusion and inhibition of cytokine release, which has shown to prevent cognitive impairment in AD mouse models. These inhibitors have also been postulated to increase the activity of ACh, opposing the effect exerted by ang II [49]. Furthermore, inhibition of ACE has demonstrated retardation of neurodegeneration symptoms and hyperphosphorylation of tau protein in vivo [50]. The improvement of cognition following treatment with ACE inhibitors is independent of the blood pressure effects and is said to be superior to beta-blockers [48]. One reported downside of ACE inhibitors is a decline in Intelligence Quotient (IQ) following long-term treatment in hypertensive patients. The conversion of toxic Aβ42 to neuroprotective Aβ40 is mediated by ACE and inhibition of ACE maintains a high level of Aβ42 in the plasma and brain, impairing the IQ [51].

2.2.1.1. Captopril

A decline in ACE mRNA level has been reported in the cortex of hypertensive rat models, which were treated with captopril [46]. As a result of reduced ACE level in the brain, there will be a drop in the expression of ang II as well as level of APP [48]. Decreased level of APP is expected to reduce the formation of Aβ, but in vivo studies have demonstrated the inability of captopril to alter the deposition of senile plaques.
Hemming et al. reported that captopril neither affected cerebral Aβ levels nor altered the deposition of senile plaques [52]. Yamada et al. reported similar findings, suggesting that it is unlikely that ACE inhibitors can provide symptomatic benefits to AD by inhibiting degradation of toxic Aβ in humans [53]. In fact, there has been an in vitro study that reported an increase in Aβ accumulation, further aggravating the symptoms of AD [50]. This finding could be attributed to the fact that the existing toxic Aβ12 in the brain failed to be converted to the less toxic Aβ40 by ACE.

Conversely, there were also in vivo studies that have reported the impedance of Aβ plaques development following captopril treatment. AbdAlla et al. discovered a reduction in ROS and protein oxidation in the hippocampal region, due to a reduced AT1 activation [2]. Perindopril is a central-acting ACE inhibitor that can block AT1. These antagonists are different in terms of their affinity for AT1, duration of the blockade and thus, the duration of the action exerted [58]. In contrast to ACE inhibitors, ARBs do not reduce the levels of ang II, allowing ang II to bind to AT2 [59]. Treatment with ARBs was reported to slow cognitive decline and reduce the conversion to the AD of patients with MCI by one third [60]. ARBs are highly effective in slowing the progress of AD in comparison to other AHT, including ACE inhibitors. As ang II facilitates the progression of AD, ARBs can block the effect of ang II for 24 hours [58].

In addition to modulating the inflammatory cascade, perindopril has been reported to decrease activation of the receptor for advanced glycation end products (RAGE) in vivo. RAGE has a role in regulating the transport of peripheral Aβ1-42 into the brain, resulting in an increase in Aβ1-42 deposition, formation of senile plaques and eventually memory impairment. Thus, reduced RAGE activation could help in benefiting the Aβ-induced neurodegeneration in AD [45].

### 2.2.2. Angiotensin II Receptor Blocker

ARBs are non-peptide antagonists that selectively block AT1. These antagonists are different in terms of their affinity for AT1, duration of the blockade and thus, the duration of the action exerted [58]. In contrast to ACE inhibitors, ARBs do not reduce the levels of ang II, allowing ang II to bind to AT2 [59]. Treatment with ARBs was reported to slow cognitive decline and reduce the conversion to the AD of patients with MCI by one third [60]. ARBs are highly effective in slowing the progress of AD in comparison to other AHT, including ACE inhibitors. As ang II facilitates the progression of AD, ARBs can block the effect of ang II for 24 hours [58].

Candesartan shows an exceptional affinity for AT1, relative to other ARBs. It dissociates slowly from the receptor to produce a long-lasting and effective inhibition in the brain, exerting a longer duration of action. Culman et al. reported that even at doses five to ten-fold lower than other ARBs such as losartan, candesartan can block the effect of ang II for 24 hours [58].

Findings from existing studies revealed the potential of candesartan as a potent anti-inflammatory agent, with limited benefits on cognition as the Aβ pathology was unaltered. One study reported increased levels of neurogenesis markers besides showing little to no improvement in spatial learning and a consistent load of amyloid plaque [60].

However, another study by Torika et al. reported a significant reduction in amyloid burden by an observed decline in the deposition of Aβ in younger AD mouse models. Candesartan treatment was suggested to have induced phagocytosis of Aβ1-42 by microglia, which helps in degrading the Aβ aggregates and possibly halt-
ing AD progression [61]. The discrepancy of results between studies can possibly be attributed to the potential of candesartan in treating only early or mild stages of AD. Candesartan treatment has also shown to reduce the expression of pro-inflammatory markers in a dose-dependent manner besides mitigating the levels of pro-inflammatory cytokines by reducing their release from microglial cells [61]. Another study has reported that shorter treatment (3 weeks) of candesartan led to a decline in CD11b and thus microglial activation in the animal models, displaying its anti-inflammatory effect [61].

Other reported effects of candesartan treatment are the restoration of CBF, increase in ACh level and suppression of AChE activity [62]. Candesartan is currently in a phase II trial (CEDAR, NCT02646982) to study its effect on patients with MCI, in terms of cognition and thinking skills, besides evaluating its safety and response when administered at an escalating dose. This study is estimated to reach primary completion in September 2021 [39].

2.2.2.2. Valsartan

Valsartan has previously been reported to reduce the oligomerization of Aβ peptides into high molecular weight (HMW) oligomeric peptides, which have a role in deteriorating cognition. This finding was reported by Wang et al. [63] when they screened a total of 55 clinically prescribed AHTs to test out the potential of each drug in modifying AD. The in vivo study using AD mouse models was performed with doses of either 10 or 40 mg/kg daily, which is twice as low as the recommended dose used to treat hypertension in humans. A two to three-fold decrease in HMW Aβ oligomers in the brain was observed [63]. Valsartan treatment was also shown to promote Aβ-related retention of spatial memory and learning [63]. From the non-Aβ aspect, another study reported the potential of valsartan in attenuating oxygen and nitrogen free radicals, which has shown to ameliorate oxidative stress. This study also reported an improvement in memory and cognition upon administration of valsartan [64]. From the previous studies, valsartan has shown to have minimal adverse effects and is generally considered safe [64].

2.2.2.3. Telmisartan

Telmisartan is both an ARB and a partial peroxisome proliferator-activated receptor (PPAR-γ) agonist, which exerts AT₁ blockade and PPAR-γ activation, respectively, contributing to its high potency. Tsukuda et al. demonstrated that even at a low dose of 0.35 mg/kg daily, telmisartan treatment successfully restored the lowered CBF in AD mouse models to promote clearance of Aβ and suppression of β-secretase enzyme. Aβ clearance attributed to an improvement in reduced CBF significantly reduces the concentration of Aβ₄₀ in the brain. They also revealed that pre-treatment with telmisartan ameliorated cognitive decline [65]. Mogi et al. have reported similar findings whereby pre-treatment with telmisartan at a non-hypertensive dose managed to improve cognitive function. This finding could be attributed to an improvement of Aβ clearance from the brain, attenuating Aβ deposition [66]. Another study reported that a low dose of orally-administered telmisartan (0.3 mg/kg daily) reduced the levels of Aβ and phosphorylated tau in the brain, whereas high dose (3 mg/kg daily) facilitated further reduction [67]. Telmisartan has also been reported to improve cholinergic activity besides attenuating the Aβ-induced cognitive decline [68, 69]. In addition to the benefits aforementioned, telmisartan has been evidenced to exert potent anti-inflammatory benefits. Telmisartan treatment has shown to suppress the expression of pro-inflammatory cytokines and inducible nitric oxide synthase (iNOS) in the brain [65].

Similar to candesartan, telmisartan is a selective ARB that exerts a long-acting response as it has been reported to have the strongest binding affinity to AT₁ among the other ARBs. Additionally, it also has a well-established ADME/T profile besides high lipophilicity, which potentially enhances its penetration across the BBB [58, 67, 70]. Telmisartan is currently undergoing phase II and Ib trials, which are estimated to reach primary completion in March 2020 and June 2020 respectively. The phase II trial (SARTAN-AD, NCT02085-265) aims to deduce if one-year of treatment will lead to brain atrophy, in comparison to treatment with perindopril, an ACE inhibitor [39]. The phase Ib trial (HEART, NCT02471833), on the other hand intends to evaluate if telmisartan treatment exerts similar beneficial effects to prevent AD in African Americans who possess high susceptibility to AD. The action of telmisartan in modifying the levels of CBF, Aβ and inflammatory markers in the brain will be assessed [71].

2.2.2.4. Losartan

Losartan is an AHT that has been reported to exert anti-amyloidogenic, anti-oxidant and anti-inflammatory benefits. Losartan treatment (10 mg/kg/day) administered intranasally for two months has demonstrated a 3.7-fold reduction in Aβ plaques besides modulating the inflammation cascade in the brain of AD mice. The levels of pro-inflammatory cytokines,
IL-12 and IL-1β were found to be lower prior to the treatment, while the level of anti-inflammatory cytokine, IL-10 increased [72]. Similar findings were reported by Drews et al. following intranasal administration of losartan in vivo. Treated AD mice showed a reduction in both Aβ40 and Aβ42 levels, which may be due to an increase in the levels of proteins involved in the metabolism and clearance of Aβ from the brain. A few of the proteins are nuclear export protein, insulin-degrading enzyme and transthyretin [73]. Another in vivo study demonstrated attenuation of neuroinflammation, accumulation of NO metabolites and lipid peroxidation following pre-treatment of losartan administered intraperitoneally [74]. There is one in vivo study, however, that has failed to demonstrate anti-amyloidogenic benefits. Losartan treatment administered orally did not restore cognitive impairment of the AD mice and the load of Aβ plaques was not altered [75]. The contrariety of findings could be due to the different routes of administration (i.e. intranasal vs. intraperitoneal vs. oral), which may have affected the benefits exerted by the drug. The oral bioavailability of losartan tablets has been previously reported to be as low as 33% [76].

In addition to the benefits aforesaid, losartan has shown to enhance cognitive function. As the drug crosses BBB to antagonise AT1, there would be a resulting increase in the level of ang IV. Ang IV then binds to ATIV. Activation of ATIV has been revealed to play a part in memory acquisition and recall, possibly by regulating the release of neurotransmitter and modulating both the hippocampal cholinergic and glutamatergic pathways [77]. Besides, in vitro and in vivo studies conducted by Drews et al. have demonstrated the protection exerted by losartan against hypoxia and exposure to a toxic concentration of glutamate. An increase in the levels of IL-10, NEP and choline acetyltransferase (ChAT) was observed [73]. Losartan is currently in phase II trial (HIPAC, NCT03354143) to evaluate if its blood pressure-lowering benefit is able to reduce the accumulation of Aβ protein in the AD brain. This study is estimated to reach primary completion in May 2022 [78].

2.3. Beta-Blockers (BBs)

BBs are commonly used for the treatment of hypertension. As BB antagonises β1-adrenoreceptor, cardiac output will be reduced. This causes an increase in the peripheral vascular tone to regulate blood pressure. Another proposed mechanism of action is the anti-renin activity attributed to the suppression of renin release from the juxtaglomerular apparatus. The release of renin, which is stimulated by the binding of a catecholamine to β1-adrenoreceptor, is blocked as BBs competitively antagonize the receptor. BBs have been reported to poorly penetrate BBB [79] in addition to having a lower AHT potency as compared to CCBs and RAS inhibitors [80].

2.3.1. Propranolol

Propranolol is a non-selective antagonist of β-adrenoreceptor, which has been used widely as an AHT. A 6-month study assessed the efficacy of propranolol in improving the disruptive behaviours of residents in the nursing home with probable AD. This study reported that propranolol may be beneficial in ameliorating aggression and uncooperativeness [81], suggesting potential in treating AD in terms of non-cognitive dysfunction. Wang et al. screened 1600 drugs which have been approved by the Food and Drug Administration, for their ability to modify the activity of Aβ. Propranolol was reported to decrease the levels of Aβ in vitro [82]. Findings from an in vivo study conducted by Dobarro et al. have demonstrated that even at doses lower than that prescribed for hypertension in patients (5mg/kg/day), propranolol was able to ameliorate memory deficits and hence restore cognitive function. In addition, propranolol was also reported to reduce levels of Aβ42, provide protection against Aβ neurotoxicity and reduce hyperphosphorylation of tau protein [83]. The findings from this study were postulated to be independent of the AHT effect of BB, in contrary to what Gelber et al. have reported. Their study suggested that attenuation of cognitive impairment was not observed among patients with a higher baseline of systolic blood pressure (SBP) ≥ 150 mmHg, proposing that the effects exerted by propranolol are partly dependent on the control of SBP [84]. Propranolol was shown to be well-tolerated at doses up to 40 mg/administration thrice daily [81].

2.3.2. Carvedilol

Carvedilol is a non-selective β-adrenergic receptor blocker, prescribed to treat mild-to-moderate hypertension [85, 86]. The anti-oxidant property of carvedilol has previously been demonstrated in numerous studies, mainly due its ability to scavenge free radicals and thus, inhibiting lipid peroxidation. In fact, according to Yue et al. carvedilol serves as an antioxidant, which is way more potent in comparison to other BBs, including propranolol, atenolol and pindolol [87]. In vivo studies on AD mice with colchicine- and D-galactose-induced
Repurposing Antihypertensive Drugs for Managing Alzheimer's Disease

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Hypertension

Atherosclerosis

Impairment of cerebral autoregulation

Cerebral hypoperfusion

Ischemia and hypoxia

White matter lesions

Alzheimer's disease

Activation of NADPH oxidase

ROS production

Oxidative stress

Formation of senile plaques and NFTs

Inflammatory response

Fig. (1). Scheme for the proposed mechanisms relating hypertension to AD.

Calcium Channel Blocker

Isradipine

Nilvadipine

Nimodipine

Angiotensin Converting Enzyme Inhibitors

Captopril

Perindopril

Angiotensin II Receptor Blockers

Candesartan

Valsartan

Telmisartan

Losartan

Beta-blockers

Propranolol

Carvedilol

Fig. (2). Chemical structures of the reviewed AHTs for the treatment of AD.
Table 1. Summary of the results obtained from preclinical studies and clinical trials of the AHTs reviewed.

<table>
<thead>
<tr>
<th>AHT Class</th>
<th>AHT Drug</th>
<th>AD Related Observation in Preclinical Studies</th>
<th>Clinical Trials</th>
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</table>
| **CBB**   | Isradipine | • ↓ level of hyperphosphorylated tau [23, 25, 26] \(^a,b\)  
• ↓ Aβ oligomer toxicity [23, 26]  
• ↓ neuronal apoptosis induced by oxidative stress [23] | n/a \(^d\) |
|           | Nilvadipine | • ↑ Aβ clearance [25, 26, 29, 33] \(^c\)  
• ↑ CBF [25, 26, 29, 30]  
• ↓ neuronal apoptosis [33]  
• ↓ level of hyperphosphorylated tau [33]  
• ↓ neuroinflammation [33] | (i) NCT020173400 (NILVAD); Phase III  
Status: Failed [34, 35] |
|           | Nimodipine | • ↓ neuronal apoptosis [36]  
• ↓ level of hyperphosphorylated tau [36] | (i) NCT01220622 (NICE); Phase IV  
Status: Failed [37] |
| **ACEI**  | Captopril | • ↓ generation of ROS [49]  
• ↓ production of toxic Aβ\(_{1-42}\) [49]  
• ↓ neuroinflammation [50] | n/a |
|           | Perindopril | • ↓ neuroinflammation [42]  
• ↓ transport of peripheral Aβ\(_{1-42}\) into the brain [40] | n/a |
| **ARB**   | Candesartan | • ↓ neuroinflammation [56]  
• ↑ phagocytosis of Aβ\(_{1-42}\) [56]  
• ↑ CBF [57] | (i) NCT02646982 (CEDAR); Phase II  
Status: Ongoing [34] |
|           | Valsartan | • ↓ oligomerization of Aβ peptides [58]  
• ↓ oxygen and nitrogen free radicals [59] | n/a |
|           | Telmisartan | • ↑ CBF [60]  
• ↑ Aβ clearance [60, 61]  
• ↓ level of hyperphosphorylated tau [62]  
• ↓ neuroinflammation [60] | (i) NCT02085265 (SARTAN-AD); Phase II  
Status: Ongoing [34]  
(ii) NCT02471833 (HEART); Phase Ib  
Status: Ongoing [67] |
|           | Losartan | • ↓ Aβ plaques [68]  
• ↑ metabolism and clearance of Aβ [69]  
• ↓ neuroinflammation [68, 70] | (i) NCT03354143 (HIPAC); Phase II  
Status: Ongoing [73] |
| **BB**    | Propanolol | • ↓ level of Aβ [77, 78]  
• ↓ Aβ neurotoxicity [78]  
• ↓ level of hyperphosphorylated tau [78] | n/a |
|           | Carvedilol | • ↓ oxidative damage [81, 83, 84]  
• ↓ oligomerization of Aβ peptides [86]  
• ↓ neuroinflammation [85] | (i) NCT01354444; Phase IV  
Status: Failed [87] |

\(^a\) Refer to the numbered reference in the text.  
\(^b\) ↓: decreased  
\(^c\) ↑: increased  
\(^d\) n/a: not available

oxidative stress showed an improvement in the resulting oxidative damage following carvedilol treatment. In addition to its anti-oxidant property, carvedilol treatment was reported to significantly attenuate cogni-
tive impairment and behavioural abnormalities [88, 89]. In vitro studies have also reported similar findings. Cells when treated with carvedilol exhibited increased susceptibility to hydrogen peroxide-induced cell death in a dose-dependent manner [87]. In an in vitro cell model, carvedilol provided protection against cell toxicity by inhibiting hypoxia-induced generation of ROS [90].

Additionally, structural analysis has suggested the ability of carvedilol to bind Aβ due to its 3-dimensional pharmacophore conformation. Aβ binding helps in preventing the formation of oligomeric fibrils. Wang et al. [91] discovered that with carvedilol treatment, oligomerization of Aβ1-42 was not observed, while oligomerization of Aβ1-40 was interfered in a dose-dependent manner. Reduced level of oligomeric Aβ is important to help in improving synaptic neurotransmission. Nonetheless, carvedilol treatment does not have any impact on the expression of APP transgene [91].

Furthermore, inhibition of NF-κB following carvedilol pre-treatment suggests that it may also possess anti-inflammatory properties. NF-κB is a regulator of the inflammatory cascade and has a role in mediating the levels of pro-inflammatory cytokines. When pre-treated with carvedilol, a reduction in the levels of TNF-α, IL-1β and IL-6 as well as the expression of iNOS was reported. An in vitro study by Gao et al. demonstrated that carvedilol can potentially be used to treat hypoxia or ischemia, in which both conditions will eventually lead to Aβ-induced neurotoxicity [90]. Despite various neuroprotective benefits exerted by carvedilol, it has failed a phase IV trial for AD [92].

3. PSEUDO-ANTIHYPERTENSIVES

β-hydroxy β -methylglutary-coenzyme A (HMG-CoA) reductase inhibitor or commonly known as statin, is one of the most widely used medications for its cholesterol-lowering property. Apart from its role as an antihyperlipidemic agent, statin has also been reported to have clinical benefits in treating hypertension [93].

Thus, it is not surprising that statin therapy comes with anti-inflammatory and anti-oxidant effects, similar to most of the AHTs. Amelioration of inflammation and oxidative damage upon statin therapy has been reported to have reversed neurovascular dysfunction, which eventually slows down the progression of disease [94]. In vivo studies have also postulated that the cholesterol-lowering effect exerted helps in reducing the formation of Aβ and NFTs [95]. A meta-analysis performed by Chu et al. involving fourteen studies has suggested that statin therapy may help to reduce the risk of developing AD [95].

4. POTENTIAL LIMITATIONS TO USING ANTIHYPERTENSIVES FOR AD

The idea of repurposing AHTs for managing AD is still relatively new. Although there are strong and concrete evidences that AHTs are useful in the management of AD, there are also potential limitations to it. A recent study by Vazirinejad et al. suggested that the improvement of cognitive function was only observed among AD patients aged 40 years and above [96]. Although the efficacy of AHTs seems to be limited by the age of patients, this may not be a handicap as AD mostly affects people aged over 65 years old [97]. Recent findings from an observational cohort study conducted by van Dalen et al. should also be taken note. Their results demonstrated that discontinuation of AHTs in the elderly aged 70-78 years not only did not preserve cognition but may possibly impose a higher risk of dementia [98]. Although not many downsides have been reported, the use of AHTs in AD still needs to be thoroughly investigated.

CONCLUSION AND FUTURE PROSPECTS

Collectively, a vast range of AHT has been proposed to exert effects that can potentially treat AD (Table 1). While some of the drugs presented in this review have failed, there are those that are still in various phases of clinical trials pending the results. A meta-analysis performed to compare the effect of different AHTs on AD incidence reported that ARBs have a more substantial inverse relation with AD risk, based on findings from prospective studies. However, since most of the randomized controlled trials and prospective studies included in this meta-analysis were short-term, further longer-term trials might be more beneficial in providing more conclusive evidence to determine the impact of different AHT classes on AD risk [99]. Among the four types of AHT reviewed, ARBs may have the best potential to treat AD, mainly because of the drawbacks of the other AHTs. For example, two out of the three CCBs evaluated have failed to demonstrate good efficacy in their respective trials, while ACE inhibitors might prevent the conversion of neurotoxic Aβ42 to Aβ40, causing a risk of IQ deterioration. The last class of AHT, BBs have lower potency relative to other AHTs besides having poor penetration across the BBB. Poor pharmacokinetic profile of BBs calls for drug modification or a change in drug delivery method. For example, repurposed drugs with poor bioavailability can be modified into its prodrug before
administration [100]. They can also be prepared in a different formulation, such as in nanoparticle form, to improve their PK/PD profile [44]. In addition, another potential area to explore is the use of AHTs in conjunction with the current approved AD drugs. This should be further investigated as a positive synergistic effect between AHTs and cholinesterase inhibitors that have recently been reported [101].

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CONFLICT OF INTEREST
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Repurposing Antihypertensive Drugs for Managing Alzheimer’s Disease


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