



EXPLORING THE POTENTIAL OF ANTIHYPERTENSIVE AGENTS IN DEMENTIA MANAGEMENT: A COMPREHENSIVE REVIEW INCLUDES PHARMACEUTICAL APPROACHES

Sarika R. Jadhav^{*1}, Shashikant N. Dhole², Hemant P. Alhat³ and Nilesh S. Kulkarni⁴

PES's Modern College of Pharmacy, For Ladies, Moshi, Pune.



***Corresponding Author: Sarika R. Jadhav**

PES's Modern College of Pharmacy, For Ladies, Moshi, Pune.

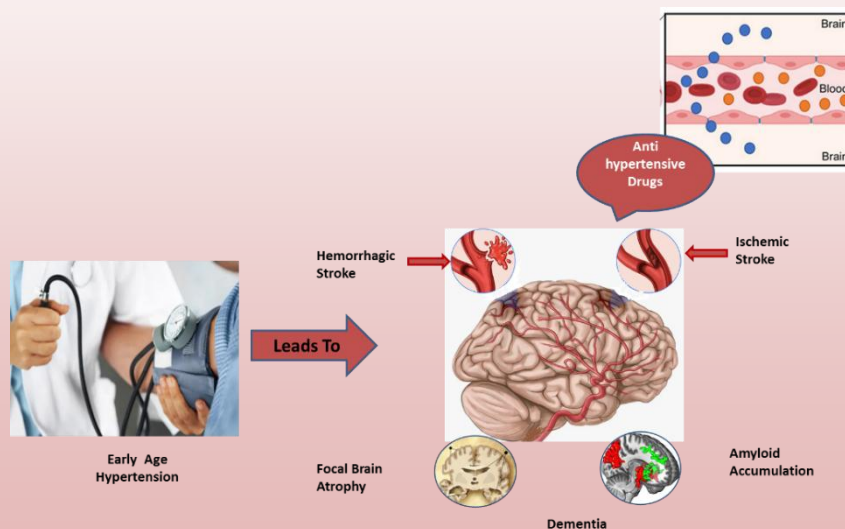
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ABSTRACT

Over the time of period prevalence of the hypertension and dementia increases worldwide and they are interdependent. The early age onset of hypertension responsible for different kind of diseases includes coronary heart diseases, cerebrovascular accident and vascular infraction, in some cases leads to white matter lesions, micro bleeds, cognitive deformities and impairment, dys-functioning of the vessels which leads to the vascular dementia. 35 to 84 % patients with hypertension suffering from dementia. The patients who are taking antihypertensive medication significantly reduces the risk of dementia. Randomized clinical trials studies shows that antihypertensive agents like calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors reduces the risk of dementia by 50%. Novel pharmaceutical approaches help to improve the performance of antihypertensive in the control and management of dementia. This article focuses on potential of antihypertensive agents in control and treatment of dementia also highlighted the pharmaceutical approaches.



KEYWORDS: Hypertension, Dementia, Antihypertensive drugs, Potential.

INTRODUCTION

In recent era of unhealthy modernization in lifestyle, sub-quality of food available, sudden and fast mutations in the viruses, complications arises in rare diseases like neurodegenerative diseases get in increased in last decade and going to be increased in future.^[1] Drug repurposing which is growing trend in recent year because of lack of therapies for many rare diseases which

involves reuse of the existing drug for new identified therapeutic purpose.^[2] Antihypertensive agents has potential to act centrally and improve the symptoms of cognitive decline. Our research article focused on to discussion of relationship between hypertension and dementia and related diseases, possible role of different antihypertensives in management of neurodegenerative diseases. Review also aims to investigate the different

pharmaceutical approaches that are helpful to increase the efficacy of mentioned drug in dementia.

Relationship between Hypertension and Dementia and Related Diseases

Early age high blood pressure without symptoms is slowly and silently harm the body badly. Uncontrolled and untreated hypertension responsible for inability to function, fatal heart attack or even stroke. Transient ischemic attack (TIA) also called mini-stroke is one of

the threaten effect of hypertension. TIAs can be caused by blood clots or hardened arteries caused by high blood pressure. A TIA can often to be followed by a full-blown stroke. Hypertension is the most significant risk factor for particular vascular dementia and cognitive decline. It may inhibit, burst or leak the blood vessel. Sometimes it may responsible for blood clot formation in arteries which supply blood flow to brain, obstructing the blood flow and hence induce the stroke^[3] [Figure 2].

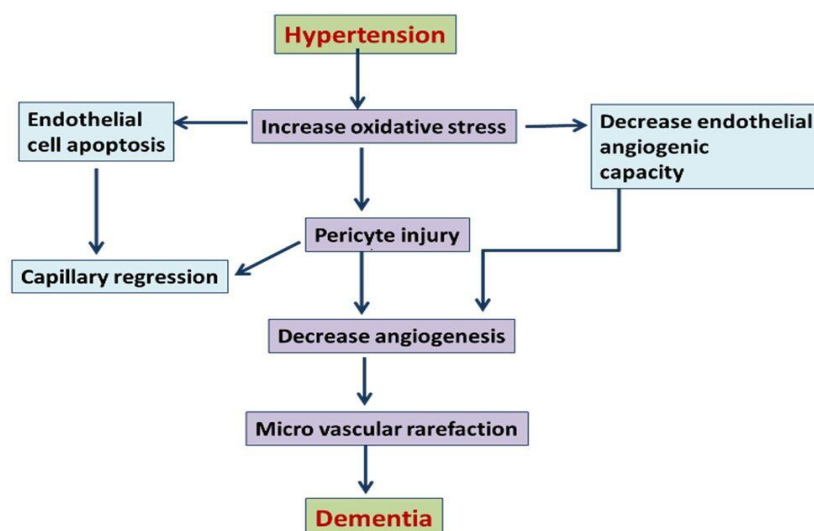


Figure 1: Pathophysiology of Hypertension induced Dementia.

Dementia is a disorder which raised because of neurodegeneration which is slowly responsible for deterioration of intellectual function ultimately increases the dependency to live. Some of the important types of dementia are vascular dementia responsible for disturbance in blood flow and cerebrovascular illness, Lewy bodies' dementia caused abnormal protein deposition, fronto-temporal dementia affects behavior and language, Alzheimer's disease with progressive loss of memory. The intellectual functions of an alert patient that gradually deteriorate over yestime, some typical sign and symptoms includes dream enacting behavior, visual hallucination and trouble in focusing and paying attention. Other symptoms are tremors, stiffness, and sluggish or uncoordinated movement (Parkinsonism).^[4] Vascular dementia is a particular type of dementia raised because of large and multiple strokes leading to cognitive impairment. Different classes of antihypertensive agents available which helps to decrease the risk of dementia and consecutively Alzheimer diseases and other related complications. The results of different comparative and retro-scopical studies shows that the percentage of neurogenerative disorders reduced by 12-16 %.^[5]

The linkage between hypertension and dementia can be well explained with the help of magnetic resonance imaging studies which shows that less or disrupted blood flow to the brain induced lesions on white matter which considered as good predictor of dementia. In this sense

hypertension have major contribution in vascular dementia. In one of the largest clinical investigations, three months after a stroke 453 individuals were assessed and 26% of them tested as having dementia, the stroke which is considered to raise the chance of dementia.^[6] The recent review which examined the relationship between hypertension with that of cognitive decline showed untreated hypertension leads to many floods increase in risk of cognitive deteriorations.^[7] Review study, on small vessel diseases associated with hypertension and its relation with dementia with some clinical evidences showed that it was responsible for lacunar stroke which will be major cause for cognitive impairment and consequently dementia.^[8] The seven years longitudinal study of period during 1991 to 1998 concluded that persons with a history of hypertension (8.6 % per person-year) had nearly twice the relative risk for vascular dementia as compare to normal (4.2% per person-year).^[9] According to the study it is observed that occurrence of hypertension is more in Asian country which is increasing with time. Many studies proved that hypertension was the risk factor for induction of Alzheimer's disease and vascular dementia with cognitive disorders.^[10]

Potential of Antihypertensives in Management of Dementia

Every type of antihypertensive agent has its own potential to reduce elevated blood pressure along with progression of dementia.

Diuretics

Two types of diuretics potassium sparing diuretics and thiazide diuretics used more prominently. Potassium sparing diuretics helps in maintaining adequate concentration of potassium in serum which inhibits the reactive oxygen species formational rate, which is responsible for the neuronal damage. Increase level of potassium reduce oxidative stress and leads to neuroprotective effect. The hyperuricemia is the side effect of thiazide diuretics getting beneficial in case where cause of dementia is inadequate level of uric acid

which acts in the form of antioxidant. It helps in prevention of toxic accumulation of extra nitrous oxide which could be reason of neurotoxicity and neurogenerative diseases.^[11] Recent study on loop diuretics bumetanide shows its effect in improving memory formation through reversing gene expression related to the disease in animal models.^[12] Possible reasons as diuretics can use in dementia, research summary which support the use of diuretics in dementia and related diseases tabulated in Table 1.

Table 1: Diuretic research summary supports the use in dementia and related diseases.

Type	Effect on dementia risk	Study Finding
Thiazide Diuretics	The inverse proportional shows that shows benefits in Alzheimer disease.	It has been found that thiazide diuretics lowers the risk of developing Alzheimer disease. Combination of thiazide and potassium sparing diuretics shows aHR of 0.63 (95 % CI 0.42 -0.94) Thiazide diuretics showed the aHR of 0.7 (95 % CI 0.53-0.93). ^[11]
Potassium sparing diuretics	Reduce the risk of dementia and related symptoms	This particular class showed the aHR of 0.09 (95 % CI 0.01-0.41) while other antihypertensives shows aHR 0.76 (95 % CI 0.49-1.15). ^[11] Another study shows aHR of 0.69 (95 % CI 0.48 -0.99) which indicates the greatest reduction in Alzheimer risk. ^[12]
Thiazide and potassium sparing diuretics	Associated with decreased the risk of Alzheimer risk	Thiazide diuretics - aHR of 0.7 (95 % CI 0.53-0.93) Potassium directics - aHR of 0.69 (95 % CI 0.48-0.99). ^[13]
Loop Diuretics (e.g. Bumetanide Furosemide)	Potential reduce the risk of dementia.	Loop diuretics showed significant association with reduced Alzheimer disease. Bumetanide OR = 0.23 and 95 % CI 0.15 - 0.36, and furosemide OR = 0.42 and 95 % CI 0.38 - 0.47). ^[14]

* adjusted Hazard Ratio: (aHR), CI: Cognitive Impairment, OR: Odds Ratio

Angiotensin converting enzymes (ACE) inhibitors

They are potent vasoconstrictors gives vasodilatory effect by inhibiting the conversion of angiotensin I to angiotensin II improve cerebral blood flow leads to beneficiary action in dementia control. ACE inhibitors having ability to cross the blood brain barrier which

exerts direct effect on the brain and give neuroprotective action. Stimulation of the renin angiotensin system leads to activation of inflammatory cytokines which is major cause of degenerative dementia.^[15] Research summary which support the use of ACE inhibitors in dementia given in Table 2.

Table 2: Angiotensin converting enzymes (ACE) inhibitor research summary support the use in dementia and related diseases.

Type	Study Finding
Retrospective Analysis	Study shows that centrally acting ACE may provide better cognitive outcome. Mini-mental health state examination scores after 9 months diagnostic study get increase 0.72 and 0.19 which indicate the benefit of drug in dementia. ^[15]
Observational Study	Study try finds the treatment option for the dementia in the form of centrally acting ACE inhibitors. Mini-mental state examination showed reduced rate of cognitive decline after 6 months after starting treatment. ^[16]
Review article	Gives in detail review which concluded that as centrally acting ACE inhibitors are the additional possible option for the early-stage Alzheimer as they retards symptoms of neurodegeneration. ^[17]

Angiotensin II receptor blockers (ARBs)

This class prevent the binding of angiotensin to its type I receptors responsible for activation of type II receptors which helps to relax the blood vessels and reduce oxidative stress. It gives its positive effect in management of dementia and related diseases by preventing ischemic damage, mitigating the

neuroinflammation, reducing amyloid beta deposition. Some studies provide the evidences that ARBs responsible for improving microcirculation provide helps in preventing neuronal damage. ARBs show its neuroprotective activity especially in vascular dementia.^[18] Research summary which supports the use of ARBs in dementia mentioned in Table 3.

Table 3: Angiotensin II receptor blockers (ARBs) research summary support the use in dementia and related diseases.

Type	Study Finding
Review article	Review article focused on adjuvant approach of ARB for neuroprotection. ARB use was associated with 22 % and 26 % reduction in dementia and Alzheimer's respectively. ^[18]
Retrospective Cohort study	Study emphasized angiotensin receptor blockers with aHR= 0.45 (95 % CI , 0.25-0.81) were associated with lower risk of progression to dementia as compared to other hypertensive agents. ^[19]
Cohort Study	This particular study concerned about dementia with chronic kidney diseases. Multivariate aHR for dementia with ARB usage per medication possession ratio were 0.578 (95 % CI 0.52 -0.643) and 0.996 (95 % CI 0.995 – 0.998) which showed that patients with ARB having protective effects and had decreased risk of dementia. ^[20]

* adjusted Hazard Ratio: (aHR), CI: Cognitive Impairment

Calcium Channel blockers (CCBs)

This particular class showing its effect by inhibiting calcium entry into the heart cells and blood vessels responsible for relaxation of vascular smooth muscles leads to reduced blood pressure. Calcium channel blockers having permeability for the blood brain barrier and has potential to occupy brain voltage gated calcium

channels which lowers the incident of neuropsychiatric disorders. It having protective action against the excitotoxicity induced by the amyloid beta accumulation considered as indication of Alzheimer disease.^[21] Research summary which supports the use of CCBs in dementia management tabulated in Table 4.

Table 4: Calcium channel blockers research summary support the use in dementia and related diseases.

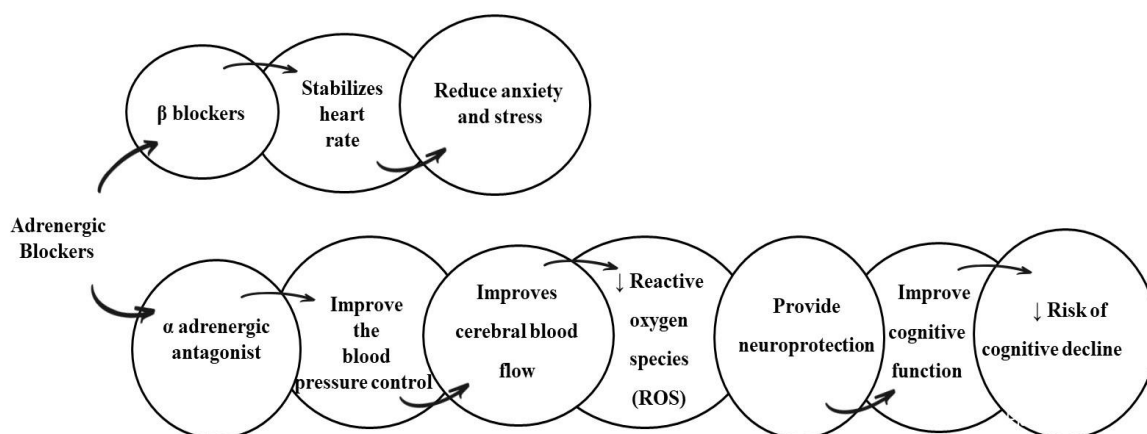
Type of study	Study Finding
Pharmacoepidemiological study	This study had been used to compared the effect of brain penetrant CCBs and non-penetrant CCBs against dementia and related diseases, which showed approximate 12 % decrease in symptoms in patients who had of brain penetrant CCBs and proves that the novel brain penetrant CCBs with more selective central action has greater therapeutic potential for neurodegenerative diseases. ^[21]
Cohort study	Nifedipine and amlodilone was considered in this study. It shows better result with amlodipine compared with nifedipine aHR of 0.89 (95 % CI 0.80-0.98) for Alzheimer and an aHR of 0.58 (95 % CI 0.38 -0.86) for dementia with Lewy bodies and Parkinson's diseases dementia. ^[22]
Retrospective cohort study	10 years data from National health insurance research database of Taiwan showed that dementia in CCB-exposure group (HR = 0.53, 95 % CI 0.39 – 0.72) was significantly lower as compared to CCB-nonexposure group. ^[23]
Review article	Nimodipine and nilvadipine helps to prevent cognitive decline in some trials where as other CCBs shows no effect. ^[24]

* adjusted Hazard Ratio: (aHR), CI: Cognitive Impairment

Adrenergic blockers

α and β adrenergic blockers block the α adrenergic receptor and β adrenergic receptor leading to reducing heart rate, cardiac output and gives vasodilatory effect simultaneously. β blockers are more effective in reducing

the risk of dementia because having an ability to cross the blood brain barrier, enhance the clearance of amyloid beta considered as hall mark of Alzheimer's.^[25] [Figure 2].

**Figure 2: Exploring connection between adrenergic blockers and dementia prevention.**

Central Sympatholytic

They reduce the sympathetic outflow and hence reduce the heart rate and vascular resistance. Study shows that they improve the cognitive functions by modulating neurotransmitter system. They help to manage the

dementia symptoms like agitation and aggression. They are having sedative properties which help to make the patient calm. It has limited use in dementia and related diseases^[26] [Figure 3].

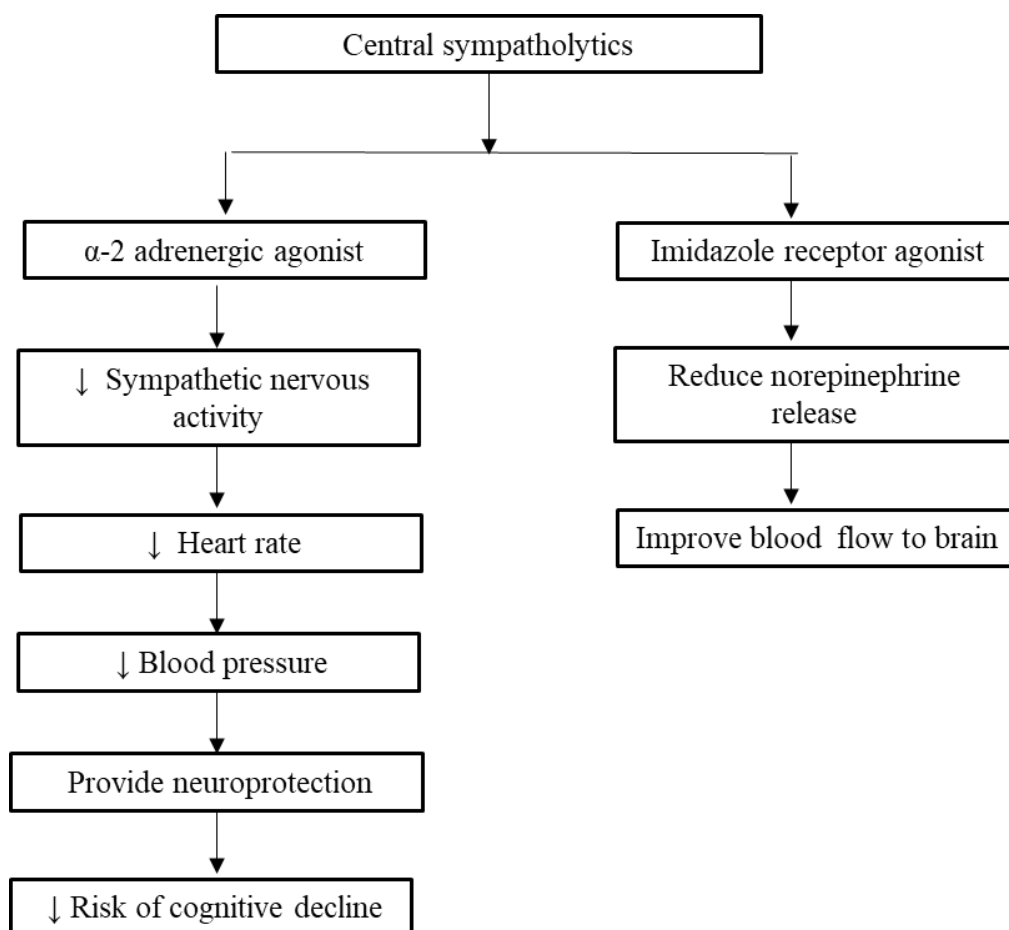


Figure 3: Exploring connection between central sympatholytics and dementia prevention.

Direct Vasodilators

They relax the smooth muscles in blood vessels and give its action as antihypertensive. They improve the cerebral blood flow, improve the neuronal metabolism which might be helpful for management of vascular dementia. Direct renin inhibitors; the aliskiren having blood brain barrier penetration ability acts as direct acting renin inhibitors shows neuroprotective action by cognitive function improvement, ameliorate the brain damage and improve the memory associated with chronic cerebral ischemia also helps to reduce the neuroinflammation.^[27] [Figure 4].

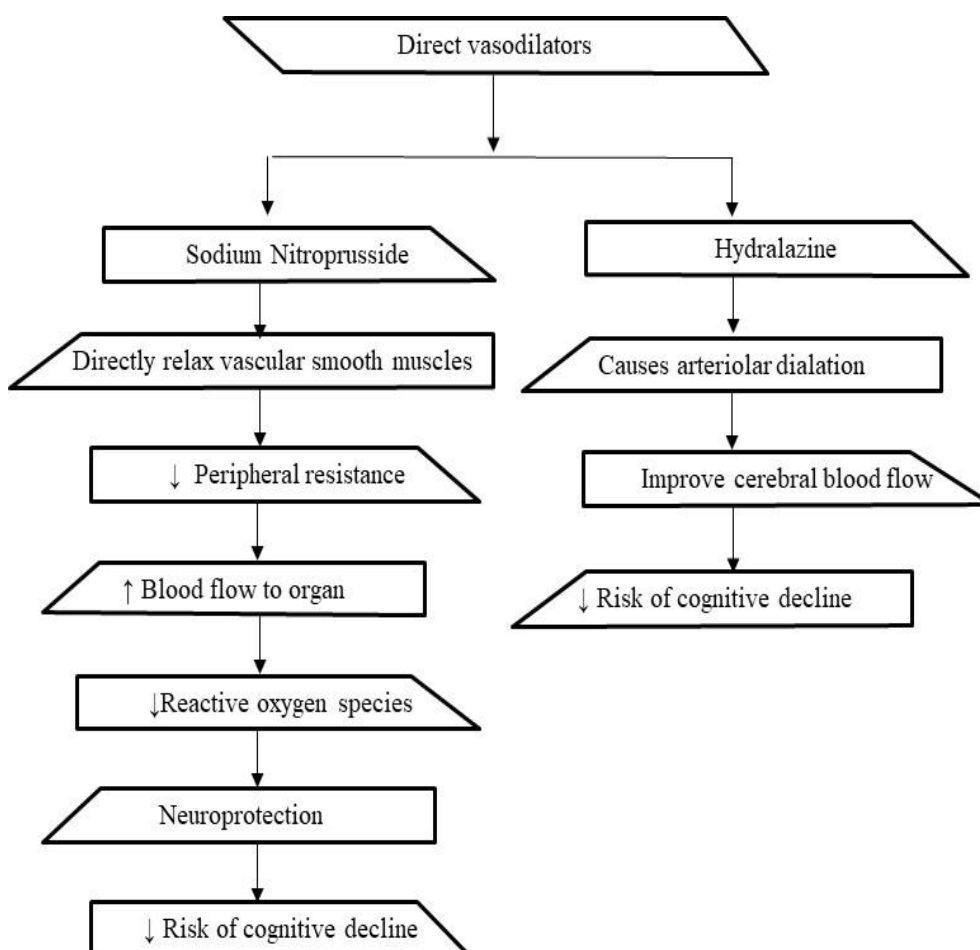


Figure 4: Exploring connection between direct vasodilator and dementia prevention.

Other Clinical Statistical Data Support the Use of Antihypertensives in Management of Dementia

Many randomized and retroscopical meta-analysis had been reported which support the benefit of antihypertensives agents in management of dementia. Some original research and study of clinical trials which have been conducted on selective antihypertensive drugs like calcium channel blockers, diuretics and ACE inhibitors. Finding observed that all drugs help to reduce the dementia but during bulk trials proved only ACE inhibitors and diuretics gives considerable good results and decreased dementia risk and its progression. For in detail inter-linkage large-scale randomized clinical trials are required to investigate.^[28]

Dihydropyridine-calcium channel blockers were associated with a trend towards a reduced chance of developing Alzheimer's disease and Cognitive outcomes in patients with Alzheimer's disease are improved by antihypertensive drugs.^[29] Practiced based case control study shows substantial negative correlation between beta blocker prescriptions (1 per year over 3 years) and newly diagnosed dementia was seen. Moreover the incidence of dementia seemed to be inversely related to ACE inhibitor use which suggested that some hypertension drugs (beta blockers, ACE-inhibitors) may have a preventive effect against dementia

development.^[30] In general, low blood pressure may reduce the risk of dementia, but a clear and reliable association between diuretics and reduced risk of cognitive decline or dementia was observed when each group compared with no treatment group and other groups of antihypertensive drugs.^[31] Lowering BP offers defense against this high BP problem. Both those with dementia and those who are cognitively intact experience this impact. Beyond lowering blood pressure antihypertensive that penetrates the blood-brain barrier and impact the renin-angiotensin-aldosterone system or brain calcium metabolism (such as perindopril or losartan) or both offer further defense against cognitive deterioration. Candesartan clinical study shows high potential in early Alzheimer disease, helps to improve executive functions.^[32] A different class of antihypertensive medicines plays an immortal role in management of dementia with various extents as given in Figure 5.^[33]

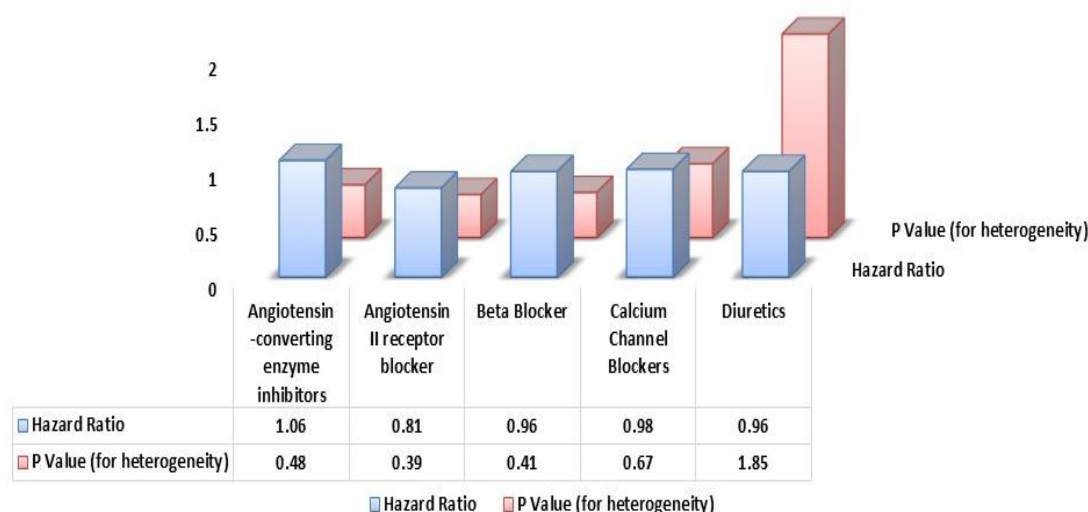


Figure 5: Association between classes of antihypertensive medicines with incidents of dementia.

Pharmaceutical Approaches to Repurposing of Antihypertensive Drugs on Treatment of Dementia

With the development of the novel drug delivery system which helps to improve the solubility, bioavailability and effect of drugs such as nanoparticles, nanoemulsions, sustain release formulation can apply for the betterment of the drug efficacy. The important characteristic of drugs which make them suitable for use in dementia is ability to cross the blood brain barrier. Anti-hypertensives like telmisartan, candesartan, captopril, fosinopril, lisinopril, perindopril, ramipril, trandolapril^[34], dihydropyridines like nitrendipine, nilvadipine, azelnidipine^[35] able to cross blood brain barrier and hence provides opportunity to study them for the use in management of dementia along with its antihypertensive activity.

Some pharmaceutical and pharmacological studies had been conducted to learn the applicability of these drugs in dementia management. Chitosan coated nanoemulgel of telmisartan through the nasal route provides potential way for the delivery of telmisartan which provides effective tool to cross the blood brain barriers and gives effects in controlling of dementia.^[36] Telmisartan containing nanocrystals provides promising results in management of Alzheimer disease.^[37] Long term use of R-carvedilol β adrenergic blocker (nonselective type) interferes with some neuropathology, biochemical, and electrophysiological mechanisms responsible for cognitive deterioration.^[38] Chronic use of azelnidipine can reduce the symptoms of Alzheimer type dementia by improving memory functions with suppressing oxidative stress and inflammatory symptoms also shows antioxidant properties.^[39] Bosentan is endothelin receptor antagonist (ET-A and ET-B) shows efficacy in STZ induced cognitive and vascular endothelial deficits. It has a good potential in vascular dementia.^[40]

CONCLUSION

Early-onset hypertension contributes to the later development of dementia. Dementia is better controlled

when hypertension well managed with antihypertensive medications. Antihypertensive medication very specifically angiotensin converting enzyme inhibitors and diuretics may control the induction and progression of dementia development. To learn in detail about the link between antihypertensive drugs and dementia in detail large-scale clinical study on hypertensive patients are needed. Pharmaceutical approach will help to improve the performance of different antihypertensive agent against the dementia and related diseases. Researchers has significant opportunities for further development, evaluation and analysis to explore the potential of antihypertensive medication in management of dementia.

COMPETING INTEREST

The authors have declared that no competing interest exists.

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REFERENCES

1. Stevenson-Hoare J, Schalkamp A-K, Sandor C, Hardy J, Escott-Price V. (2023). New cases of dementia are rising in elderly populations in Wales, UK. *Journal of Neurological Science*, 15(451): 120715. doi:10.1016/j.jns.2023.120715.
2. Grabowska ME, Huang A, Wen Z, Li B, Wei WQ. (2023) Drug repurposing for Alzheimer's disease from 2012-2022—a 10-year literature review. *Frontiers in Pharmacology*, 07(14): 1257700. doi:10.3389/fphar.2023.1257700.
3. Dariusz G, Mariusz K, Walenty N, Krzysztof N. (2013). Hypertension, brain damage, and cognitive decline. *Curr Hypertens Rep.*, 23(15): 547-558. doi:10.1007/s11906-013-0398-4.

4. Zohuri B, Dalili S. (2023). Understanding dementia: types and their impact. *Science Set Journal of Medical and Clinical Case Studies*, 2(3): 1-4.
5. Jie D, Kendra L, Sanaz S, Phillip J, Wanmei W, Caroline P, et al. (2020). Antihypertensive medications and risk for incident dementia and Alzheimer's disease: a meta-analysis of individual participant data from prospective cohort studies. *Lancet Neurol.*, 19(1): 61-70. doi:10.1016/S1474-4422(19)30393-X.
6. Desmond W, Moroney T, Paik C, et al. (2000). Frequency and clinical determinants of dementia after ischemic stroke. *Neurology*, 54(5): 1124-31. doi: 10.1212 /WNL. 54.5. 1124.
7. Pacholko A, Iadecola C. (2024). Hypertension, neurodegeneration, and cognitive decline. *Hypertension*, 81(5):991-1007. doi:10.1161/HYPERTENSIONAHA.123" 21 356.
8. Hainsworth AH, Markus HS, Schneider JA. (2024). Cerebral small vessel disease, hypertension, and vascular contributions to cognitive impairment and dementia. *Hypertension*, 81(1): 75-86. doi:10.1161/HYPERTENSIONAHA.123.19943.
9. Posner H, Tang M, Luchsinger J, Lantigua R, Stern Y, Mayeux R. (2002). The relationship of hypertension in the elderly to AD, vascular dementia and cognitive function. *Neurology*, 58(8): 1175-1181. doi:10.1212/wnl.58.8.1175.
10. Yuda T, Jeslyn T, Yook C, Satoshi H, et al. (2019). Hypertension and dementia: A comprehensive review from the HOPE Asia Network. *Journal of Clinical Hypertension*, 21(8): 1091-1098. doi:10.1111/jch.13558.
11. DeLoach T, Beall J. (2018). Diuretics: A possible keystone in upholding cognitive health. *Mental Health Clinician*, 8(1): 33-40. doi:10.9740/mhc.2018.01.033.
12. Gharaylou Z, Shafaghi L, Oghabian MA, Yoonessi A, Tafakhori A, Shahsavand Ananloo E, Hadjighassem M. (2019). Longitudinal Effects of Bumetanide on Neuro-Cognitive Functioning in Drug-Resistant Epilepsy. *Frontiers in Neurology*, 10: 483. doi:10.3389/fneur.2019.00483.
13. Chuang Y-F, et al. (2014). Use of diuretics is associated with reduced risk of Alzheimer's disease: the Cache County Study. *Neurobiol Aging*, 35(11): 2429-2435. doi:10.1016/j.neurobiolaging.2014.05.002.
14. Graber-Naidich A, Lee J, Younes K, Greicius MD, Le Guen Y, He Z. (2023). Loop diuretics association with Alzheimer's disease risk. *Frontiers in Aging*, 4: 1211571. doi:10.3389/fragi.2023.1211571.
15. Fazal K, Perera G, Khondoker M, Howard R, Stewart R. (2017). Associations of centrally acting ACE inhibitors with cognitive decline and survival in Alzheimer's disease. *BJPsych Open*, 3(4): 158-164. doi:10.1192/bjpo.bp.116.004184.
16. Gao Y, O'Caoimh R, Healy L, Kerins DM, Eustace J, Guyatt G, Sammon D, Molloy DW. (2013). Effects of centrally acting ACE inhibitors on the rate of cognitive decline in dementia. *BMJ Open*, 3(7): e002881. doi:10.1136/bmjopen-2013-002881.
17. Ursula Q, Said A. (2020). Improvements of symptoms of Alzheimer's disease by inhibition of the angiotensin system. *Pharmacological Research*, 154: 104230. Doi:10.1016/j.phrs.2019.04.014.
18. Zhou Z, Orchard SG, Nelson MR, Fravel MA, Ernst ME. (2024). Angiotensin Receptor Blockers and Cognition: a Scoping Review. *Current Hypertension Reports*, 26(1): 1-19. doi: 10.1007/s11906-023-01266-0. Epub 2023 Sep 21.
19. Deng Z, Jiang J, Wang J, Pan D, Zhu Y, Li H, Zhang X, Liu X, Xu Y, Li Y, Tang Y. (2022). Angiotensin Receptor Blockers Are Associated With a Lower Risk of Progression From Mild Cognitive Impairment to Dementia. *Hypertension*, 79(10): 2159-2169. doi:10.1161 /HYPERTENSIONAHA.122.19378.
20. Chen YH, Chen YY, Fang YW, Tsai MH. (2021) Protective Effects of Angiotensin Receptor Blockers on the Incidence of Dementia in Patients with Chronic Kidney Disease: A Population-Based Nationwide Study. *Journal of Clinical Medicine*, 10(21): 5175. doi: 10.3390/jcm10215175.
21. Colbourne L, Harrison PJ. (2022). Brain-penetrant calcium channel blockers are associated with a reduced incidence of neuropsychiatric disorders. *Molecular Psychiatry*, 27(9): 3904-3912. doi:10.1038/s41380-022-01615-6.
22. Kalar I, Xu H, Secnik J, Schwertner E, Kramberger MG, Winblad B, Von Euler M, Eriksdotter M, Garcia-Ptacek S. (2021). Calcium channel blockers, survival and ischaemic stroke in patients with dementia: a Swedish registry study. *Journal of Internal Medicine*, 289(4): 508-522. doi: 10.1111/joim.13170.
23. Wu CL, Wen SH. (2016). A 10-year follow-up study of the association between calcium channel blocker use and the risk of dementia in elderly hypertensive patients. *Medicine (Baltimore)*, 95(32): e4593. doi: 10.1097/MD00000000000004593.
24. Nimmrich V, Eckert A. (2023). Calcium channel blockers and dementia. *British Journal of Pharmacology*, 169(6): 1203-1210. doi:10.1111/bph.12240.
25. Beaman EE, Bonde AN, Larsen SMU, Ozenne B, Lohela TJ, Nedergaard M, Gíslason GH, Knudsen GM, Holst SC. (2023). Blood-brain barrier permeable β -blockers linked to lower risk of Alzheimer's disease in hypertension. *Brain*, 146(3): 1141-1151. doi: 10.1093 /brain /awac076.
26. Vongpatanasin W, Kario K, Atlas SA, Victor RG. (2011). Central sympatholytic drugs. *Journal of Clinical Hypertension (Greenwich)*, 13(9): 658-661. doi: 10.1111/j.1751-7176 . 2011.00509.x.
27. Yagi S, Akaike M, Ise T, Ueda Y, Iwase T, Sata M. (2013). Renin-angiotensin-aldosterone system has a pivotal role in cognitive impairment. *Hypertension Research*, 36(9): 753-758. doi: 10.1038/hr.2013.51.

28. Shah K, Qureshi SU, Johnson M, Parikh N, Schulz PE, Kunik ME. (2009). Does use of antihypertensive drugs affect the incidence or progression of dementia? A systematic review. *American Journal of Geriatric Pharmacotherapy*, 7(5): 250-261. doi: 10.1016/j.amjopharm.2009.11.001.
29. Yasar S, Corrada M, Brookmeyer R, Kawas C. (2005). Calcium channel blockers and risk of AD: the Baltimore Longitudinal Study of Aging. *Neurobiology of Aging*, 26(2): 157-163. doi:10.1016/j.neurobiolaging.2004.03.009.
30. Wagner G, Icks A, Abholz HH, Schröder-Bernhardi D, Rathmann W, Kostev K. (2012). Antihypertensive treatment and risk of dementia: a retrospective database study. *International Journal of Clinical Pharmacology and Therapeutics*, 50(3): 195-201. doi: 10.5414/cp201284.
31. Peters R, Yasar S, Anderson CS, Andrews S, Antikainen R, Arima H, et al. (2020). Investigation of antihypertensive class, dementia, and cognitive decline: A meta-analysis. *Neurology*, 94(3): e267-e281. doi: 10.1212/WNL.00000000000008732.
32. Ihab H, Maureen O, Limeng W, Zhiyi Y, Jonathon A N, Anastasia B, et al. (2022). Safety and biomarker effects of candesartan in non-hypertensive adults with prodromal Alzheimer's disease. *Brain Communications*, 4(6): fcac270. Doi: 10.1093/braincomms/fcac270.
33. Ding J, Davis-Plourde KL, Sedaghat S, Tully PJ, Wang W, Phillips C, et al. (2020). Antihypertensive medication and risk for incident dementia and Alzheimer's disease: a meta-analysis of individual participant data from prospective cohort studies. *Lancet Neurol.*, 19(1): 61-70. doi:10.1016/S1474-4422(19)30393-X.
34. Glodzik L, Santisteban MM. (2021). Blood-Brain Barrier Crossing Renin-Angiotensin System Drugs: Considerations for Dementia and Cognitive Decline. *Hypertension*, 78(3): 644-646. doi:10.1161/HYPERTENSIONAHA.121.17595.
35. Paris D, Bachmeier C, Patel N, Quadros A, Volmar CH, Laporte V, et al. (2011). Selective Antihypertensive Dihydropyridines Lower A β Accumulation by Targeting both the Production and the Clearance of A β across the Blood-Brain Barrier. *Molecular Medicine*, 17(3-4): 149-162. doi:10.2119/molmed.2010.00180
36. Chin LY, Tan JYP, Choudhury H, Pandey M, Sisinthy SP, Gorain B. (2021). Development and optimization of chitosan coated nanoemulgel of telmisartan for intranasal delivery: A comparative study. *Journal of Drug Delivery Science and Technology*, 62: 102341. doi:10.1016/j.jddst.2021.102341.
37. Madani AF, Syauqi MA, Permatasari JA, Putri AA, Fadel M, Permana AD. (2024). Development of Telmisartan Nanocrystal-Based Dissolving Microneedle for Brain Targeting via Trigeminal Pathway: A Potentially Promising Treatment for Alzheimer's with an Improved Pharmacokinetic Profile. *ACS Applied Bio Materials*, 7(4): 2582-2593. doi:10.1021/acsabm.4c00246.
38. Yao J, Chen SRW. R-carvedilol, a potential new therapy for Alzheimer's disease. (2022). *Frontiers in Pharmacology*, 13: 1062495. doi:10.3389/fphar.2022.106249
39. Teng T, Devin MR, Andrey T, Grace YS, Sholpan A, and James C. (2019). Azelnidipine Attenuates the Oxidative and NF κ B Pathways in Amyloid- β -Stimulated Cerebral Endothelial Cells. *ACS Chemical Neuroscience*, 10(1): 209-215. doi:10.1021/acschemneuro.8b00368.
40. Singh G, Sharma B, Jaggi AS, Singh N. (2014). Efficacy of bosentan, a dual ETA and ETB endothelin receptor antagonist, in experimental diabetes induced vascular endothelial dysfunction and associated dementia in rats. *Pharmacology Biochemistry Behavior*, 124: 27-35. doi: 10.1016/j.pbb.2014.05.002