Benzodiazepine as an Antihypertensive Agent on Adult and Elderly: A Review

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Abstract

The relationship between benzodiazepine and hypertension has long been known and well-documented, but, the character of γ-aminobutyric acid (GABA)-A and GABA-like peripheral receptors (PBR complexes) in blood pressure regulation is intricate. However, this 'literature review'-facilitated argumentative paper went through an inclusive view into past studies, meta-analyses and case studies that had underlined the potential antihypertensive roles of benzodiazepines, which exert their anti-hypertensive mechanism through GABA-A receptors in the CNS alongside PNS and GABA like receptors (PBR Complexes) in vasoactive smooth muscles and blood vessels via "tempering anion channels (Ca^{++} channels)" as well as "modulating glucocorticoid synthesis" in many parts including suprarenal gland and brain by directly acting on PBR complexes of inner mitochondrial membrane close to voltage-gated anion channels and cholesterol transports along with "exerting adenosine reuptake inhibitor" activities throughout the CVS including coronary vessels that could potentially prevent morbidity and CVDs in hypertensive elderly. Despite benzodiazepine's anti-hypertensive effects on multiple cardiovascular clinical incidences and emergencies including their use as a prophylaxis for hypertensive elderly and adult, very few past studies were found to have addressed benzodiazepine's anti-hypertensive action, that remains a critical limitation and challenge to this paper, as its motto is to find out the correlation between benzodiazepine and their CVS effects alongside the risks and benefits of benzodiazepine in hypertensive patients, in particular in elderly. Despite the limitations, this paper had reached a conclusion following an argument on findings of past studies, that, certain benzodiazepines could be useful as an anti-hypertensive agent with or without conventional anti-HTN. However, in case of elderly, often antidepressants are prescribed in patients with hypertension despite their increasing risks, but use of benzodiazepines in elderly could decrease a number of risks and therefore it could be said that benzodiazepines are comparatively safer to use in elderly as an anti-hypertensive, while before introducing antidepressants, the patients' history should provide enough evidences that the risks such as suicidal ideation, mania and exacerbation of underlying psychological disorders might not be outweighing the benefits. Alongside this, it could also be said that the long- and centrally-acting benzodiazepines such as Diazepam and Clonazepam act better to lower mean BP in both adults and elderly, but those exerting both peripheral and central actions to reduce mean BP such as intermediate-acting bromazepam, showed better response in elderly. However, further researches ought to be conducted to reach a comprehensive resolution.

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1.0. Introduction

Background:

The aim of this "literature review"-based argumentative study is to find out the correlation between benzodiazepine and its impact on patients with HTN with or without underlying psychotic clinical conditions, as benzodiazepines are often being prescribed as a prophylaxis or treatment of essential hypertension in combination with typical anti-hypertensives such as ACE inhibitors, Beta blocker, Calcium channel blocker and Diuretics among others. Aside from that, benzodiazepines are frequently used as a prophylaxis or a treatment modality in elderly patients who could be exempted from the risks of fall. Besides, long acting benzodiazepines such as Diazepam, Clonazepam and Lorazepam are thought to be exerting their functions through CNS and work efficiently irrespective of age and sex, while intermediate acting benzodiazepines such as bromazepam or alprazolam are believed to be more effective in elderly to lower blood pressure and both of them act on both CNS and PNS. Short-acting benzodiazepines such as midazolam are effective in emergencies such as hypertensive crisis, but have had little or no roles in maintenance of a low blood pressure for a longer duration. Several meta-analyses of past studies have found that the elderly hypertensive patients being treated with benzodiazepines alongside conventional anti-HTN would lessen the risks of developing CVDs or related morbidities and hospitalization. Furthermore, hypertensive patients who already have experienced an episode of ischemia would less likely to require hospitalization due to CVDs following long-term combination therapy of intermediate-acting benzodiazepines alongside traditional anti-hypertensive agents.

1.1. History and origin of benzodiazepines

Benzodiazepines' origin is rooted back in the 1955s when Leo Sternbach had synthesized the first benzodiazepine, chlordiazepoxide, during working on tranquilizers in Hoffmann-La Roche. However, initial findings of the drug were disappointing and Leo Sternbach had other projects in mind, therefore, he left the work on Chlordiazepoxide. Two years later, during cleaning the lab, Sternbach's co-worker Earl

Reeder had found a “nicely crystalline” compound which had actually been a left-over of Sternbach’s initial project. Without much expectation, the compound, later named chlordiazepoxide, had been trialed on animals and the compound had shown a strong sedative, anti-convulsive and muscle relaxant impact, thus leading to a quicker introduction into the market in 1960s under the brand name Librium. After that, diazepam was marketed in 1963 and after introduction of two potent benzodiazepines, prescription of barbiturates had been depreciated by a substantial scale. However, according to Shorter, E., (2005), in the 1980s, concerns rose over the benzodiazepines’ dependence, which later led to the world’s largest-ever class-action lawsuit that alleged drugmakers in the UK of withholding information about benzodiazepines’ dependence potential. However, consultant psychiatrists, expert witnesses, had shown a conflict of interest and the £30 million lawsuit had botched to reach a conclusion, thus reducing the chances of yielding a result in such lawsuits relating to newer benzodiazepines in future given the costs of a legal proceedings and uncertainties about finding a conclusive verdict in the court [Shorter, E., 2005].

1.2. A prelude to benzodiazepines

Benzodiazepines are a class of psychoactive drugs, a chemical agent that alters nervous system functions and leads to an altered perception, mood, cognition, behavior, consciousness. Benzodiazepines’ basic chemical structure contains a fusion of a benzene ring and a diazepine ring.

As beforementioned, benzodiazepines exert their effects by enhancing the impact of neurotransmitter GABA at the GABA-A receptor, the most potent inhibitory neurotransmitter, thereby stemming properties of a sedative, hypnotic, anxiolytic, muscle relaxant and anti-convulsant. According to Oikkola and Ahonen (2008), despite being a widely prescribed medication for anxiety, panic disorder, insomnia, seizures, alcohol withdrawal, GABA and benzodiazepine both have significant roles in cardiovascular system, as benzodiazepines could lower blood pressure in both adults and elderly peripherally by vasodilation and centrally by inhibiting actions of neurotrophic neurotransmitters in many parts of brain, in particular in hypothalamus, hippocampus and amygdala [Oikkola and Ahonen, 2008)]. However, Lader, Tylee and Donoghue (2009) as well as Penninkilampi and Eslick (2018) had told that the long term use of

benzodiazepine could lead to a decline in effectiveness, benzodiazepine withdrawal syndrome, dementia and physical as well as psychological dependency [Lader, Tylee and Donoghue, 2009; Penninkilampi and Eslick, 2018]. Although, benzodiazepines are less toxic and less prone to develop physical dependency than its predecessor barbiturates, yet benzodiazepine toxicity, overdose and addition when metabolized with other addictive substances, could lead to a wide-ranging complication such as deep unconsciousness, potentially fatal respiratory depression in combination with other depressants such as alcohol and opioids and retrograde amnesia among others. Besides, use of benzodiazepine in elderly could lead to fall. Though, alone benzodiazepines rarely lead to death as stated by Fraser, A., D., (1998) [Fraser, A., D., 1998].

1.3. Classifying benzodiazepines

According to Katzung, Kruidering-Hall and Trevor (December 2019) commonly used benzodiazepines are the following.

- Midazolam (Tmax 1-2 hours, half-life- 2-3 hours) [Tmax: Time required to reach peak blood concentration] (Short acting)
- Triazolam (Tmax 1 hour, half-life- 2-3 hours) (Short acting)
- Zaleplon (Tmax less than ½-1 hour, half-life 1-2 hours) (Short acting)
- Bromazepam (Tmax 2-3 hours, half-life- 3-6 hour) (Intermediate acting)
- Alprazolam (Tmax 1-2 hours, half-life – 12-15 hours) (Intermediate acting)
- Zolpidem (Tmax 1-3 hours, half-life- 1.5 -3.5 hours) (Intermediate acting)
- Lorazepam (Tmax 1-6 hours, half-life- 10-20 hours) (Long acting)
- Diazepam (Tmax 1-2 hours, half-life- 20-80 hours) (Long acting)
- Clonazepam (Tmax 1-2 hours, half-life 6-12 hours) (Long acting)

[Katzung, Kruidering-Hall and Trevor, December 2019]

1.4. Understanding relationship between benzodiazepines and GABA-A and GABA-like receptors (PBR Complexes)

In order to understand the correlation between benzodiazepine and its cardiovascular effects, roles of GABA (gamma amino butyric acid) neurotransmitters in regulating blood pressure should be precisely elaborated. Benzodiazepines exerts their actions by enhancing the effect of neurotransmitter GABA, the chief inhibitory neurotransmitter in central nervous system whose principal role is to reduce neuronal excitability. At GABA-A receptor, a ligand-gated ion channel upon opening of which the permeability of chloride ion and to a lesser extent bicarbonate ion, increase. Hence, activation of GABA-A receptor will lead to an influx of chloride into the cell, reducing the chance of a successful action potential in post-synaptic neurons, thus inducing an inhibitory effect on neurotransmission. GABA-A-mediated IPSP (Inhibitory postsynaptic potential) in normal physiological condition is -70mv and GABA-B (a G-protein coupled receptor for GABA where potassium ion concentration induces hyperpolarization at the end of an action potential) is -100mv, while a depolarization between +10 mv to +15 mv is sufficient to result a firing and leading to a spike and generation of excitatory effects as stated by Barrett et al. (2016) [Barrett et al., 2016)].

GABA-A is an active binding site for benzodiazepine, benzodiazepine like agents, barbiturates, alcohol, inhaled anesthetics, psychostimulants such as kavalactones among others as cited by Chua and Chebib in 2017 and Ashton, H., (May 2005). [Chua and Chebib, 2017; Aston, H., May 2005].

Usually, a majority of GABA-A receptors contain alpha, beta and gamma subunits, though delta, epsilon, theta and pi could be found, too. Intensive studies had revealed that GABA binding sites are located in the inter-surface between alpha and beta subunits and antagonists bind in a vacuum on cell surface which is partially overlapped with the agonist site.

A subset of GABA-A receptors that bind benzodiazepines are known as benzodiazepine receptors. Unlike GABA, benzodiazepines binding sites are located at the interface between GABA-A receptors' alpha and

beta sub-units, in presence of a histidine amino acid residue which is found in alpha1, alpha2, alpha3 and alpha5 containing GABA-A receptors. For this reason, benzodiazepine shows no affinity for GABA-A receptors with alpha 4 and alpha 6 subunits containing arginine, according to Watford et al., (2004) [Watford et al., 2004].

After binding to benzodiazepine receptors, the benzodiazepines receptors are locked by benzodiazepine ligands in such a formation that has a greater affinity for GABA neurotransmitters, which eventually accelerates the frequency at which chloride ion channels are opened and hyperpolarization of the post-synaptic membrane takes place.

Furthermore, Arvat et al., (2002) and Zavala, F., (1997) had stated that benzodiazepine drug classes also act on Translocator Proteins (TSPO), an 18 kDa protein located on the outer member of mitochondria on PNS, glial cells and CNS, and modulate the immune system of the body that responds to injury [Arvat et al., 2002; Zavala, F., 1997]. Narimatsu et al., said in the June of 2006 that acting as a weak adenosine reuptake inhibitor, benzodiazepines excel some of their properties such as anticonvulsant, muscle relaxant as well as anxiolytic [Narimatsu et al., June 2006].

1.5. How benzodiazepines lower blood pressure

Since benzodiazepine induces their actions via enhancing the effects of several isoforms of GABA, the most potent inhibitory neurotransmitter in central nervous system, GABA pathway activation in central and peripheral nervous system and its pathophysiological mechanism should be considered for benzodiazepine's anti-hypertensive actions.

GABA receptor chiefly has two sub-types such as ionotropic GABA-A receptors as well as metabotropic GABA-B receptors. However, GABA-C receptors could also be found. GABA isoforms and their corresponding receptors could be found in cardiovascular system as well as cited by Mayer, Osorio and Lunte (2013) [Mayer, Osorio and Lunte, 2013].

According to Matsukawa et al., (2013), Postsynaptic GABA-A receptor could dilate blood vessels and GABA-B could effectively suppress sympathetic excitement at nerve ending. GABA-B indirectly acting in endothelium could also dilate blood vessels in a poorly understood mechanism of action and safely reduce blood pressure. Besides, GABA receptors take part in regulating cardiovascular activities in many parts of the brain such as hypothalamus, ventrolateral medulla and amygdala nucleus [Matsukawa et al., 2013].

Here is a depiction of anatomical distribution of GABA receptor types in brain and in the body, though a description of GABA receptor isoforms is beyond the scope and opportunity of this paper.

Distribution of Receptor Types according to Mortensen, Patel and Smart (2011)

Isoform	**Synaptic/Extrasynaptic**	**Anatomical location**
α1β3γ2S	Both	Widespread
α2β3γ2S	Both	Widespread
α3β3γ2S	Both	Reticular thalamic nucleus
α4β3γ2S	Both	Thalamic relay cells
α5β3γ2S	Both	Hippocampal pyramidal cells
α6β3γ2S	Both	Cerebellar granule cells
α1β2γ2S	Both	Widespread, most abundant

α4β3δ	Extrasynaptic	Thalamic relay cells
α6β3δ	Extrasynaptic	Cerebellar granule cells
α1β2	Extrasynaptic	Widespread
α1β3	Extrasynaptic	Thalamus, hypothalamus
α1β2δ	Extrasynaptic	Hippocampus
α4β2δ	Extrasynaptic	Hippocampus
α3β3θ	Extrasynaptic	Hypothalamus
α3β3ε	Extrasynaptic	Hypothalamus

[Mortensen, Patel and Smart, 2011]

As beforementioned, activation of GABA-A could selectively let chloride ions pass, induce hyperpolarization and prevents entrance of electric signals into postsynaptic neurons, thereby partially barring activities of stimulatory neurotransmitters such as acetylcholine, dopamine and norepinephrine, eventually leading to a decrease in heart rate, respiratory rate and blood pressure. Richter et al., had stated in the March of 2012 [Richter et al., March 2012].

Besides, activation of peripheral GABA-like receptors which have greater affinity for benzodiazepines, could act on vasoactive smooth muscles, coronary blood vessels, endothelium. PBR complexes in suprarenal gland acting on steroidogenesis help lower blood pressure through modulating concentration of cholesterol into inner mitochondrial membrane in the cytoplasm of cortisol producing adrenal glands,

thereby leading to an alteration of influx of cholesterol into mitochondria and a reduced level of glucocorticoid synthesis. However, benzodiazepines' active role as an immunosuppressant have never been witnessed but its inhibition of IL-8 and Mast Cells.

Aside from the CNS, GABA has been profusely found in other peripheral tissues such as intestine, stomach, fallopian tube, uterus, ovaries, kidneys, bladder, testes, lungs and liver, however, at a much lower extent than those of CNS. Beyond the brain, GABA is also formulated in the beta cells of pancreas alongside insulin, thereby exerting a potential role in diabetic patients.

However, according to LoTurco et al., (1995), Hayder et al., (2000) alongside Maric et al., (2001), embryonically, GABA is thought to be responsible for development of brain by proliferating neural progenitor cells, the elongation of neurites and the formation of synapses, while GABA also regulates the growth of embryonic and neural stem cells and could influence the development of neural progenitor cells through expression of brain derived neurotrophic in the childhood [LoTurco et al., 1995; Hayder et al., 2000; Maric et al., 2001]. GABA performs as a growth modulator in embryonic & the brain's developmental phase, however, in a mature human, GABA turns to an inhibitory neurotransmitter as stated by Wang, Kriegstein and Ben-Ari (2008) [Wang, Kriegstein and Ben-Ari, 2008].

2.0. Literature review

Although the roles of benzodiazepine signaling a blood pressure regulation through GABA activation is complex, multiple previous studies, case studies and meta-analyses have reported that an induction of benzodiazepine could significantly reduce blood pressure, heart rate alongside renal sympathetic nerve activities. Other studies had revealed that the benzodiazepine-induced activities in different areas of brain could effectively impact neural regulation of blood pressure through inhibiting sympathomimetic signals as beforementioned and a stimulation of GABA-A receptors in posterior hypothalamus would dramatically decrease blood pressure in hypertensive subjects, according to Antonaccio and Taylor (1977) [Antonaccio and Taylor, 1977].

Being a "literature review"-based argumentative paper, this study will have had a probing view on past studies, literature reviews, meta-analyses and case studies underlining the anti-hypertensive role of benzodiazepines in both adult and elderly. According to the findings of previous studies, an elaborative argument will be conducted in order to reach an incisive resolution regarding correlations between benzodiazepines and hypertension alongside the risks and benefits of using benzodiazepine as a prophylaxis or treatment with or without conventional anti-hypertensive drugs.

Albeit, essential hypertensions frequently require a combination therapy, patients who have been in risk of developing hypertension with frequent surge in blood pressure above normal are often prescribed with a benzodiazepine or antidepressants in a non-invasive approach.

2.1. Roles of benzodiazepines on cardiovascular system & vasoactive smooth muscles and their anti-hypertensive effects

benzodiazepine-induced GABA receptors' activation has an immense effect on spike timing, neuronal rhythm alongside the activity patterns of electro-chemical regulation in neuronal circuits. Apart from CNS effects, the benzodiazepines have had a substantial scale of impact on CVS as GABA-A receptors and

GABA-like PBR Complexes could impact both electrical as well as hemodynamic parameters. DiMicco and Gale found in 1979 that benzodiazepine could affect the CNS-regulated chronotropic impacts on heart through nucleus ambiguous, that had been found to be affecting the vagal tones and heart rates as well [DiMicco and Gale, 1979]. Previous studies also had found that the benzodiazepines could exert direct or indirect impact on cardiac rates and reduce blood pressure by directly acting on of endothelium as noted by Zhang and Mifflin in 2010 [Zhang and Mifflin, 2010].

As beforementioned, although benzodiazepines are chiefly prescribed for their anxiolytic and hypnotic effects, the drug class also exerts potential muscle relaxant and vasodilatory effects as stated by Klockgether-Radke et al., (2005) [Klockgether-Radke et al., 2005]. Besides, it was found in a study conducted by Veenman and Gavish (2006) that Midazolam, a short acting benzodiazepine, excels its vasodilatory effects by directly acting on endothelium which might be a response to a change in voltage-gated calcium ion channels. Interestingly, in a study conducted on mammal subjects, aortic rings of those were precontracted with an alpha-adrenergic agonist, phenylephrine along with a hyperpolarizing potassium chloride solution, midazolam was found to have a reversible vasodilatory effect on low doses, however, on a higher dose above oral 15 mg in human subject, the benzodiazepine was found to be too sedative and its endothelial effects became too irrelevant as well [Veenman and Gavish, 2006].

Furthermore, benzodiazepines incline its effects further on CVS by binding with the TPSO or 18 kDa translocator protein that could be found primarily in mitochondria and is directly involved in genesis of cortisol. During conducting its steroidogenesis activities, TPSO controls wide-ranging intra-cellular activities ranging from mitochondrial respiration to cell's response to stress and activation of microglia alongside regulation of calcium ion channels, which in effect have had profound impact on programmed cell death, cell proliferation or growth alongside immune response. Surprisingly, TPSO, previously known as a peripheral benzodiazepine-receptor (PBR complex) that acts alike GABA-A in the central nervous system, is widely distributed in cardiovascular tissues and prompts myocardial response to ischemia and could have had a role in endothelial response to benzodiazepine, as cited by Papadopoulos et al., (1998),

Musman et al., (2017) and Erne et al., (1989) [Papadopoulos et al., 1998; Musman et al., 2017; Erne et al., 1989].

In an alignment with the previous studies, benzodiazepines were found to have dynamic impacts on the acute decrease of blood pressure alongside sympathomimetic symptoms in healthy individuals, while two controlled trial studies conducted by Grossman et al., (2005) and Yilmaz et al., (2011) had found that benzodiazepines are as effective as ACEi in treatment of CVS emergencies like of hypertensive crises [Grossman et al., 2005; Yilmaz et al., 2011].

Apart from hypertensive emergencies, benzodiazepines could be effective in maintaining lower blood pressure level in long-term benzodiazepine treatment as found in a retrospective study conducted by Mendelson et al., (2018). It was also found that the patients who had been treated with more than 3 months with benzodiazepines showed better response to essential hypertension than those who had never been treated with benzodiazepines on their lives [Mendelson et al., 2018].

Furthermore, while GABA is also released from the pancreatic beta cells along with insulin and have active roles in converting pancreatic alpha cells to insulin producing beta cells and a survival of beta cells in the islets, after being secreted from the beta cells alongside insulin, GABA binds to GABA receptors of neighboring islets alpha cells and deter them from releasing glucagon which would have countered the impacts of insulin and could have had therapeutic roles in diabetes as stated by Yarom et al., (2016), through neogenesis of b-cells of islets in long-term benzodiazepine therapy. Surprisingly, often patients with diabetics and hypertension are presented with long-term use of benzodiazepine with better prognosis [Yarom et al., 2016].

Besides, past studies had revealed that people above 60 years of age had shown an independent association between lower blood pressure and benzodiazepine treatment combined with antihypertensive drugs, while the elderly patient group receiving benzodiazepine treatment in combination with conventional anti-hypertensive drug had shown to have a better maintenance of lower systolic and diastolic pressure than

those who were being treated with only conventional anti-hypertensive drugs. This could be caused by a tolerance developed against long-term antihypertensive drugs, while patients with anxiety associated hypertension could have responded better to a benzodiazepine treatment as suggested by Mendelson et al., (2018) [Mendelson et al., 2018]

Moreover, past meta-analyses also had reported that the lowering of blood pressure in use of benzodiazepines had not been associated to age, while a long-term benzodiazepine treatment could stem a better response to hypertensive patients of all ages. Hypertensive patients above 58 years of age being treated with benzodiazepines had low chances of developing cardiovascular diseases and associated morbidity as well as hospitalizations.

According to a retrospective study conducted by Wu Ck et al., (2014), a patient group who had been followed just a notch shy of 5 years after suffering from an ischemic attack at least once in their lives and had been treated with benzodiazepine, had found to have lower rate of mortality and hospitalization due to cardiac events [Wu Ck et al., 2014].

However, according to Parsaik et al., (2016) and Lader, M., (2014), elderly patients with history of drug dependence, memory deficits, depression and suicidal ideation, should be monitored after prescribing benzodiazepines, though the risks of developing psychotic events in benzodiazepine use in hypertensive patients are negligible when compared to antidepressants. Elderly hypertensive patients who are prone to fall and fracture due to physical aging or rheumatological clinical conditions, should be appropriately counselled before prescribing benzodiazepines. Also, in this particular incident, risks are greater by far in patients with antidepressants therapy in contrast to benzodiazepine treatment [Parsaik et al., 2016; Lader M., 2014].

Another potential negative impact of benzodiazepine use in elderly has been there inappropriate use which could increase the risks of paradoxical hypertension instead lowering blood pressures as not all benzodiazepines are identically effective to decrease blood pressure, for instance, long-term use of long-

acting benzodiazepines like of diazepam could be beneficial in maintenance of a lower blood pressure and short-acting benzodiazepine such as midazolam, could be more effective in hypertensive emergencies. Nonetheless, intermediate acting benzodiazepines like of bromazepam alongside other atypical benzodiazepines are found to have paradoxical impact on blood pressure, which will be elaborated in the later part of this literature review. In tandem, an indiscriminate and without prescription use of benzodiazepine in elderly, which usually is associated with an increased chance of abuse, must be prevented.

2.2. Impacts of benzodiazepines in vasoactive and airway smooth muscle

French, Rapoport and Matlib (1989) had probed the mechanism of benzodiazepine-induced relaxation of vascular smooth and had found that both clonazepam and diazepam could induce relaxation of vascular smooth muscles alongside others by an inhibition of Ca^{++} induced contraction, while the benzodiazepines relaxed smooth muscles even counter more potentially the vasoconstrictor effects exerted by norepinephrine or prostaglandin F2 alpha (PGF2 alpha) [French, Rapoport and Matlib, 1989]. It is well established that carotid sinus baroreceptors produce a tonic effect on upper airway by initiating a vagal cholinergic pathway, but Koga et al., had found in 1992 that benzodiazepines could relax airway smooth muscle by exerting a direct action on airway smooth muscles [Koga et al., 1992].

2.3. Benzodiazepine as a vasodilator

Several GABA-like peripheral benzodiazepine receptor ligands, often called as PBR complexes, are copious in the cardiovascular system, CVS lumens, platelets, erythrocytes, lymphocytes, mononuclear cell, mast cells alongside endothelium, striated cardiac muscle and vascular smooth muscle. Primarily those receptors could be located in inner mitochondrial membrane and contain an IBP (isoquinoline binding receptor), a voltage-gated anion channel (frequently Ca^{++} channel) and an adenine nucleotide transporter, while according to Veenman and Gavish (2006), an inhibition of PBR could yield various functions such

as reducing damages related to ischemia, anxiety disorders and stress alongside a lowering of blood pressure [Veenman and Gavish, 2006].

Peripheral benzodiazepine receptor ligands such as PK 11195 and Ro 5-4864 had shown to have a substantial scale of inhibitory impact on L-type Ca^{++} channels, thereby exerting antihypertensive effects by dilating blood vessels, though the abovementioned receptors did not show selectivity between cardiac and vascular tissue. According to Campiani et al., (1996), benzodiazepines or benzodiazepine-like compounds having had three distinctive features such as saturation of C(6)-C(7) double bond with a higher molecular flexibility, benzo-fused ring with a substituent and a side chain at C-10 on pyrrolobenzothiazepine 62 had been found to have exerted the most potent Ca++ blocker with better selectivity on cardiac tissues rather than vascular tissues [Campiani et al., 1996]. Furthermore, Leducq et al., (2003), a novel peripheral benzodiazepine receptor ligand, SSR180575, a mitochondrial inner membrane protein, had developed a substantial scale of reduction in size of infarct following coronary artery occlusion and reperfusion, thereby explaining low morbidity and lower incidences of cardiovascular diseases in elderly hypertensive patients with long-term use of benzodiazepines [Leducq et al., 2003].

2.4. Benzodiazepine as an adenosine reuptake inhibitor

Benzodiazepines acting as an active adenosine reuptake inhibitor could lower blood pressure through exerting their functions on several PBR receptors spread across the CVS. The therapeutic benefit of a higher concentration of adenosine is undisputed, while benzodiazepines acting as an adenosine reuptake inhibitor, could be an effective as an antiarrhythmic agent by accumulating interstitial adenosine acting on A-1 adenosine receptors. However, according to Seubert et al., (2000), midazolam by irreversibly inhibiting adenosine transport on A-2A adenosine receptors could lead to an extracellular accumulation of adenosine in cardiac striatal muscle and coronary blood vessels, thereby preventing or limiting the risks of ischemic incidences [Seubert et al., 2000].

2.5. Role of benzodiazepines as a renal sympatholytic, on cortisol and steroidogenesis

Besides, benzodiazepines usually act through 18-kDa PBR protein which is a mitochondrial contact site of anion channel, and disrupt hormonal response to cholesterol transport and reduce circulatory glucocorticoid level, eventually lowering blood pressure.

Benzodiazepines could act as an active ingredient to lower blood pressure by exerting their actions through increasing cholesterol concentration in steroid producing cells' cytoplasm such as suprarenal gland and brain among others.

It is known that a benzodiazepine-mediated inhibition of PBR complexes present at inner mitochondrial membrane of the cytoplasm of glucocorticoid producing cells such as adrenal glands could impact steroid synthesis by affecting cholesterol transport.

In factuality, the rate at which steroid is synthesized, has been mediated by hormone-induced and constitutive signals. Nonetheless, according to Brown and Papadopoulos (2001), an inhibitory effect on PBR Complexes in the microenvironment initiated by benzodiazepines' actions such as selective disruption of PBR Complexes in steroidogenic cells, could regulate the rate at which cholesterol is inserted into the mitochondrial membrane through a cholesterol pore, thereby controlling the rate at which glucocorticoids are produced [Brown and Papadopoulos, 2001].

2.6. Use of Different benzodiazepines as anti-hypertensive agent

When it comes to using different classes of benzodiazepines in treatment of hypertension, Lasagna, L., had been quoted saying about four and a half decades earlier that there had been significant reasons to believe that benzodiazepine could not only be used as anxiolytic, but also those might have substantial role in treating complaints related to cardiovascular system and GIT in addition to tension headache alongside hypochondriac pain [Lasagna, L., 1977].

2.6.1. Long-acting benzodiazepines

In terms of using long-acting benzodiazepines for hypertension, it is well established that long-term benzodiazepines such as clonazepam or diazepam could excel a hypotensive effect regardless of their actions on CNS and PNS. Kitajima et al., had found in 2003 that an administration of 5 mg of diazepam in healthy volunteers could lead to significant fall in both systolic and mean blood pressure, while sympathomimetic activity in smooth muscles were diminished, however, heart rate was not reduced, suggesting that the hypotensive effect of diazepam might take place due to central mechanism [Kitajima et al., 2003]. Another long-acting benzodiazepine Lorazepam, had found to have decreased anxiety associated hypertension by a substantial scale following oral introduction of a dose regimen of 3mg/day for 4 weeks [13 pubmed …767]. However, Lorazepam is often used as a safer anti-convulsant for neonates and children.

2.6.2. Intermediate-acting benzodiazepines

Furthermore, according to Shader et al., (1978), physicians frequently prescribe benzodiazepines as a long-term management of anxiety-associated autonomic nervous system hyperactivity resulting clinical conditions such as hypertensions, while several previous studies had suggested that benzodiazepines could be highly effective in yielding symptomatic benefits in patients with unstable MI and hypertension, as Mendes, Chernoff and Blatt had told in 1986 that intermediate acting benzodiazepines such as alprazolam in combination with propranolol had been found to be effective in treating angina in OPD [Mendes, Chernoff and Blatt, 1986]. Besides, another combination of intermediate acting benzodiazepines such as bromazepam or lorazepam alongside metoprolol had been found to be effective in lowering blood pressure. Patients being treated with propranolol and transdermal nitroglycerine along with bedtime oral alprazolam (0.5 mg) had found to have reduced the duration of silent MI in 70 per cent patients in a double-bind placebo-controlled study conducted by Shell and Swan in 1986 [Shell and Swan, 1986]. Besides, bromazepam had been found effective in controlling labile essential hypertension in a randomized study conducted by Mabadeje and Adebayo back in the 1989s [Mabadeje and Adebayo, 1989]. Wu et al., (2014), had found that BZDs independently could lower the risk of cardiac mortality alongside hospitalization in

patients after new incidents of MI when given in low to medium dosage [Wu et al., 2014]. According to Pozenel, Buckert and Amrein (1977), a study had found that a control group of 68 hypertensive patients had shown a significant scale of mean reduction in blood pressure in use of 9mg of oral bromazepam per day, while the study also had illustrated a reduced myocardial pressure effort and a reduce oxygen demand in heart [Pozenel, Buckert and Amrein, 1977].

2.6.3. Short-acting benzodiazepines

Matsuo et al., (1992) had found short-acting benzodiazepines such as a benzodiazepine analogue, etizolam having had a half-life of 0.5-2 hours, highly effective in treating patients with essential hypertension while being used in addition with conventional anti-hypertensives, while a substantial scale of lowering in systolic and diastolic pressure in essential hypertension with an overall improvement in patient compliance had also been observed. Furthermore, Midazolam, a short acting benzodiazepine which is about 1-1/2-fold potent of diazepam and replaced the role of diazepam in pre-anesthetic medication, is often used to treat hypertensive crisis with or without anti-HTN medications [Matsuo et al., 1992].

2.7. Case studies elaborating benzodiazepines' anti-HTN effect

Despite a relative lack of available research works on benzodiazepine uses as an antihypertensive agent which remains a limitation of this argumentative paper as beforementioned, a number of meta-analyses and studies of previous clinical cases had reported that a general cohort in clinical practice has been a frequent use of benzodiazepine in combination with anti-hypertensives in patients with essential hypertension, mild or benign hypertension alongside hypertension with underlying psychological disorders.

2.7.1. Reduction of BP irrespective of age and sex with long-acting benzodiazepines such as diazepam

when it comes to using benzodiazepines with or without antihypertensive, Divac et al., in 2006 had conducted a dynamic study to establish a correlation between hypertension and benzodiazepines, while subject inclusion criteria involved hypertensive patients being treated with anti-hypertensive with or

without benzodiazepines irrespective of age, gender, education, body weight and smoking habits and a special questionnaire set was used for patients chronically treated with anti-HTN drugs. The study had found that the patients taking benzodiazepines alongside anti-HTN require a lower number of anti-HTN drugs, while benzodiazepines were used for anxiety associated hypertension in about 62 per cent patients and in about 21 per cent for only hypertension. The questionnaire revealed that diazepam was used in 82 per cent among a study group of 171 patients [Divac et al., 1992].

2.7.2. Efficacy of benzodiazepine in lowering blood pressure in elderly

A retrospective analysis of 538 hypertensive and elderly patients' data who were being treated in an OPD, conducted by Rivasi et al., (2020), had found out that about 6.1 per cent patients who had been treated with benzodiazepines in combination with antihypertensives had had lower baseline systolic blood pressure values with a decrease in mean blood pressure as cited in many past studies reflected so far in the literature review, while the hypotensive effects of benzodiazepines in elderly had not been associated with comorbidities and weakness, though the study had found to have the benzodiazepines' hypotensive effect had been related to an increase in risk of falling in certain elderly patients having had chances of fall [Rivasi et al., 2020].

2.7.3. Efficacy of benzodiazepine in lowering blood pressure in elderly with reduced risk of CVDs and hospitalization

Moreover, a retrospective analysis of an ABPM (Ambulatory blood pressure monitoring) database between 2009 and 2015 conducted by Mendelson et al., (2017), that contained a total of 4,938 ABPM studies with 670 ABPMs including patients being treated with benzodiazepines, had shown a close relation between benzodiazepine use and a significant decrease in ABPM measurements, while the study was divided between two patient groups with one group aged above or equal to 60 years and another group aged below, it had been unveiled that benzodiazepine associated reduction in blood pressures had been more profound

in patients above 60 years of age and the use of benzodiazepine had not been associated with an increase in risk of CVD or mortality considering a mean follow-up period of 42.1+-20.0 [Standard Deviation (SD)] months. A similar retrospective analysis of 5020 ABPM studies conducted by Mendelson et at. in 2017 [19 journals.lww], that contained 713 ABPMs having benzodiazepines-treated patients and 4307 ABPMs of untreated patients, patients treated with benzodiazepines had been associated with a low ABPM gauge, while benzodiazepines were found to be more active to treat hypertension in patients aged 60 or above [Mendelson et al., 2017].

2.7.4. Reduction of blood pressure with clonazepam in patients suffering from Labile hypertension and anxiety mediated hypertension

A comparative study on autonomic regulation of blood pressure and effects of clonazepam on patients with labile hypertension, a particular type of HTN where conventional anti-hyptertensive medications could not stabilize blood pressure, conducted by Nedostup, Fedorova and Dmitriev (2000), had found that an induction of 1-2 mg of clonazepam per day led to a significant stabilization of blood pressure in 82 per cent patients with Labile Hypertension, while about 56 patients with a mean age of 67.0+-6.3 (SD) years who had entered the study and undergone psychological evaluation, had shown a higher level of anxiety and depression, meaning that labile hypertension could be linked to anxiety mediated hypertension aside from disorders in heart rate stemming from. However, labile hypertension could be referred to a clinical condition that is an original form of HTN characterized by rapid, short-term, spontaneous and symptomatic fluctuation of blood pressure with presence of both hypotensive and hypertensive episodes [Nedostup, Fedorova and Dmitriev, 2000].

2.7.5. Reduction of blood pressure by enhancing GABA inhibitory activities by using anesthetics similar to benzodiazepines

Frolich et al., (2013), found in a randomized, single-blinded and placebo-controlled study which included 60 healthy adults and 1 volunteer that a substantial scale of dose-dependent blood pressure reduction took place with patients with dexmedetomidine, an anesthetic that induces sedation with significant risk of respiratory depression by diminishing activity of noradrenergic neurons in the locus ceruleus in brain stem, hence leading to a rise in downstream activity of GABA neurons in the ventrolateral preoptic nucleus in anterior hypothalamus just above the optic chiasma, while propofol, another anesthetic with that acts directly on GABA, lowered blood pressure by a lesser extent [Frolich et al., 2013].

2.7.6. Management of hypertensive crisis via induction of midazolam with or without traditional anti-HTN such as captopril

A latest randomized controlled trial conducted by Enayatrad, Yekesadat and Khodayar in June of 2020 had shown that midazolam could successfully lower blood pressure in patients suffering from hypertensive crisis, a hypertensive emergency where a sudden rise in blood pressure occurs that even could lead to organ failure. In the double-blinded study, 43 patients admitted into the Imam Hossein Hospital of Shahroud in 2018 with a sudden rise of blood pressure above 180/110 mm Hg had been included as subjects and subdivided into three patient groups, while an introduction of midazolam into a patient group led to a fall of systolic blood pressure, diastolic blood pressure and mean blood pressure by 20.6 per cent, 17.4 per cent and 19.1 per cent respectively. In contrast, use of conventional anti-hypertensive agents such as captopril had shown a decrease in SBP, DBP and Mean BP by 19.9 per cent, 13.5 per cent and 16.7 per cent respectively, while a patient group receiving a combination therapy of captopril and midazolam had averaged a reduction of 23.5 per cent, 17.4 per cent and 20.5 per cent in SBP, DBP and Mean BP

respectively, meaning that a combination of midazolam and captopril had lowered the SBP and Mean BP by the most in patients with hypertensive crisis [Enayatrad, Yekesadat and Khodayar, June 2020].

2.8. Risks of use of benzodiazepine as an anti-HTN agent

Despite benzodiazepines' efficacy in treatment of HTN in adults and elderly that often is associated with a lower risk of CVDs and associated mortalities and hospitalization as beforementioned, benzodiazepine use for treating HTN in elderly could not come up without risks. However, after careful observation of risks as cited in previous studies, meta-analysis and case studies, it would be contemplated whether the benefits of use of benzodiazepine could outclass the risks in elderly.

A systematic review and meta-analysis conducted by Islam et al. (2016), had underscored that the patients being treated with benzodiazepines could be in 78 per cent higher risk of developing dementia, though, retrograde amnesia which is a common side-effect of benzodiazepine could be overlapped and the authors had underlined requirement of further researches on whether benzodiazepine-induced dementia had not been a systemic manifestation of retrograde amnesia [Islam et al., 2016].

Furthermore, a meta-analysis of past studies of benzodiazepine use in elderly conducted by Sithamparanathan, Sadera and Leung (December 2012) had revealed that elderly patients with mean age above 65 having been treated with benzodiazepine for anxiety or insomnia could develop mild adverse effects like of fall, confusion, dizziness, headache, depression and paradoxical hypertension in inconsistent use of benzodiazepines. Nonetheless, use of anti-HTN agents such as thiazides and lisinopril alongside amlodipine could increase the risk of fall in elderly as well, but thiazides could decrease the risk of fracture following a fall in hypertensive elderly by 21 per cent compared to lisinopril or amlodipine, suggesting that anti-hypertensive medications should be used with caution in elderly whether these are benzodiazepines or conventional anti-HTNs. However, thiazides had shown a better response to HTN with a long track record of CVD protection [Sithamparanathan, Sadera and Leung, December 2012]. Besides, Singh and Sarkar

(2016) had underscored the risk of benzodiazepine abuse or inconsistent use in elderly HTN patients which could lead to paradoxical hypertension as beforementioned [Singh and Sarkar, 2016].

2.9. Use of benzodiazepine as a prophylaxis to hypertension

Given benzodiazepines' efficacy in lowering blood pressure with or without traditional anti-HTN in emergencies and long-acting and intermediate-acting benzodiazepines' role in reduction of BP in essential hypertension in combination with anti-hypertensive agents, it could be said indubitably that benzodiazepines have had an active role in controlling blood pressure irrespective of their central or peripheral mechanism of action.

Previous studies mentioned in the literature review suggested that certain benzodiazepines could be used as primary or secondary prophylaxis of certain medical conditions including cardiovascular diseases such as hypertension, while it was also stressed that possible action of benzodiazepines on cortisol or stress hormones, antiplatelet activation factor or an alteration in parasympathetic tone could be investigated further for benzodiazepine's non-psychiatric usages.

Besides, when combined with benzodiazepines, anti-HTN treatments had shown to have lower incidences of CVDs or associated risks and hospitalization, while patients with risk of developing HTN or with benign HTN, benzodiazepines could be effective, hence establishing benzodiazepines' role as an effective prophylaxis of hypertension along with cardiovascular diseases.

2.10. Antidepressants vs benzodiazepine in hypertensive elderly

Lapane et al., (1995), had found a strong correlation between ischemic cardiac events and use of antidepressants [Lapane et al., 1995], while Krantz et al. said in 2009 that, although, baseline anxiolytic such as benzodiazepines were not found to be increasing the risks of CVD events, but the use of antidepressants had been associated with CVD events in woman and an increased risk of ischemic heart disease related mortality in elderly men, apparently due to an accumulation of endothelial lipid, higher blood cholesterol level, underlying Diabetes Mellitus, fat deposition and increased appetite despite a

lowering of platelet aggregation, which are very common in use of both TCA and non-TCA antidepressants [Krantz et al., 2009]. According to a study conducted by Wu et al., (2014), benzodiazepines could lower the risk of cardiac mortality alongside hospitalization in patients after new incidents of MI when given in low to medium dosage [Wu et al., 2014].

Furthermore, Taylor, W., (2015), had warned that the use of antidepressant medication in elderly could be accompanied by a number of nefarious clinical incidences like of medical morbidity, suicidal ideation alongside cognitive decline [Taylor, W., 2015]. Therefore, benzodiazepines instead of antidepressants in patients with depression and HTN in elderly might be contemplated. Considering the risks of antidepressants, in particular SSRIs in elderly, a combination treatment of benzodiazepine and SSRIs in elderly patients with comorbid anxiety and depression had been recommended by Dunlop and Davis (2008) [Dunlop and Davis, 2008].

Furthermore, according to Cloos et al., (2015), several epidemiological studies had unfolded that the risks associated with BZDs in CVD patients are significantly lower than those with antidepressants [Cloos et al., (2015)].

3.0. Research methodology

Since this has been a “literature review”-based argumentative research, past studies and meta-analysis of past research works alongside case studies on benzodiazepines’ use on hypertension have been discussed with an incisive approach, while the literature review also had highlighted multiple case studies and meta-analysis of previous works related to benzodiazepines’ efficaciousness on elderly alongside the drug classes’ pragmatism in lowering the risk of CVDs, related hospitalization and morbidity. However, the literature review section had underscored the benefits of using benzodiazepine as an anti-HTN irrespective of the hypertensive patient groups’ age and sex. Considering the comely that benzodiazepines could yield in quality of life in hypertensive elderly in use of benzodiazepines alongside traditional anti-hypertensive agents, this review will look at the benefits of benzodiazepines benefits in elderly. Besides, this research

also had looked at past case studies underscoring potential risks of using antidepressants in patients with hypertension.

3.1. Data collection and analysis

Having been a literature review-based argumentative paper, in order to identify the benefits of benzodiazepines in hypertensive elderly and adults alongside patients with benign hypertension, this paper had taken a comprehensive approach to analyze the past works. In order to reach an inclusive resolution on whether the benefits of use of benzodiazepines in elderly and adult could outweigh the risks, an elaborative argument will take place based on the findings of the past research works, while discoveries of the arguments will be disbursed in the recommendation.

4.0. Results, arguments and recommendations

When it comes down to an evaluation of benzodiazepine's use as an anti-hypertensive on elderly and adult, this literature review-based argumentative paper had looked into past studies in order to have a precise understanding on relationship between benzodiazepine and its CVS and CNS effects. It was discussed how benzodiazepines downsize mean blood pressure alongside their elaborate mechanism of action which is exerted by an enhancement of the GABA-A neurotransmitter's inhibitory actions and PBR complexes in the CNS and PNS. The Literature review section has looked into past studies to find out how benzodiazepine could affect CVS, CNS, vasoactive smooth muscles and steroidogenesis while exerting a renal sympatholytic action alongside acting as a vasodilator. Different benzodiazepines impact on blood pressure was discussed to reach a conclusive resolution on whether the benefits of use of benzodiazepine in hypertensive adults and elderly with or without the use of conventional anti-hypertensive drugs could offset the risks.

This particular section will yield a synopsis of the findings of past studies and meta-analysis of researches on benzodiazepines' impact on blood pressure, while according to the synopsis, an argument will be conducted.

4.1. Findings

In terms of benzodiazepines' CVS effect, GABA-A receptor could act both centrally and peripherally as GABA-A receptors in many parts of the brain such as hypothalamus, ventrolateral medulla and amygdala nucleus among others could take part in modulating CVS activities while decreasing blood pressure and PBR complexes in blood vessels could dilate them, effectively suppress sympathetic excitement at nerve ending, and sometimes act directly on striatal cardiac muscles and coronary arteries by acting as an adenosine reuptake inhibitor, eventually increasing concentration of adenosine in microstructural environment while helping depreciate the risks of CVDs in elderly [33 adenosine]. Besides, studies had found that stimulus on GABA-A receptors in posterior hypothalamus could dramatically reduce blood pressure.

Almost all benzodiazepines could affect the CNS-regulated chronotropic impact on heart through nucleus ambiguous, which has found to be linked with parasympathetic vagal tones, and play a pivotal part on spike timing, neuronal rhythm and the activity patterns of electro-chemical regulation in neuronal circuits, though it is also found that benzodiazepines could exert direct or indirect impact on cardiac rates and reduce blood pressure and change other hemodynamic parameters by dilating blood vessels and exceling renal sympatholytic activities.

This goes without saying that the benzodiazepines could effectively lower blood pressure, in particular systolic blood pressure and thereby reducing mean blood pressure, however, questions raise on divergences of modalities on benzodiazepines according to their duration of action and chemical structure.

Addressing the issue, it has been found that short-acting benzodiazepines such as midazolam potentiate their antihypertensive actions through vasodilation, which might be a response to voltage gated Ca^{++} channels in the neurocytes of blood vessels and as a weak adenosine reuptake inhibitor. Even in a study conducted on a mouse with precontracted aortic ring, midazolam was found to have a reversible vasodilatory effect at low doses. Besides, in a study conducted on a human subject, TPSO, a peripheral

GABA-A-like receptor that acts similar to GABA-A in CNS, had found to have prompted myocardial response to ischemia and might have had a role in endothelial response of benzodiazepines. In acute cases, such as hypertensive crisis and other life-threatening sympathomimetic events, midazolam as well as long-acting benzodiazepines were found to be as effective as ACE inhibitors.

When it comes to intermediate-acting benzodiazepines such as bromazepam or alprazolam, those benzodiazepines were found to have a profound impact on maintaining a lower blood pressure in both adult and elderly in combination with a typical anti-hypertensive agent. However, those drugs acted better in elderly to maintain a low blood pressure level, in treatment of labile hypertension and to decrease the risks of cardiovascular diseases or cardiovascular disease-related hospitalizations. A meta-analysis of past studies also had found that the intermediate-acting benzodiazepines in combination with traditional antihypertensives could decrease the rate of cardiovascular disease-associated morbidity or hospitalization in elderly patients aged above 65 who had experienced an ischemic attack at least once in their lives. Besides, although, a lowering of blood pressure in benzodiazepine usage had not been entirely related to age and sex, but, both long-acting and intermediate-acting benzodiazepines in elderly patients aged above 58 with hypertension and anxiety- or depression-associated HTN acted better than those with only conventional anti-HTN treatment.

Long-acting antidepressants alone could have significant role in decreasing blood pressure regardless of their actions in CNS and PNS, as previous studies and meta-analysis had found that an oral administration of as little as 5mg diazepam, could to a significant fall in both systolic and mean blood pressure. Sympathomimetic activities in smooth muscles were also diminished. However, long-acting benzodiazepines such as diazepam did not lead to a decrease in heart rate, suggesting that the long-acting benzodiazepines might have exerted their hypotensive effects by acting on CNS. Lorazepam, which is used as an anti-convulsant in neonates and children, has been effective in decreasing anxiety-associated hypertension following a dose regimen of 3mg/day for 4 weeks.

Past case studies had revealed that long-acting benzodiazepines such as diazepam could reduce effectively irrespective of age and sex, while elderly hypertensive patients usually respond better in long-term benzodiazepine therapy. Clonazepam has found to be effective in treating patients suffering from labile hypertension and anxiety mediated hypertension. It has also been unveiled that the benzodiazepines could reduce the risk of CVDs and hospitalization in elderly hypertensives in combination with traditional anti-hypertensives better than those taking only traditional anti-hypertensives. Besides, in treating patients with hypertensive crisis, midazolam had shown better efficacy than anti-hypertensive agents such as captopril, however, a combination of midazolam and captopril has been found be to be more efficacious in decreasing mean blood pressure.

In terms of benzodiazepine-associated risks in hypertensive elderly, inappropriate or erratic use of benzodiazepines could lead to paradoxical episodes of hypertension and hypotension. Concomitantly, use of benzodiazepines in both adults and elderly are often associated with abuse. After prescribing benzodiazepines, patients with prior history of substance abuse, memory deficits and suicidal ideation should be monitored. Besides, elderly patients who have been in risks of fall due to physical aging or rheumatological clinical conditions among others, should be counselled before prescribing benzodiazepines. Even though, risks of benzodiazepines' use in elderly are much lower than those in use of antidepressants.

4.2. Arguments

Aside from benzodiazepines' wide-spread use as an anti-hypertensive with or without in combination of an anti-hypertensive or a prophylaxis to HTN, previous past studies also revealed the benzodiazepine's efficacy in limiting the CVD-related emergencies, morbidities or hospitalization. However, use of benzodiazepines come up with a greater risk in adults and elderly who have a prior history of substance abuse or psychotic disorders such as suicidal ideation. However, with proper monitoring and history-taking before introduction of benzodiazepines could, those risks could be curbed out and thereby the study finds that the roles of benzodiazepines should be contemplated as an effective treatment in reducing blood

pressure in both adult and elderly, as a prophylaxis in adult individuals with benign hypertension and as a rational treatment modality to limiting the risk of ischemia or CVDS in hypertensive elderly, as the risks of benzodiazepines treatment in hypertensive adult and elderly could be easily outclassed by their benefits.

However, often antidepressants are used in hypertensive adults in combination with typical anti-HTNs, but past studies had shown those treatment regimens came in with an increased risk of CVDs associate morbidity and CVDs related hospitalization, psychotic events such as suicidal ideation and mania alongside a higher chance of fall.

5.0. Conclusion & Recommendation

In conclusion, despite benzodiazepines' representation as a useful tool for limiting the access of hypertensive patients into emergencies, use of all classes of benzodiazepines could not be recommended for long-term use for all age-groups, benzodiazepines might and could be used in treating patients with hypertension in both adults with benign hypertension and elderly depending on their specific clinical condition. Low-to-moderate dose of long-acting or intermediate-acting benzodiazepines could be highly effective in limiting the risks of CVDs in hypertensive elderly, as past studies had found an addition of benzodiazepines in hypertensive patients could decrease the hospitalization with MI, angina, essential hypertension and congestive heart failure. Following conducting a vigorous argument on the findings of this literature review-based argumentative research that addressed benzodiazepines' efficacy in hypertensive elderly and adults to lower blood pressure and to be used as a prophylaxis to hypertension, it could be concluded that benzodiazepine is safer as a prophylaxis/treatment for HTN in elderly with or without presence of psychiatric disorders such as anxiety and depressive disorders among others. However, as antidepressants are widely prescribed in hypertensive elderly despite their gruesome side effects, before prescribing antidepressants, history must show that there has never been any underlying psychiatric disorder. After induction, patients must be monitored regularly for suicidal ideation, violent behavior and mania. Unlike anti-depressants, benzodiazepines are more versatile with low side effects when it comes to

CVDs. In long-term anti-hypertensive medication, a benzodiazepine could be added with anti-HTNs to increase efficacy and decrease the risks of myocardial ischemia and alongside other CVDs, while the benefits of benzodiazepines could easily outsmart the associated risks.

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