## **Do anti-hypertensive medicines increase the risk of depression?**

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**Abstract**

Depression is a common and often debilitating mental health disorder affecting a significant proportion of the population. Antihypertensive drugs are prescribed for the pharmacological management of high blood pressure, which affects approximately one-third of adults globally. While these drugs are generally well-tolerated, concerns remain about the potential risk of depression associated with their use. Several studies have investigated the link between antihypertensive drugs and depression, with mixed results. Some studies have reported an increased risk of depression in patients taking certain classes of antihypertensive drugs, such as beta-blockers and calcium channel blockers. Others have found no significant association between these medicines and depression, or report a reduction in risk of depression. This review gathered the evidence to consider whether any differences in risk exist between antihypertensive class or if any particular drugs stand out from the crowd. We found no substantial evidence of any class effect although lipophilic beta-blockers are associated with increased reports of sleep disturbance and fatigue. Given the high prevalence of hypertension and depression, further well-designed studies are needed to clarify the potential link between antihypertensive drugs and depression. Healthcare professionals should be aware of the potential risk and closely monitor patients for signs of depression during antihypertensive treatment.

**Key words**

Antihypertensive, depression, risk/benefit, hypertension.

**Introduction**

For more than 50 years, the link has been made between the use of antihypertensive drugs and the new onset or re-emergence of symptoms of major depression. Since propranolol became available in the 1960s, both anecdotal and, later, more empirical evidence has emerged that antihypertensive drugs of all classes may have some influence on mood disorders and possibly even on the risk of suicide(1-5). The direction of the evidence (increased vs. decreased risk of depression) and expert opinion is very mixed which does not provide much in the way of helpful guidance for prescribers. The majority of antihypertensive prescriptions today are based on the NICE guideline “*Hypertension in adults: diagnosis and management*” last updated in March 2022, which promotes the use of drugs that target the renin-angiotensin system (angiotensin converting enzyme inhibitors and angiotensin receptor blockers), dihydropyridine calcium channel blockers and thiazide diuretics at the earlier steps of hypertension management because of their relatively good profiles in reducing cardiovascular events such as stroke and myocardial infarction(6). Other antihypertensive agents such as β-blockers and α-blockers have a less favourable risk/benefit ratio and so appear only as adjuncts or where other agents are contraindicated, and other antihypertensive agents including the centrally acting agents (such as clonidine and α-methyldopa) and the vasopressors (such as hydralazine and sodium nitroprusside) are only used in more specialist cases. Nevertheless, there is evidence linking all classes of antihypertensive drugs with depression and other psychological disorders in the clinical literature, with some classes and especially some agents making more frequent appearances than others(7-9). This review explores the association and recent evidence which suggests that the risk, if or where it exists at all, may differ between sub-classes of antihypertensives.

**Antihypertensives and depression: a prescribing dilemma**

In the late 1960s, just a few years after this prototype beta-blocker became available as an antihypertensive drug, the BMJ reported observations of depression in patients taking propranolol (1) . Even earlier antihypertensives, such as reserpine and α-methyldopa, have also been linked to the development of depressive symptoms(10, 11). Observations of adverse effects reported in reserpine users, in particular, formed the basis of the development of the monoamine hypothesis of depression in the 1950s(12). The monoamine hypothesis posits that depression is associated with a deficit of the monoamines serotonin, noradrenaline and dopamine in the CNS, although today it is recognised that this theory likely explains only a part of the underlying pathology of depression. As the armoury of antihypertensive drugs has increased giving us the wide range of options available in today’s formularies, the question of whether this now very diverse class of drugs influences mood on either a subclinical or clinical level continues to be posed. Over the years, further evidence has emerged supporting arguments that at least some antihypertensive drugs may actually *reduce* the risk of depression, that others continue to pose an *increased* risk, or that their influence as a broad class is negligible(7, 8, 13-16). Two large-scale prominent trials considered the effect of antihypertensive use on depression and other patient outcomes. The ACCORD trial, published in 2012, investigated intensive versus standard blood pressure control on depression and health-related quality of life in patients with type 2 diabetes, and found there was no clinically meaningful difference between the two approaches to managing hypertension(17). In 2017, the findings of SPRINT (Systolic Blood Pressure Intervention Trial) were published, which focused on the effect of intensive blood-pressure treatment on patient-reported outcomes, concluding that there was no effect of intensive BP reduction on depression(18).

To deliver and receive the best possible person-centred interventions, prescribers and patients will no doubt take an interest in identifying an antihypertensive drug that best meets the patient’s overall needs, including consideration of the adverse effect profile. This may very well mean that what is recommended for one individual, based on previous experiences or their ability to tolerate certain adverse effects, will not suit another. History of mental health, or risk of depression, should be considered if there is any risk involved from antihypertensive drugs. But the question is: are these effects real, and if so what weight should be applied to this variable when selecting a suitable antihypertensive drug?

**Is there a biological basis?**

Largely based on observations of changes in mood in patients who were being treated with reserpine to manage their hypertension, the monoamine theory, introduced above, began to emerge in the 1950s and 1960s that depression in humans might be caused by the depletion of biogenic amines in the synapses of the CNS(12). Reserpine is one of many alkaloids isolated from extracts of the plant *Rauvolfia serpentina*, and its mode of action as an antihypertensive is now understood to be through irreversible blockade of the vesicular monoamine transporters VMAT1 (in neuroendocrine cells) and VMAT2 (in neurons), resulting in the depletion of both central and peripheral sympathetic amines(19). At around the same time, seminal work by Joseph Schildkraut showed that monoamine depletion, especially of noradrenaline, appeared to be associated with depression(12). Based on the reported observations of a number of clinicians that patients taking reserpine were more likely to experience symptoms of depression, and taking into consideration reserpine’s presumed mode of action, an extrapolation was made that biologically connected reserpine use with mood disorders influencing the generation of the *monoamine hypothesis of depression*. But reserpine is a drug that is associated with a wide variety of perceived adverse effects and was not well tolerated by many patients at the doses prescribed(20).

Shortly after propranolol became available as an important new development in the management of hypertension, evidence slowly began to emerge that also connected this drug with symptoms of depression(1, 21). Propranolol is a non-selective beta-adrenergic antagonist, more commonly known as a beta-blocker, which has lipophilic properties allowing passage across the blood-brain barrier resulting in both central and peripheral effects(22). Its pharmacology and pharmacodynamic properties are more complex than the class name suggests, but of particular relevance to this review are its weak effects on noradrenaline availability (increased) in the synapses of the CNS and weak blockade of a number of serotonin receptors, which may impact in some way on arousal and mood(23, 24). Needless to say, the story is likely to be far more complex than this.

The advancement of antihypertensive therapy in the intervening years has seen the rise of numerous other beta-blockers, diuretics, calcium channel blockers and drugs that target the renin-angiotensin system (ACE inhibitors and angiotensin receptor blockers) appearing in the BNF and clinical guidelines but the question of their impact on mood has not been resolved. In contrast with the attempts outlined above to understand the involvement of monoamines, many of the antihypertensives used clinically today are reported to either *increase* or *decrease* the risk of depression based, perhaps, on other biological mechanisms(2). Theories have been posed based on genetic differences and neuroinflammatory mechanisms, which remain inconclusive but nevertheless plausible(25-28).

There is mixed evidence for an association between cerebral blood flow and mood in the elderly. Saper argues that maintaining a systolic blood pressure at or below 120 mmHg, as recommended following the Systolic Blood Pressure Intervention Trial (SPRINT), is insufficient for adequate cerebral perfusion in the elderly(29). In an epidemiological study, Hildrum et al found that there is an association between low blood pressure and mood, but an RCT by Moonen et al found no evidence that discontinuing antihypertensives in the elderly led to any improvement in cognitive function(30, 31).

**A review of the evidence**

For this review, 21 articles (Table 1) were identified that are exemplars of the range of evidence and opinion available to practitioners to inform their recommendations and shared decision making. Articles were included based on guiding criteria, which were (i) articles must be published in English; (ii) articles must report investigation of a possible relationship between use of one or more antihypertensive drug in humans and any symptoms commonly associated with depression as defined by ICD-10 criteria, either as part of a trial or in routine clinical practice; (iii) studies of any kind reporting primary data or meta-data, but not review or opinion articles. Six of the 21 studies explored the association between β-blockers and depression (including symptoms, formal diagnoses, associated mental health disorders or risk of suicide) and fifteen articles explored the same relationship for two or more antihypertensive drugs. The studies were a mixture of systematic reviews of RCTs with meta-analyses, cohort and case-control studies, cross-sectional and other observational studies. 10 studies concluded that there was no substantial evidence of any association between antihypertensive use, of any class, and depression. Two studies concluded that all of the antihypertensive drugs investigated had a protective effect against depression. One study found dichotomous class effects with drugs divided into “increases risk” and “decreases risk” categories. The remaining 8 studies concluded that there may be an increased risk of depression for one or more of the antihypertensives investigated in the study. These findings are summarised in table 1.

*Table 1. A summary of the reported associations between antihypertensive use and depression. BBs: beta-blockers; CCBs: calcium channel blockers; ACEIs: angiotensin-converting enzyme inhibitors; ARBs: angiotensin receptor blockers; DIUs: diuretics; AHT: antihypertensive; HT: hypertension; CV: cardiovascular; QoL: Quality of Life; AD: antidepressant; MDD: major depressive disorder.*

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Characteristics** | | | | | | | **Effect** | | | | |
| **Study** | **Participants, n** | **Sex**  **(% female)** | **Mean age in yrs (SD)** | **Inclusion criteria\*** | **Exclusion criteria\*** | **Control group** | **Indicators of depression** | **BBs** | **CCBs** | **ACEIs** | **ARBs** | **DIUs** |
| Agustini, 2020(32) | 14,195 | 55.8 | 75 (4.5) | Age 70+ | CV disease or event, severe hypertension | Not taking AHT | ≥8 on CES-D 10 scale | ↑ risk with lipophilic BBs | No notable effect | No notable effect | No notable effect | - |
| Boal, 2016(33) | 144,066 | 52 | 55.5 | Age 40-80 | None reported | Not taking AHT | Based on ICD-10 | ↑ risk | ↑ risk | ↓ risk | ↓ risk | No notable effect |
| Bornand, 2022(34) | 237,410 | 61.3 | 40.3 (15.8) | Age 18-80 | >2 AHT drugs; History of prevalent depression | Case controls: no depression | Based on Read codes | No notable effect | - | - | - | - |
| Brownstein, 2018(15) | 4,605  (in 11 studies) | 44 | Unknown | RCTs inc. any ACEi or ARBs | Major physical symptoms, only physical QoL scores | Placebo or non-angiotensin AHT drug | QoL scores for psychological domains | - | - | No notable effect | No notable effect | - |
| Cao, 2019(16) | 181,709 | 52 | 52.8 | Newly diagnosed HT, age 18 - <80 | Previous AD medications, use of combined AHT drugs | (Nominally) ARBs | First use of AD drug | ↑ risk | No notable effect | ↑ risk | No notable effect | No notable effect |
| Chowdhury, 2018(35) | 6,083 | 51.1 | 71.9 (4.9) | Age 65 – 84, with HT | Not described | Thiazide diuretic | Diagnosis of depression, or prescribed AD | - | - | No notable effect | - | No notable effect |
| Gerstman, 1996(36) | 3,782 | 59.5 | 46.7 | Received prescription for AHT drug | Coded diagnosis indicative of depression | (Nominally) propranolol | New diagnosis of depression | No notable effect | No notable effect | No notable effect | - | No notable effect |
| Johansen, 2012(37) | 55,472 | Varies by group | Varies by group | Age 20+ inhabiting defined geographical region | History of established CVD | - | HADS-D ≥8 and HADS-A <8 | No notable effect | No notable effect | No notable effect | - | - |
| Kessing, 2020(8) | 5.4 million | Varies by group | Varies by group | Entire population of Denmark | Purchase of AD drugs, or diagnosed with depression prior to entry | No exposure to AHT drugs | Diagnosis of depression or use of AD drugs | ↓ risk | ↓ risk | ↓ risk | ↓ risk | - |
| Ko, 2002(38) | > 35,000 (in 15 studies) | Varies by study | Varies by study | Symptoms of depression, fatigue, and sexual dysfunction | Not reported | Placebo | Symptoms of depression, fatigue, and sexual dysfunction | No notable effect | - | - | - | - |
| Li, 2021(7) | 414,873 | Varies by study | Varies by study | Categorical measure of depression | Sample size <100 | Non-medicated or users of other medications | Varies by study | ↑ risk | ↑ risk | - | ↑ risk | - |
| Michal, 2013(39) | 5,000 | Varies by group | Varies by group | Age 35 - 74 | Cannot consent, insufficient German language | No AHT drugs | PHQ-9 score ≥10 | No notable effect | No notable effect | No notable effect | No notable effect | No notable effect |
| Ranchord, 2016(40) | 3,470 | 57.9 | 30.8 | Age 18+, clinical indication of AMI | Multifactorial | No beta-blocker | PHQ-8 score ≥10 | No notable effect | - | - | - | - |
| Riemer, 2021(14) | 53,533 | Varies by study | Varies by study | Beta blocker monotherapy | No reference to occurrence or absence of any psychiatric adverse events | Placebo or non-beta blocker therapy | Report of psychiatric adverse events (varies by study) | No notable effect | - | - | - | - |
| Ringoir, 2014(9) | 573 | 70 (6.6) | 57 | primary care patients aged 60–85 years, with diagnosed hypertension | Diagnosis of HF, history of psychiatric illness (other than mood disorder/anxiety) | Non beta blocker therapy | Category of PHQ-9 score | ↑ risk with lipophilic BBs | No notable effect | No notable effect | No notable effect | No notable effect |
| Shaw, 2021(41) | 801,008 | Varies by group | Varies by group | With or without history of mood disorder | Assigned to cohort according to AD status and MDD admission | Cohort comparison | Prescription for any AD drug or psychiatric admission for MDD | ↑ risk | ↑ risk | ↑ risk | ↑ risk | ↑ risk |
| Simonson, 2011(13) | 7,272 | 81.8 | - | Data from National Nursing Home Survey | - | Comparison of AHT drug classes | Diagnosis of depression | ↓ risk | ↓ risk | ↓ risk | ↓ risk | ↓ risk |
| Sørensen, 2001(5) | 58,529 | Varies by group | Varies by group | Taking BB, CCB or ACEi | Taking any other drug or combinations of drugs | Comparison of AHT drug classes and against general population | Death associated with suicide | ↑ risk (of suicide) | No notable effect | No notable effect | - | - |
| Spencer, 2022(42) | 10,256 | 50 | 51 | Age 18 – 80 with PHQ-9 score | Taking AHT drugs for indication other than HT | Not taking any AHT drug | PHQ-9 score ≥10 | No notable effect | No notable effect | ↑ risk | No notable effect | No notable effect |
| Thiessen, 1990(43) | 3,218 | Varies by group | Varies by group | Taking BB or other AHTs | Not taking any drug for chronic disease | Other AHT or treatment for chronic disease | Incidence of AD drug use | ↑ risk (propranolol) | - | - | - | - |
| Verbeek, 2011(44) | 118,705 | 40.3 (15.8) | 61.3 | Age 18 – 80 with incident depression diagnosis, and ≥ prescriptions for AD drugs | Patients with mild depression or history of suicidal ideation, cancer, HIV or alcoholism | Matched controls with no incident depression diagnosis | Diagnosis of depression (by Read codes) | No notable effect | - | - | - | - |

\*Summarised.

In total, 18 of the studies reviewed investigated the association between beta-blockers and depression. Eight of these studies reported an increased risk of new onset or recurrence of a previous diagnosis of depression with beta-blocker use. One study – a cross sectional study of 3,218 new β-blocker users - found that the proportion of propranolol-users receiving antidepressant prescriptions was 9.5%, several times greater than for any other lipophilic or hydrophilic β-blocker(43). Two other studies in this group(9, 32) specifically highlighted the more lipophilic beta-blockers as having a notable association with depression, whereas four other studies(7, 16, 33, 41) reported a more general class effect of beta-blockers. Sørensen et al reported that compared to the general population, patients taking lipophilic beta-blockers are at 2.7 times increased risk of mortality associated with suicide in the first 12 months of use, though there are numerous confounding factors in the lipophilic beta-blocker cohort which may explain at least part of this effect(5). Li et al conducted a systematic review followed by a network meta-analysis of five studies involving 263,025 patients and found that when compared to diuretics, beta blockers, calcium channel blockers and angiotensin antagonists were all associated with an increased risk of depression(7). It isn’t clear whether hypertension was the indication for all drugs and therefore there is a possibility that the findings are dependent on other underlying confounders that are also predictors of depression.

Amongst the 10 studies that found no substantial evidence of any increased risk of depression associated with beta-blockers was a large systematic review and meta-analysis by Riemer et al which identified 285 randomised controlled trials (RCTs) of 24 beta-blockers(14). The authors of this systematic review highlight the fact that, compared to placebo, reports of fatigue/tiredness and unusual dreams were increased in users of beta-blockers and suggest that these specific adverse effects may in many cases be misinterpreted as depression. The authors of at least two other studies also make this point and given the relative subjectivity of depression scoring and diagnosis, even guided by DSM-5 or ICD-10 criteria there is likely to be considerable variability in the differential diagnoses between physicians and even, for every physician, between patients (38, 39, 45, 46).

Of the 13 studies that considered calcium channel blockers, three reported an increased risk of depression(7, 33, 41), two reported a decreased risk(8, 13), and the remainder found no substantial evidence of any impact on the risk of depression. Those reporting a decreased risk found a similar effect for most antihypertensives included. Kessing et al report the findings of a Danish population-based study to investigate 41 antihypertensive drugs which found that none of the drugs increased the risk of depression, while a number of individual drugs were associated with a decrease in depression diagnoses or antidepressant use for each category of calcium channel blockers, drugs that target the renin-angiotensin system and beta blockers (including propranolol)(8).

The risk associated with drugs that target the renin-angiotensin systemappears to be inconclusive, and the majority of studies did not find any substantial evidence associating the use of these drugs and depression. Three studies(8, 13, 33) reported a decrease in the risk for both ACEIs and ARBs compared to other agents or placebo, whereas two studies found an increased risk for ARBs(7, 41) and three studies reported an increased risk associated with ACEIs(16, 41, 42). The magnitude of these effects was small though statistically significant in all studies reporting an association.

For diuretics, seven studies did not find substantial evidence of any effect, though one study reported an increased risk of depression(41), with one further study reporting a decreased risk(13).

To summarise, when pooling the findings from a range of published studies none of the drugs used to treat hypertension appear to be entirely absent of risk for either depression or symptoms that are associated with depression. However, there is a greater body of evidence covering beta-blockers and almost half of these studies associate this class of drugs, and particularly the more lipophilic beta blockers, with increased risk of depression. But we must be extremely cautious when interpreting these findings as there are numerous other important variables that may have influenced the outcomes of these studies and that in turn influence risk prediction for depression based on the published data. Our observations of many of these factors are discussed in more detail later in this article, but it is important to first consider the key similarities and differences between the antihypertensive drug classes which may affect the respective depression risk and also how these agents are prescribed to manage hypertension.

**ACE inhibitors and Angiotensin II receptor blockers**

For step 1 treatment of hypertension NICE recommends the use of ACE inhibitors or ARBs in under 55s for some categories of patients(6). There is evidence that chronic activation of the renin-angiotensin system (RAS) may contribute to neuroinflammation, leading to both neurogenic hypertension and increasing risk of numerous psychological and neurological disorders including depression (where emotion pathways are involved) and dementia(25, 27). The arm of the RAS responsible for the proinflammatory effects is known as the classical RAS, which is balanced by the counter-regulatory RAS which has a neuroprotective role.

In both arms of the RAS, angiotensinogen is cleaved by renin to produce angiotensin I, which in turn is cleaved by angiotensin converting enzyme (ACE) to angiotensin II. Through the type 1 angiotensin II receptor (AT1R), angiotensin II promotes vasoconstriction and inflammation, as part of the classical RAS pathway. But in the counter-regulatory RAS pathway, angiotensin II acts through another receptor type known as the type 2 angiotensin II receptor (AT2R) to promote vasodilation and reduced inflammation. At the same time, angiotensin II is cleaved by ACE2 forming angiotensin-(1-7) peptide, which also promotes vasodilation and reduced inflammation but via the Mas receptor (MasR)(25).

Inhibition of ACE counters the chronic activation of the classical RAS pathway, whereas A2RBs target angiotensin II AT1 receptors thus inhibiting the classical arm of the RAS. Both mechanisms lead to vasodilation, reduced secretion of vasopressin and reduced production and secretion of aldosterone, combining overall to reduce blood pressure. However, it isn’t clear if the action of ACE inhibitors and A2RBs on the peripheral RAS is replicated in the central RAS to exert any neuroprotective effects, though it is known that a number of these antihypertensives are active in the CNS (perindopril, candesartan)(47, 48).

**Calcium channel blockers**

The NICE guideline for hypertension recommends the use of calcium channel blockers in other categories of patients for step 1 of treatment, rather than using an ACE inhibitor(6). There is evidence from genetic data that dysfunctional L-type calcium channels are associated with an increased risk of depression and other psychiatric disorders, and that intracellular calcium dysregulation is apparent in depressed patients(49).

Following activation of the voltage-gated calcium channels in the cell membrane, the entry of calcium into the cell is vital for key cellular processes including neurotransmitter release, hormone release and gene expression. A dysfunctional calcium channel will disrupt this very sensitive, discreet signalling, as it may have a lower or higher activation threshold leading to consequences for the normal functioning of the cell(26). In CNS pathways responsible for mood and emotion, this may manifest as a set of symptoms characterising one or more psychiatric disorders.

This has implications for the use of the groups of drugs known as dihydropyridine calcium channel blockers (CCBs) in patients at risk of or diagnosed with depression, and the prescribing of CCBs has been associated with a decreased risk of depression in some small studies. For many years, despite the more mainstream, evidence-based approach to managing bipolar disorder with lithium and antiepileptics, calcium channel blockers have sometimes been used where tolerability to other agents has been poor(50). Clinical evidence supporting this approach is scant, though recently genetic studies have identified possible connections between L-type calcium channels and the pathology of bipolar disorder (51-53). Verapamil and diltiazem have been investigated in a number of studies and it is possible that all calcium channel blockers (dihydropyridines, phenylalkylamines and benzothiazepines) may be associated with changes in psychiatric function – but further studies are needed to explore this relationship(54).

**Diuretics**

NICE does not recommend thiazide diuretics as part of the step 1 intervention unless one of the first-line options is not tolerated, but this class of drugs is one of the recommended escalation options at step 2. There is very little evidence pointing to thiazide diuretics being implicated in depression and the presumed mechanisms of action of thiazides and thiazide-like agents in reducing blood pressure, or their pharmacodynamic properties, are not easily extrapolated to the possible explanations of the underlying pathophysiology of mood disorders. Low-dose thiazide diuretics inhibit the resorption of Na+ and Cl- ions by blocking the Na+/Cl- transporter in the distal convoluted tubules of the kidney, and this results in a greater loss of water in the urine. The reduced overall volume in the blood vessels reduces outward pressure on the vessel walls, thereby producing an antihypertensive effect(55).

**Beta-blockers**

NICE does not recommend the use of beta-blockers before step 4, as part of a treatment strategy for resistant hypertension, and only then if the patient is at risk of (or has) hyperkalaemia and would not therefore tolerate spironolactone(6). Beta blockers have fallen out of favour in the management of hypertension because evidence shows they are less effective than drugs that target the renin-angiotensin system, CCBs and diuretics at preventing cardiovascular events, though they are more effective than placebo(56, 57).

Beta-blockers are competitive antagonists of the adrenaline and noradrenaline binding sites of the beta-adrenergic receptors in the sympathetic nervous system. Some beta-blockers are non-selective and will block all three sub-types of beta receptor, whereas other agents will more selectively block activity at β1, β2 or β3 receptors. The target for beta-blockers in hypertension management is β1 receptors which are found predominantly in the heart and in the kidneys(58).

The mechanism by which beta-blockers induce an antihypertensive effect is probably multifactorial. Beta-blockers are known to have negative chrono- and inotropic effects, leading to a reduced cardiac output and therefore possibly reduced pressure on the vessel walls. The action of beta-blockers on the sympathetic nervous system (for those agents that can enter the CNS) and the direct effect of systemic beta-blockers on the kidney leads to a reduction in renin output and a consequent decrease in aldosterone secretion. This causes more Na+ and water to be excreted in the urine, decreasing blood volume and pressure(59).

Beta-blockers have been implicated in depression almost since they were first used more than 50 years ago, although there remains no consensus on whether or not this effect is real. Those beta-blockers that are more lipophilic, such as propranolol, have a greater ability to diffuse through the blood-brain barrier and can therefore enter the CNS more readily compared with hydrophilic beta-blockers, such as atenolol(60). Lipophilic agents are therefore more likely to be associated with central effects such as fatigue, sleep/dream disorders or depression(61). Beta-blockers disrupt rapid eye movement (REM) sleep and can therefore cause insomnia, which in turn leads to poor concentration and attention, impaired performance and even mood disturbance during the daytime(62, 63). This impact on sleep and disruption to the sleep/wake cycle is the mechanism some have proposed which connects beta-blocker use with reports of depression(32).

**Other antihypertensives**

Clonidine, α-methyldopa and moxonidine are centrally acting antihypertensive drugs. Clonidine is an α2-antagonist, suppressing noradrenaline and renin release, and is not routinely used in modern hypertension management because sudden withdrawal can lead to a hypertensive crisis(64). α-methyldopa is also an α2-antagonist and is used, off-label, for managing hypertension in pregnancy but can cause fluid retention with long-term use(65). Moxonidine causes its antihypertensive effect through activity at the imidazoline receptor I1. It is sometimes, but rarely, used in resistant hypertension or where other antihypertensives are not suitable(66).

Guanethidine is obsolete in modern hypertension management, except in a hypertensive emergency although other agents are usually preferred. It works by preventing the release of noradrenaline from nerve endings in the sympathetic nervous system and can lead to a rapid antihypertensive effect, but postural hypotension is common(67).

Hydralazine, sodium nitroprusside, minoxidil and nitrates are all vasodilators that have strong and rapid antihypertensive effects. A number of other drugs, including sildenafil, tadalafil and ambrisentan, are licensed for the treatment of pulmonary arterial hypertension. All of these agents are initiated only in specialist cases(68).

α1-antagonists (prazosin, doxazosin, alfuzosin) may be introduced at step 4 of the NICE Hypertension guideline for managing resistant hypertension as an alternative to beta-blockers, or patients with hypertension may be prescribed α1-antagonists for another indication such as benign prostatic hyperplasia(69). These agents have vasodilator properties and can induce a rapid antihypertensive effect after the first dose. α1-antagonists act by blocking the action of noradrenaline at the α1 adrenergic receptors in the vascular smooth muscle, preventing vasoconstriction.

**Consideration of other contributing factors and uncertainties**

It is reported that around 20% of patients with ischaemic heart disease (IHD) have major depression, and many more present with symptoms that are often associated with depression such as fatigue or unusual dreams, independent of antihypertensive use(70). These important factors very likely contribute to the association being made between antihypertensives and depression and raise important questions about how depression is diagnosed and underlying causal factors.

The psychological burden of living with long-term illnesses or risk factors can itself be the cause of a patient developing symptoms of depression or anxiety, and many patients will have a history of mood disorders that may re-emerge when triggered by a new or worsening co-morbidity, by hospitalisation, or multiple other factors associated with a change to their quality of life(71, 72).

For many years, beta-blockers (especially propranolol) have been used very effectively to help patients manage their anxiety by controlling the somatic symptoms associated with sympathetic nervous system activity, such as trembling, tachycardia and sweating. There is a strong, recognised association between anxiety and depression and these disorders often manifest as co-morbidities, which poses a problem when trying to understand the role of beta-blockers in raising the risk of mood disorders when other key risk factors are already present(73).

It is also important to acknowledge that depression itself is a predictor of heart disease and stroke, with an increased incidence of hypertension in patients who are depressed(74-76). We are therefore faced with the age-old chicken-and-egg problem when we further confound this relationship with treatments to control blood pressure.

Reduced adherence to antihypertensive treatment is recognised to be predicted by depression and is an important confounding factor that should be controlled for wherever possible in studies exploring this relationship(77). Interestingly, depression does not appear to be a predictor of statin intolerance – a treatment for another silent risk factor for IHD(78). What is not clear is whether poor adherence to antihypertensives could be a reliable predictor of depression, though uncontrolled hypertension does appear to have a detrimental effect on depression(79).

There are also limitations to the evidence available to us when trying to understand this relationship. Although coming to different conclusions, both Li et al and Riemer et al reported moderate to considerable heterogeneity between studies, reducing the reliability of their findings(7)(14). Earlier in this review, we considered the relatively subjective nature of depression diagnosis and we cannot rule out the likelihood of unintended clinician bias when attempting to differentiate between chronic sleep disorders (for example) and depression. It is also likely that there is some degree of reporting bias and publication bias, which may disproportionately add weight to studies reporting a positive correlation between antihypertensive use and depression(80).

**Conclusion and future perspectives**

While the relationship between antihypertensive use and depression remains unclear it is important that clinicians continue to work with patients to manage hypertension, for which of course there is substantial evidence of increased risk of incident stroke or MI. It is prudent to consider the risk of depression for each individual based on their medical history and act accordingly, including the patient in the discussion about their treatment options and taking their personal goals and choices into account. The most effective management of hypertension is likely when the clinical guidelines are followed, when the most appropriate dose is prescribed for the patient, and when adverse effects are being monitored.

Further studies that investigate the effects of individual antihypertensives are needed, since the physicochemical and pharmacological properties of agents within each class differ sufficiently that there is varying CNS exposure, a varying degree of specificity of receptor activity, and therefore presumably varying risk of inducing symptoms associated with depression or other psychiatric illness. Well-designed prospective trials in primary care could provide useful evidence, and large-scale epidemiological studies with carefully considered co-variables would help to refine our understanding of the risk.

**Key points box**

* It remains unclear whether there is a risk of depression associated with taking any antihypertensive drug. Adverse effects such as fatigue and unusual dreams may be misinterpreted as depression in many cases.
* It is possible that some antihypertensives carry a greater risk compared with others, but a number of well-designed studies do not consistently provide any substantial evidence that this is the case for any particular agent and there appears to be no class effect.
* Prescribers should not avoid the use of antihypertensives based on an unclear risk profile, as this could lead to undertreatment of hypertension and ischaemic heart disease. But it may be prudent to avoid lipophilic beta-blockers if there is a clinical concern about depression since alternative antihypertensive drugs are available.
* Patients who are considered to be at increased risk of depression or the psychological burden associated with long-term illness should be monitored closely for changes to their mental health.
* If a patient presents with symptoms of depression that may be associated with an antihypertensive drug, a switch within class may be a sensible first step if the hypertension is responding well. This will help to balance the risk/benefit in co-morbid disease management.

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**References**

1. Waal HJ. Propranolol-induced depression. Br Med J. 1967;2(5543):50.

2. Koella WP. CNS-related (side-)effects of beta-blockers with special reference to mechanisms of action. Eur J Clin Pharmacol. 1985;28 Suppl:55-63.

3. Beers MH, Passman LJ. Antihypertensive Medications and Depression. Drugs. 1990;40(6):792-9.

4. Hallas J. Evidence of Depression Provoked by Cardiovascular Medication: A Prescription Sequence Symmetry Analysis. Epidemiology. 1996;7(5):478-84.

5. Sørensen HT, Mellemkjaer L, Olsen JH. Risk of suicide in users of beta-adrenoceptor blockers, calcium channel blockers and angiotensin converting enzyme inhibitors. Br J Clin Pharmacol. 2001;52(3):313-8.

6. NICE. National Institute for Health and Care Excellence: Guidelines. Hypertension in adults: diagnosis and management. London: National Institute for Health and Care Excellence (NICE). ; 2022.

7. Li Y, Fan Y, Sun Y, Alolga RN, Xiao P, Ma G. Antihypertensive Drug Use and the Risk of Depression: A Systematic Review and Network Meta-analysis. Frontiers in Pharmacology. 2021;12.

8. Kessing LV, Rytgaard HC, Ekstrøm CT, Torp-Pedersen C, Berk M, Gerds TA. Antihypertensive Drugs and Risk of Depression. Hypertension. 2020;76(4):1263-79.

9. Ringoir L, Pedersen SS, Widdershoven JW, Pouwer F, Keyzer JM, Romeijnders AC, et al. Beta-blockers and depression in elderly hypertension patients in primary care. Fam Med. 2014;46(6):447-53.

10. Freis ED. Mental depression in hypertensive patients treated for long periods with large doses of reserpine. N Engl J Med. 1954;251(25):1006-8.

11. DeMuth GW, Ackerman SH. alpha-Methyldopa and depression: a clinical study and review of the literature. Am J Psychiatry. 1983;140(5):534-8.

12. Schildkraut JJ. The catecholamine hypothesis of affective disorders: a review of supporting evidence. Am J Psychiatry. 1965;122(5):509-22.

13. Simonson W, Han LF, Davidson HE. Hypertension Treatment and Outcomes in US Nursing Homes: Results From the US National Nursing Home Survey. Journal of the American Medical Directors Association. 2011;12(1):44-9.

14. Riemer TG, Villagomez Fuentes LE, Algharably EAE, Schäfer MS, Mangelsen E, Fürtig MA, et al. Do β-Blockers Cause Depression?: Systematic Review and Meta-Analysis of Psychiatric Adverse Events During β-Blocker Therapy. Hypertension. 2021;77(5):1539-48.

15. Brownstein DJ, Salagre E, Köhler C, Stubbs B, Vian J, Pereira C, et al. Blockade of the angiotensin system improves mental health domain of quality of life: A meta-analysis of randomized clinical trials. Australian & New Zealand Journal of Psychiatry. 2018;52(1):24-38.

16. Cao YY, Xiang X, Song J, Tian YH, Wang MY, Wang XW, et al. Distinct effects of antihypertensives on depression in the real-world setting: A retrospective cohort study. Journal of Affective Disorders. 2019;259:386-91.

17. O'Connor PJ, Narayan KM, Anderson R, Feeney P, Fine L, Ali MK, et al. Effect of intensive versus standard blood pressure control on depression and health-related quality of life in type 2 diabetes: the ACCORD trial. Diabetes Care. 2012;35(7):1479-81.

18. Berlowitz DR, Foy CG, Kazis LE, Bolin LP, Conroy MB, Fitzpatrick P, et al. Effect of Intensive Blood-Pressure Treatment on Patient-Reported Outcomes. New England Journal of Medicine. 2017;377(8):733-44.

19. Yaffe D, Forrest LR, Schuldiner S. The ins and outs of vesicular monoamine transporters. Journal of General Physiology. 2018;150(5):671-82.

20. Saseen JJ. Chapter 29 - Pharmacologic Management of Hypertension. In: Antman EM, Sabatine MS, editors. Cardiovascular Therapeutics: A Companion to Braunwald's Heart Disease (Fourth Edition). Philadelphia: W.B. Saunders; 2013. p. 474-89.

21. Srinivasan AV. Propranolol: A 50-Year Historical Perspective. Ann Indian Acad Neurol. 2019;22(1):21-6.

22. Al-Majed AA, Bakheit AHH, Abdel Aziz HA, Alajmi FM, AlRabiah H. Chapter Six - Propranolol. In: Brittain HG, editor. Profiles of Drug Substances, Excipients and Related Methodology. 42: Academic Press; 2017. p. 287-338.

23. Tuross N, Patrick RL. Effects of propranolol on catecholamine synthesis and uptake in the central nervous system of the rat. J Pharmacol Exp Ther. 1986;237(3):739-45.

24. Hoyer D, Clarke DE, Fozard JR, Hartig PR, Martin GR, Mylecharane EJ, et al. International Union of Pharmacology classification of receptors for 5-hydroxytryptamine (Serotonin). Pharmacol Rev. 1994;46(2):157-203.

25. Tran S, Kuruppu S, Rajapakse NW. Chronic Renin-Angiotensin System Activation Induced Neuroinflammation: Common Mechanisms Underlying Hypertension and Dementia? Journal of Alzheimer's Disease. 2022;85:943-55.

26. Saddala MS, Lennikov A, Mukwaya A, Yang Y, Hill MA, Lagali N, et al. Discovery of novel L-type voltage-gated calcium channel blockers and application for the prevention of inflammation and angiogenesis. Journal of Neuroinflammation. 2020;17(1):132.

27. Mowry FE, Biancardi VC. Neuroinflammation in hypertension: the renin-angiotensin system versus pro-resolution pathways. Pharmacological Research. 2019;144:279-91.

28. Osimo EF, Baxter LJ, Lewis G, Jones PB, Khandaker GM. Prevalence of low-grade inflammation in depression: a systematic review and meta-analysis of CRP levels. Psychological Medicine. 2019;49(12):1958-70.

29. Saper CB. How low can you go? Ann Neurol. 2015;78(5):665-6.

30. Hildrum B, Mykletun A, Stordal E, Bjelland I, Dahl AA, Holmen J. Association of low blood pressure with anxiety and depression: the Nord-Trøndelag Health Study. Journal of Epidemiology and Community Health. 2007;61(1):53.

31. Moonen JEF, Foster-Dingley JC, de Ruijter W, van der Grond J, Bertens AS, van Buchem MA, et al. Effect of Discontinuation of Antihypertensive Treatment in Elderly People on Cognitive Functioning—the DANTE Study Leiden: A Randomized Clinical Trial. JAMA Internal Medicine. 2015;175(10):1622-30.

32. Agustini B, Mohebbi M, Woods RL, McNeil JJ, Nelson MR, Shah RC, et al. The association of antihypertensive use and depressive symptoms in a large older population with hypertension living in Australia and the United States: a cross-sectional study. Journal of Human Hypertension. 2020;34(11):787-94.

33. Boal AH, Smith DJ, McCallum L, Muir S, Touyz RM, Dominiczak AF, et al. Monotherapy With Major Antihypertensive Drug Classes and Risk of Hospital Admissions for Mood Disorders. Hypertension. 2016;68(5):1132-8.

34. Bornand D, Reinau D, Jick SS, Meier CR. β-Blockers and the Risk of Depression: A Matched Case-Control Study. Drug Saf. 2022;45(2):181-9.

35. Chowdhury EK, Berk M, Nelson MR, Wing LMH, Reid CM. Association of depression with mortality in an elderly treated hypertensive population. International Psychogeriatrics. 2019;31(3):371-81.

36. Gerstman BB, Jolson HM, Bauer M, Cho P, Livingston JM, Platt R. The incidence of depression in new users of beta-blockers and selected antihypertensives. Journal of Clinical Epidemiology. 1996;49(7):809-15.

37. Johansen A, Holmen J, Stewart R, Bjerkeset O. Anxiety and depression symptoms in arterial hypertension: the influence of antihypertensive treatment. The HUNT study, Norway. European Journal of Epidemiology. 2012;27(1):63-72.

38. Ko DT, Hebert PR, Coffey CS, Sedrakyan A, Curtis JP, Krumholz HM. β-Blocker Therapy and Symptoms of Depression, Fatigue, and Sexual Dysfunction. JAMA. 2002;288(3):351-7.

39. Michal M, Wiltink J, Lackner K, Wild PS, Zwiener I, Blettner M, et al. Association of hypertension with depression in the community: results from the Gutenberg Health Study. Journal of Hypertension. 2013;31(5):893-9.

40. Ranchord AM, Spertus JA, Buchanan DM, Gosch KL, Chan PS. Initiation of β-blocker therapy and depression after acute myocardial infarction. American Heart Journal. 2016;174:37-42.

41. Shaw RJ, Mackay D, Pell JP, Padmanabhan S, Bailey DS, Smith DJ. The relationship between antihypertensive medications and mood disorders: analysis of linked healthcare data for 1.8 million patients. Psychological Medicine. 2021;51(7):1183-91.

42. Spencer J, Penson PE, Henney NC, editors. Exploring the association between antihypertensive drug treatment and depression: an observational study. Pharmacology 2022; 2022; Liverpool UK: British Journal of Clinical Pharmacology.

43. Thiessen BQ, Wallace SM, Blackburn JL, Wilson TW, Bergman U. Increased Prescribing of Antidepressants Subsequent to ß-Blocker Therapy. Archives of Internal Medicine. 1990;150(11):2286-90.

44. Verbeek DEP, van Riezen J, de Boer RA, van Melle JP, de Jonge P. A Review on the Putative Association Between Beta-Blockers and Depression. Heart Failure Clinics. 2011;7(1):89-99.

45. Buch AM, Liston C. Dissecting diagnostic heterogeneity in depression by integrating neuroimaging and genetics. Neuropsychopharmacology. 2021;46(1):156-75.

46. Goldberg D. The heterogeneity of "major depression". World Psychiatry. 2011;10(3):226-8.

47. Yamada K, Horita T, Takayama M, Takahashi S, Takaba K, Nagata Y, et al. Effect of a centrally active angiotensin converting enzyme inhibitor, perindopril, on cognitive performance in chronic cerebral hypo-perfusion rats. Brain Res. 2011;1421:110-20.

48. Li NC, Lee A, Whitmer RA, Kivipelto M, Lawler E, Kazis LE, et al. Use of angiotensin receptor blockers and risk of dementia in a predominantly male population: prospective cohort analysis. Bmj. 2010;340:b5465.

49. Andrade A, Brennecke A, Mallat S, Brown J, Gomez-Rivadeneira J, Czepiel N, et al. Genetic Associations between Voltage-Gated Calcium Channels and Psychiatric Disorders. International Journal of Molecular Sciences. 2019;20(14):3537.

50. Grunze H, Vieta E, Goodwin GM, Bowden C, Licht RW, Moller HJ, et al. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2009 on the treatment of acute mania. World J Biol Psychiatry. 2009;10(2):85-116.

51. Catterall WA, Perez-Reyes E, Snutch TP, Striessnig J. International Union of Pharmacology. XLVIII. Nomenclature and structure-function relationships of voltage-gated calcium channels. Pharmacol Rev. 2005;57(4):411-25.

52. Jimerson DC, Post RM, Carman JS, van Kammen DP, Wood JH, Goodwin FK, et al. CSF calcium: clinical correlates in affective illness and schizophrenia. Biol Psychiatry. 1979;14(1):37-51.

53. Heyes S, Pratt WS, Rees E, Dahimene S, Ferron L, Owen MJ, et al. Genetic disruption of voltage-gated calcium channels in psychiatric and neurological disorders. Prog Neurobiol. 2015;134:36-54.

54. Cipriani A, Saunders K, Attenburrow MJ, Stefaniak J, Panchal P, Stockton S, et al. A systematic review of calcium channel antagonists in bipolar disorder and some considerations for their future development. Mol Psychiatry. 2016;21(10):1324-32.

55. Duarte JD, Cooper-DeHoff RM. Mechanisms for blood pressure lowering and metabolic effects of thiazide and thiazide-like diuretics. Expert Rev Cardiovasc Ther. 2010;8(6):793-802.

56. Khan N, McAlister FA. Re-examining the efficacy of β-blockers for the treatment of hypertension: a meta-analysis. Canadian Medical Association Journal. 2006;174(12):1737-42.

57. Wiysonge CS, Bradley H, Mayosi BM, Maroney R, Mbewu A, Opie LH, et al. Beta-blockers for hypertension. Cochrane Database Syst Rev. 2007(1):Cd002003.

58. Wong GW, Boyda HN, Wright JM. Blood pressure lowering efficacy of beta-1 selective beta blockers for primary hypertension. Cochrane Database Syst Rev. 2016;3(3):Cd007451.

59. Pucci G, Ranalli MG, Battista F, Schillaci G. Effects of β-Blockers With and Without Vasodilating Properties on Central Blood Pressure. Hypertension. 2016;67(2):316-24.

60. Guan L, Yang H, Cai Y, Sun L, Di P, Li W, et al. ADMET-score - a comprehensive scoring function for evaluation of chemical drug-likeness. Medchemcomm. 2019;10(1):148-57.

61. Cojocariu SA, Maștaleru A, Sascău RA, Stătescu C, Mitu F, Leon-Constantin MM. Neuropsychiatric Consequences of Lipophilic Beta-Blockers. Medicina. 2021;57(2):155.

62. Kostis JB, Rosen RC. Central nervous system effects of beta-adrenergic-blocking drugs: the role of ancillary properties. Circulation. 1987;75(1):204-12.

63. Ohayon MM. Epidemiology of insomnia: what we know and what we still need to learn. Sleep Medicine Reviews. 2002;6(2):97-111.

64. Cao C, Lorenz ML, Sojka P, Brindle AW, Topor LS. Hypertensive Crisis in a Pediatric Patient Experiencing Clonidine Withdrawal. Case Rep Pediatr. 2022;2022:9005063.

65. Redman CW, Beilin LJ, Bonnar J. Treatment of hypertension in pregnancy with methyldopa: blood pressure control and side effects. Br J Obstet Gynaecol. 1977;84(6):419-26.

66. Fenton C, Keating GM, Lyseng-Williamson KA. Moxonidine: a review of its use in essential hypertension. Drugs. 2006;66(4):477-96.

67. Kadzielawa K. Mechanism of action of guanethidine. Br J Pharmacol Chemother. 1962;19(1):74-84.

68. Houtchens J, Martin D, Klinger JR. Diagnosis and management of pulmonary arterial hypertension. Pulm Med. 2011;2011:845864.

69. Lepor H. Alpha blockers for the treatment of benign prostatic hyperplasia. Rev Urol. 2007;9(4):181-90.

70. Rudisch B, Nemeroff CB. Epidemiology of comorbid coronary artery disease and depression. Biological Psychiatry. 2003;54(3):227-40.

71. Turner J, Kelly B. Emotional dimensions of chronic disease. West J Med. 2000;172(2):124-8.

72. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Psychiatry. 2022;9(2):137-50.

73. Kalin NH. The Critical Relationship Between Anxiety and Depression. Am J Psychiatry. 2020;177(5):365-7.

74. Barlinn K, Kepplinger J, Puetz V, Illigens BM, Bodechtel U, Siepmann T. Exploring the risk-factor association between depression and incident stroke: a systematic review and meta-analysis. Neuropsychiatr Dis Treat. 2015;11:1-14.

75. Davidson K, Jonas BS, Dixon KE, Markovitz JH. Do Depression Symptoms Predict Early Hypertension Incidence in Young Adults in the CARDIA Study? Archives of Internal Medicine. 2000;160(10):1495-500.

76. Jonas BS, Franks P, Ingram DD. Are symptoms of anxiety and depression risk factors for hypertension? Longitudinal evidence from the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study. Arch Fam Med. 1997;6(1):43-9.

77. Eze-Nliam CM, Thombs BD, Lima BB, Smith CG, Ziegelstein RC. Depression and Adherence to Antihypertensive Therapy. American Journal of Hypertension. 2008;21(7):724-5.

78. Bytyçi I, Penson PE, Mikhailidis DP, Wong ND, Hernandez AV, Sahebkar A, et al. Prevalence of statin intolerance: a meta-analysis. Eur Heart J. 2022;43(34):3213-23.

79. Wang L, Liu Q, Sun D, Xie J, Lao D, Zhang L. Effects of Combination Treatment in Hypertensive Patients with Depression: A Systematic Review and Meta-Analysis of 27 Randomized Controlled Trials. Ther Clin Risk Manag. 2022;18:197-211.

80. Luijendijk HJ, Koolman X. The incentive to publish negative studies: how beta-blockers and depression got stuck in the publication cycle. Journal of Clinical Epidemiology. 2012;65(5):488-92.