The risk of a blood pressure increase during treatment with selected psychotropic drugs

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Abstract

Arterial hypertension is the most common cardiovascular risk factor in the general population. Increased mortality from arterial hypertension affects all ethnicities and ages, including those with mental disorders. Most people with arterial hypertension suffer from the primary form of the disease. The aim of this article was to analyze the influence of psychiatric drugs on blood pressure.

The articles for analysis were selected *via* the PubMed search engine in the Medline database using the names of individual drugs or a group of psychotropic drugs, the AND operator and the words "hypertension" or "blood pressure" or "cardiovascular system". The articles were then selected and 44 references were selected for analysis. Selected articles were archived on April 9, 2021.

Many medications with the potential to increase blood pressure are used to treat mental illness. These include venlafaxine, milnacipran, bupropion, esketamine, 1st and 2nd generation antipsychotics, tricyclic antidepressants and psychostimulants.

In patients using psychotropic drugs that may increase blood pressure, attention should be paid to monitoring it during treatment.

Key words: arterial hypertension; psychotropic drugs; cardiovascular risk

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Introduction

Arterial hypertension is one of the most common cardiovascular risk factors. About 45% of people worldwide suffer from hypertension, and the incidence increases with age [1]. According to a 2014 World Health Organization (WHO) report, hypertension accounted for 51% of stroke deaths and 45% of overall cardiovascular mortality, and it affected all age groups and ethnicities [1].

Blood pressure remains insufficiently controlled in approximately 50% of all treated hypertensive patients [2, 3]. The reason for such a high prevalence of hypertension and its poor control is, first of all, low public awareness of classical and non-classical risk factors for its occurrence and non-compliance with medical recommendations [4, 5]. Most patients with hypertension suffer from its primary form (90% of cases) or an identified secondary form (e.g. in the course of renal artery

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stenosis, chronic kidney disease, hyperaldosteronism, pheochromocytoma).

From a clinical point of view, the influence of psychiatric drugs on blood pressure and the interaction of these drugs with antihypertensive drugs are significant [7]. These drugs may affect both the risk of hypertension and the effectiveness of antihypertensive therapy [6]. The aim of the article was to analyze the effect of psychiatric drugs on blood pressure and to present potential interactions between these drugs and antihypertensive drugs.

Method

The analysis of available literature in English and Polish was carried out using the PubMed search engine in the Medline database. The search was performed by using the search terms with the name of the drug or group of drugs, the "AND" operator and the terms "hypertension" or "blood pressure" or "cardiovascular system". 162 abstracts were pre-selected. Those that did not refer to the research problem or contained methodological problems were excluded and 44 papers were selected for the review. Selected articles were archived on April 9, 2021.

Antidepressants

According to WHO, about 264 million people worldwide currently suffer from depressive disorders [8]. Antidepressants are among the most frequently prescribed medications [9]. The influence of these drugs on the cardiovascular system, and in particular on blood pressure, is a very important issue in the practice of practically every medical specialty. Antidepressants include tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), noradrenergic and specific serotonergic antidepressants (NaSSA), serotonin antagonist and reuptake inhibitors (SARs) and esketamine, which opens a new group of fast-acting antidepressants, and older and less frequently used monoamine oxidase inhibitors (MAOIs).

Tricyclic antidepressants

Tricyclic antidepressants work by inhibiting the reuptake of serotonin (mainly amitriptyline, imipramine, and clomipramine) and noradrenaline (mainly nortriptyline and desipramine). However, they do not affect the dopaminergic system. Currently, they are used less frequently due to their side effects resulting from the antagonistic effect on muscarinic cholinergic receptors (dry mouth, constipation, tachycardia, urinary retention), histamine H1 (sedation, weight gain) and $\alpha 1$ adrenergic receptors (tachycardia, orthostatic hypotension) [10]. The most serious side effect of TCAs is its effect on the myocardial stimulus-conductive system. Overdosing of TCA may result in atrioventricular blocks or Hiss bundle branch blocks. Despite their unquestionable effectiveness in the treatment of depressive disorders, they should not be used in patients with cardiac risk [10]. The meta-analysis of Thase (1998), including 3744 depressed patients, assessed the effect of imipramine on blood pressure. The use of TCA in therapeutic doses was associated with a small but statistically significant increase in systolic blood pressure during the treatment of the acute phase of depression [11]. However, in elderly patients with concomitant cardiovascular diseases, more frequent occurrence of orthostatic hypotension was found during the use of TCAs [11].

In a study by Licht et al. (2009) including 2028 patients with depression (of whom 1384 were not taking antidepressants, mean age 42.0 ± 11.3 years), the impact of antidepressant drugs on the risk of hypertension was assessed. It has been shown that patients using TCAs were characterized by increased systolic and diastolic blood pressure and more often had stage 1 (OR: 1.90; 95% CI: 0.94–3.84; p = 0.07) and stage 2 hypertension (OR: 3.19; 95% CI: 1.35–7.59; p = 0.008). The risk of isolated systolic and diastolic hypertension was also increased in patients using TCAs, although the effect was not statistically significant (OR 1.43; 95% CI: 0.68–3.00, p = 0.34 and OR 2.12; 95% CI: 0.69–6.49, p = 0.19, respectively) [12]. The main cause of death in patients with TCAs was arrhythmia [13].

In conclusion, the presented studies indicate that the use of TCAs may be associated with an increased risk of hypertension in adults.

Serotonin reuptake inhibitors

Serotonin reuptake inhibitors increase the concentration of serotonin in the synaptic space by reducing its reuptake. Currently, 6 drugs from this group are registered in Poland: fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram and escitalopram. Due to the lack or low affinity of drugs from this group to muscarinic, histamine and adrenergic receptors, SSRI drugs show low behavioral toxicity and are well tolerated by patients.

Drugs from the SSRI group may have a certain antihypertensive effect in some groups of patients. In the study by Valclavik et al. (2018) covering 56

patients with phaeochromocytoma who started the use of sertraline, clinical improvement was observed in 75% of them. Mean systolic and diastolic blood pressure (measured in a doctor's office) in patients receiving sertraline decreased by 12.8/7.4 mm Hg ($p < 0.001$), and complete resolution of paroxysmal increases in blood pressure was observed in 50% of patients [14]. In a meta-analysis of 23 randomized clinical trials conducted by Zhong et al. (2017) involving 13,285 subjects, the effect of SSRIs on systolic and diastolic blood pressure was assessed. There was no statistically significant effect (weighted mean difference, WMD) of paroxetine, fluoxetine, sertraline, escitalopram and citalopram compared to placebo on systolic blood pressure (total WMD 0.04; 95% CI: –0.68–0.59) and diastolic blood pressure (total WMD 0.08; 95% CI: –0.43–0.60) [15].

In a randomized placebo-controlled clinical trial by Peixoto et al. (2019) involving 30 patients with depression and hypertension, the effect of escitalopram on blood pressure was assessed. Patients were divided into escitalopram (n = 15, dose 10–20 mg/day) and placebo (n = 15) group and were followed for 8 weeks. There was no statistically significant effect of escitalopram on systolic blood pressure (140.80 ± 16.48 mm Hg *vs.* 139.61 ± 18.92 mm Hg, p = 0.85) and diastolic blood pressure (80.55 ± 12.64 mm Hg *vs.* 80, 18 16.36 mm Hg, p = 0.94) [16].

The study by Humbert et al. (2019) obtained different results. In a study of these authors, two different types of investigations were performed: a comparative study in VigiBase® (n = 14824), which is the WHO pharmacovigilance database (PVDB), from where notifications of hypertension with six SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) were extracted [relationship between the suspected SSRIs and the occurrence of hypertension was assessed by calculating reporting odds ratio (ROR)] and a descriptive study of hypertension reports associated with SSRIs in the French pharmacovigilance database (FPVDB; n = 24). Based on the VigiBase® analysis, it was shown that the use of SSRIs significantly increased the ROR of hypertension (ROR 1.71; 95% CI: 1.68–1.74). In the FPVDB, 24 reports of hypertension were found with all six SSRIs used at standard doses, mainly in women (66.7%) with a mean age of 57.8 years and a median time of onset of 6 days. In 10 cases (42%), patients had a history of hypertension. This real-life study shows a significant pharmacovigilance safety signal between the use of SSRIs and the development or worsening of hypertension [17].

Overall, the impact of SSRIs on the risk of hypertension remains controversial and requires further research.

Serotonin and norepinephrine reuptake inhibitors

This group of drugs reduces the reuptake of serotonin and noradrenaline in the synaptic space. The SNRIs include desvenlafaxine, duloxetine, milnacipram and venlafaxine. Of the SNRIs, only venlafaxine and milnacipram seems to be able to increase blood pressure.

In the previously cited meta-analysis by Thase (1998), including 3744 depressed patients, the effect of venlafaxine on blood pressure was assessed. The use of venlafaxine compared with placebo has been shown to be associated with increased systolic blood pressure. The effect of venlafaxine was highly dose-dependent and the incidence of elevated diastolic blood pressure (> 90 mm Hg) was 3 times higher than in patients treated with the lower dose (9% *vs.* 3%). Importantly, however, the study concluded that venlafaxine did not adversely affect blood pressure control with antihypertensive drugs in patients with previously diagnosed hypertension. The previously cited meta-analysis by Zhong et al. (2017) showed that the use of SNRI compared to SSRI may cause a slight but statistically significant increase in systolic (WMD –1.50; 95% CI: –2.15– –0.84) and diastolic (WMD –1.34; 95% CI: –1.92– –0.75) blood pressure in both short-term (less than 8 weeks) and long-term (more than 8 weeks) therapy [15].

The negative effect of venlafaxine on blood pressure results from the stimulation of the sympathetic nervous system [11]. Moreover, in clinical practice the interaction between venlafaxine and amlodipine is important. It has been shown that the blood levels of venlafaxine metabolites increase in patients taking amlodipine. This effect may lead to an additional increase in the stimulation of the sympathetic nervous system and significantly increased blood pressure [18].

A meta-analysis of 17 randomized clinical trials by Park et al. (2020) assessed the effects of duloxetine on heart rate and blood pressure. Intervention time was up to 13 weeks and the daily dose of duloxetine was 30–120 mg. Duloxetine has been shown to increase heart rate by 2.22 beats/min (95% CI: 1.53–2.91), diastolic blood pressure by 0.82 mm Hg (95% CI: 0.17–1.47) and systolic blood pressure by 0.64 mm Hg (95% CI: –0.24–1.52). Thus, it was found that duloxetine did not increase the heart rate and blood pressure in the short term. However, studies are

needed to assess the long-term effects of duloxetine on the cardiovascular system [19].

The effects of duloxetine on heart rate and blood pressure appear to be dose dependent. A randomized, placebo-controlled, double-blind study by Derby et al. (2007) evaluated the effect of supra-therapeutic doses of duloxetine on heart rate and blood pressure in 117 healthy subjects. Dosages were escalated from 60 mg 2×/day to 200 mg 2×/day over 16 days. Duloxetine produced increases in supine systolic and diastolic blood pressures, which reached maximums of approximately 12 mm Hg and approximately 7 mm Hg above baseline, respectively, during dosing at 120 mg twice daily and then stabilized. Supine pulse rate increased gradually with dose, reaching 10 to 12 bpm above baseline after 4 days of dosing at 200 mg twice daily. Duloxetine caused changes in orthostatic blood pressures and pulse rate that reached plateau values after 3 to 4 days of dosing at 160 mg twice daily and were generally not associated with subjectively reported orthostatic-related adverse events. All vital signs normalized by 1 to 2 days after study drug discontinuation. Thus, duloxetine used in short-term supra-therapeutic doses may significantly increase heart rate and blood pressure [20].

The effect of milnacipran on blood pressure was assessed in a randomized, placebo-controlled, double-blind clinical study by Mease et al. (2009) in 888 patients with fibromyalgia. The safety of use of 100 and 200 mg milnacipran over 27 weeks was compared to placebo. After 27 weeks, supine systolic blood pressure was shown to increase by 3.3 mm Hg from baseline in both milnacipran groups. Mean diastolic blood pressure in the supine position increased by 2.5 mm Hg and 3.5 mm Hg from baseline in the milnacipran 200 and 100 mg/day groups, respectively [21]. The randomized, placebo-controlled, double-blind study by Trugman et al. (2014) in patients with fibromyalgia also assessed the effect of milnacipran on blood pressure. Patients were randomized to receive milnacipran (n = 210) or placebo (n = 111) for 7 weeks. Half of the patients suffered from hypertension. Analyzes were performed at weeks 4 and 7, after dose escalation of milnacipran to 100 and 200 mg/day, respectively. Blood pressure was measured by means of its 24-hour recording. Systolic and diastolic blood pressure increased on average by 4–5 mm Hg and 3–4 mm Hg, respectively, at the week 4 and week 7 visit. The mean increase in blood pressure was similar and comparable both in patients with hypertension and patients with normal blood pressure. A normal 24-hour blood pressure profile was maintained in patients receiving milnacipran. Researchers concluded that milnacipran slightly increases blood pressure in both normotensive people and those with hypertension [22].

In summary, among the SNRI drugs, venlafaxine and milnacipran have significant properties that increase the risk of hypertension. Therapeutic doses of duloxetine do not increase blood pressure in the short-term treatment.

Monoamine oxidase inhibitors

This group of drugs includes older drugs such as iproniazid, phenelzine, tranylcypromine and isocarboxazid (irreversible monoamine oxidase (MAO) antagonists, older and less frequently used drugs), and moclobemide, befloxatone and brofaromine (newer and reversible antagonists of MAO). Their mechanism of action is to reduce the breakdown of amine neurotransmitters (serotonin, noradrenaline, dopamine, tyramine and phenylalanine) in the central nervous system by reducing the activity of MAO. These drugs cannot be used together with drugs from the group of SSRIs, SNRIs or SSNRIs. Such a combination may result in serotonin syndrome, in which there may be both a dangerous increase and a decrease in blood pressure [7].

Increasing blood pressure by MAOIs results from the intensification of the intracellular transport of tyramine with a simultaneous increase in the concentration of norepinephrine in the vascular system (through the norepinephrine transporter). Noradrenaline, by narrowing the blood vessels, leads to an increase in blood pressure, and in extreme cases even a hypertensive crisis. This reaction is especially intensified with the use of older generation MAOIs (which irreversible block both MAO-A and MAO-B). Therefore, when taking drugs from this group, it is recommended to avoid excessive consumption of foods containing tyramine, such as cheese, red wine, fish, avocados, bananas or chocolate [7, 23]. In the literature, there are reports of patients with depression who used MAOIs and who experienced a hypertensive crisis after consuming red wine or long-aged cheese [24–26]. Increased blood pressure occurs rarely in patients using MAOIs and adhering to the aforementioned dietary recommendations, and most often up to 2 hours after administration of the drug; the observed increase in blood pressure is transient and no serious clinical consequences are found [27].

In order to reduce the risk of increased blood pressure while taking MAOIs, over-the-counter medications such as phenylephrine and pseudoephedrine, which may increase blood pressure, should also be avoided [27]. Orthostatic hypotension may also occur during the use of MAOIs [27]. Benzodiazepines

may be used to treat hypertension secondary to an increase in tyramine levels in the blood (unless systolic blood pressure is above 200 mm Hg). In such a case, antihypertensive drugs other than nifedipine should be used [23].

In summary, during the use of MAOIs, especially older, irreversibly blocking MAOIs, there is a risk of increasing blood pressure, largely dependent on the diet used during treatment and the concomitant medications used.

Other antidepressants

Trazodone is a drug that reduces the reuptake of serotonin and acts antagonistically on 5-HT2A receptors (serotonin antagonist and reuptake inhibitors, SARI). Its side effects are mainly somnolence, headache and nausea. As a side effect trazodone can also affect blood pressure. Orthostatic hypotension is the most commonly reported episode. Thus, when using this drug in patients with hypertension, the need to modify antihypertensive treatment should be considered [28, 29].

Another group of antidepressants are the NaSSA drugs, including mianserin and mitrazapine. The mechanism of the antidepressant action of these drugs is to reduce noradrenaline reuptake and block 5-HT2A receptors. Common side effects of these drugs are increased appetite and weight gain. Drugs from the NaSSA group can also cause changes in blood pressure, but to a lesser extent than TCAs. The safety profile of mitrazapine was assessed in a meta-analysis of 25 randomized and controlled trials by Watanabe et al. (2010) of 4,842 depressed patients. It has been shown that compared to TCAs, mitrazapine was characterized by a significantly lower risk of hypertension (RR: 0.51, 95% CI: 0.31–0.86; p = 0.01) [30].

Esketamine is a new antidepressant drug. The mechanism of action of esketamine is based on the blocking of NMDA (N-methyl-D-aspartate) glutamate receptors. Esketamine nasal spray has already been approved in many countries to augment the treatment of treatment-resistant depression in adults.

In 2020, a study by Doherty et al. was published, covering 1708 patients with treatment-resistant depression. Patients were divided into esketamine plus oral antidepressant and oral antidepressant plus placebo. It was shown that the increase in blood pressure was more frequent in patients receiving esketamine compared to placebo (3.9% *vs.* 11.6%). This indicates a greater risk of elevated blood pressure in patients receiving esketamine (OR: 3.2; 95% CI: 1.9–5.8). Hypertension occurred in 1.9% of patients receiving esketamine and in 0.6% of patients receiving placebo. On the other hand, no organ complications of the increased blood pressure were found. It was also found that the increase in blood pressure after administration of esketamine is generally transient (most often resolved 90 minutes after administration), asymptomatic and not associated with serious cardiovascular safety consequences [31].

Bupropion is a norepinephrine and dopamine reuptake inhibitor. It is used to treat depression (including seasonal depression), nicotine addiction and obesity. Data on the effects of bupropion on blood pressure are inconsistent. A randomized, double-blind, placebo-controlled study by Thase et al. (2008) of 300 patients with first degree hypertension investigated the effect of bupropion on blood pressure. Patients were randomized (four arms 1:1:1:1) to receive either placebo or prolonged-release bupropion (SR) 150, 300 or 400 mg/day for 4 weeks. Systolic and diastolic blood pressure decreased in all groups by –6.53, –6.46, –4.20, –4.87 mm Hg and –2.36, –2.27, –1.95, –1.55 mm Hg, respectively [32].

Slightly different results were obtained by Roose et al. (1991) in a study involving 32 patients with depression and cardiovascular diseases. These researchers showed that bupropion increased blood pressure in the supine (but not standing) position [33]. Similar results were obtained by Kiev et al. (1994) in a randomized, double-blind, placebo-controlled trial in 115 depressed patients. It has been shown that patients treated with bupropion (225–450 mg/day) experienced a slight but statistically significant increase in supine diastolic blood pressure by 5.6 mm Hg after the first week of treatment and by 7.5 mm Hg in the fourth week of treatment [34]. In conclusion, bupropion may increase diastolic blood pressure in supine patients [35].

Antipsychotic drugs

Antipsychotics are a group of drugs that have been used to treat mental illness since the 1950s. There are two main groups of antipsychotics: classic (older) antipsychotics (i.e. first-generation antipsychotics) and atypical neuroleptics. First-generation drugs, compared to atypical neuroleptics, more often cause extrapyramidal symptoms. In contrast to classic neuroleptics, second-generation drugs are more likely to cause symptoms of the metabolic syndrome, i.e. hypertension, insulin resistance, abdominal obesity, dyslipidemia and additionally — sexual dysfunction [36]. Side metabolic effects resulting from the use

of antipsychotic drugs are most pronounced in the first 6 weeks of their use, when the body mass index and waist circumference increase [36]. Clozapine and olanzapine are characterized by the highest average weight gain risk during antipsychotic treatment. Data from prospective studies indicate a possible increase of 6 to 12 kg in the first year of treatment and 3 to 12 kg in the later period [37]. In general, the symptoms of the metabolic syndrome are quite common (40%) in patients with schizophrenia treated with antipsychotics [38].

Hypertension in patients taking antipsychotic drugs is a consequence of the metabolic disorders caused by these drugs but many of them can also cause orthostatic hypotension [39]. A review of the literature by Gonsai et al. (2018) summarized the knowledge of the mechanism of the influence of antipsychotic drugs on blood pressure. All 5 dopamine receptor subtypes (D1, D2, D3, D4 and D5) regulate sodium excretion and blood pressure. The D1, D3 and D4 receptors interact directly with the renin–angiotensin–aldosterone system, whereas D2 and D5 receptors directly interact with the sympathetic nervous system to regulate blood pressure. The authors indicate that the use of dopamine receptor antagonists may disturb the regulation of blood pressure, leading to its increase [40].

The effect of clozapine or olanzapine administered for 8 weeks on blood pressure was analyzed in a retrospective study by Woo et al. (2009) involving patients with schizophrenia. A total of 167 patients were included in the study; 70 patients in clozapine group and 97 patients in olanzapine group. There was a significant increase in systolic (115.68 ± 8.64 mm Hg *vs.* 118.64 ± 11.65 mm Hg; p = 0.031) and diastolic (75.64 ± 6.52 mmHg *vs.* 79.36 ± 8.68 mm Hg; p = 0.001) blood pressure in the clozapine group. Moreover, a significant increase in body weight and serum triglycerides concentrations was found in this group of patients. Only significant weight gain was observed in patients treated with olanzapine. The researchers concluded that treatment with clozapine may lead to an increase blood pressure [41]. In a retrospective study by Norman et al. (2017) involving patients with a DSM IV diagnosis of schizophrenia or schizoaffective disorder, the effect of treatment with clozapine on blood pressure for 24 weeks was assessed. In this study participated 18 patients, and the mean stabilized clozapine dose was 441.7 ± 171.8 mg/day. It was shown that 22% of patients met criteria for hypertension before and 67% during clozapine treatment (p = 0.0124). No significant changes in weight or renal function occurred during clozapine treatment. Thus, this study also showed that clozapine may increase the risk of hypertension [42].

Valsartan, telmisartan and topiramate have been shown to be effective in blood pressure control in patients taking antipsychotic drugs [43].

In conclusion, when taking antipsychotics, due to the risk of both blood pressure increase and decrease, patients should be monitored regularly and, if necessary, existing antihypertensive therapy should be initiated or modified.

Mood stabilizers

Mood stabilizers include antiepileptic drugs, i.e. valproic acid, carbamazepine, lamotrigine and lithium salts with neuron membrane stabilizing activity. Mood-stabilizing drugs do not directly increase blood pressure, but they may contribute to the development of obesity, which may result in secondary dyslipidemia and hypertension. When using these medications, special attention should be paid to other medications taken by the patient, as mood stabilizers have numerous drug interactions.

When lithium salts are used concomitantly with thiazide diuretics or angiotensin converting enzyme inhibitors, the blood concentration of lithium may increase (should not be higher than 1.2 mmol/L). In the case of the use of thiazide diuretics, the increase is 20–40% of the blood pressure may occur and is due to the increase of lithium reabsorption in the proximal nephron coil. Moreover, spironolactone, which is an antagonist of the mineralocorticoid receptor, by increasing the amount of urine excreted may also increase the concentration of lithium in the body [44]. Excessive increase in the concentration of lithium (> 1.5 mmol/L) in the blood leads to intoxication and potentially life-threatening condition [44]. It has been shown in studies that the use of loop diuretics in patients over 66 years of age and taking lithium salts significantly increases the risk of hospitalization due to complications resulting from the toxicity of lithium [45].

The effect of lamotrigine on the risk of hypertension was assessed by Danielsson et al. (2018) in a study involving 1778 pregnant women with epilepsy and 221662 pregnant women without epilepsy. In the group of women taking lamotrigine (n = 280), this drug has not been shown to increase the risk of disorders associated with an increase in blood pressure in pregnancy (hypertension in pregnancy, mild to severe pre-eclampsia, early-onset pre-eclampsia). The total odds ratio of the disorders associated with the increase in blood pressure was 1.20 (95% CI:

0.76–1.88, p = 0.434) [46]. A review of the literature by Katsiki et al. (2014) analyzed the effect of different antiepileptic drugs on risk factors for cardiovascular disease. It was found that lamotrigine did not increase the risk of metabolic syndrome, body weight and tissue resistance to insulin [47]. Therefore, it seems that such properties of lamotrigine confirm its neutral influence on the risk of hypertension.

The presented data indicate that although mood stabilizers do not directly increase blood pressure, when using lithium salts, particular care should be taken in the case of concomitant use of antihypertensive drugs.

Psychostimulants

The mechanism of action of these psychostimulants is to increase the concentration of noradrenaline and dopamine in the synaptic space. A slight but statistically significant increase in systolic (by 3.3 mm Hg) and diastolic blood pressure (by 1.5 mm Hg) was demonstrated in the 1-year follow-up of 432 children with attention deficit hyperactivity disorder (ADHD) aged 6–13 years receiving methylphenidate (at a dose of 18–54 mg) [48]. The effect of methylphenidate on blood pressure was assessed in a randomized 6-week clinical trial in 141 patients with ADHD. A slight but statistically significant increase in systolic (3.5 ± 11.8 mm Hg) and diastolic (4.0 ± 8.5 mm Hg) blood pressure was demonstrated [49].

The long-term cardiovascular effects of methylphenidate intake (up to 60 mg/day) have also been extensively evaluated in adults with ADHD. A 24-month study involving 223 adult patients showed a small but statistically significant increase in systolic (2.3 ± 12.5 mm Hg; p = 0.006) and diastolic (1.3 ± 9.2 mm Hg; p = 0.042) blood pressure [50]. The short-term cardiovascular safety of lisdexamfetamine has been extensively assessed in a 4-week, randomized, controlled clinical trial in 420 adult ADHD patients. There was no statistically significant effect of this drug on both systolic and diastolic blood pressure [51].

A meta-analysis of six randomized, double-blind, placebo-controlled clinical trials (6–9 weeks duration) evaluated the effects of another psychostimulant — atomoxetine on blood pressure in a pediatric ADHD population, including 280 younger children (6–7 years old) and 256 older children (ages 6–7) at the age of 8–12). A statistically significant increase in systolic (2.1 mm Hg) and diastolic (2.9 mm Hg) blood pressure in the group of older children was found [52]. A meta-analysis by Hannissen et al. (2017) covering 18 clinical trials assessed the effects of methylphenidate, amphetamines, and atomoxetine on diastolic and systolic blood pressure in children and adolescents with ADHD (n = 5837). The mean duration of therapy was 28.7 weeks. All three medications were associated with a small, but statistically significant increase of systolic blood pressure (SMD: 0.18; 95% CI: 0.10–0.27, p < 0.01). The head-to-head comparison of the three medications did not reveal significant differences [53]. A more recent meta-analysis by Liang et al. (2018) assessed the effects of atomoxetine and methylphenidate on systolic blood pressure in young people and adults with ADHD. Twenty-two studies were included and the total number of participants was 46107. Children/adolescents and adults treated with methylphenidate had more significant increases in post- *vs.* pre-treatment SBP (pooled SMD with random-effects model: 1.40, 95% CI: 0.62–2.18, z = 3.52, p < 0.001) than those treated by placebo. Subgroup analysis showed no significant difference in systolic blood pressure between children/adolescents and adults in post- *vs.* pre-treatment. Children and adolescents treated with atomoxetine had more significant increases post- *vs.* pre-treatment SBP (pooled SMD with random-effects model: 0.366, 95% CI: 0.23–0.51, p < 0.001) than those treated with methylphenidate. The researchers conclude that during treatment with methylphenidate or atomoxetine, blood pressure should be monitored regularly [54].

In conclusion, psychostimulants to a slight but statistically significant degree may increase systolic and diastolic blood pressure [55].

Summary

As presented above, many groups of psychotropic drugs potentially influencing blood pressure are used in the treatment of mental diseases (Tab. 1) [6, 7, 56].

When planning treatment with the use of psychotropic drugs, it is first necessary to determine whether the patient has normal blood pressure. If the patient has hypertension, it should be determined whether it is well controlled and what antihypertensive drugs they are currently taking. In the case of treatment with psychotropic drugs, which potentially increase blood pressure, it should be monitored regularly and, if necessary, therapy with these drugs should be started or modified.

Conflict of interests

Authors declare no conflict of interest.

Table 1. Psychotropic drugs and their influence on blood pressure

Drug group	Subgroup	Risk of hypertension	Safety in patients with cardiac burden
Antidepressants	TCAs	Yes	They should be used with extreme caution. If possible, choose a drug from a different group
	SSRIs	Probably slight increase	They seem safe however, each case must be considered individually
	SNRIs	Probably yes (especially venlafaxine and milnacipran)	They seem relatively safe; however, attention should be paid to interactions e.g. venlafaxine–amlodipine
	IMAOs	Dependent on adherence to dietary restrictions and medications used	Dependent on adherence to dietary restrictions and medications used
	Trazodone (SARI)	Probably not	Treatment may need to be adjusted in patients with arterial hypertension (i.e. drug dose reduction)
	Bupropion (NDRI)	Increases blood pressure in supine position	Particular caution should be exercised in patients lying down
	Esketamine	Yes. The effect is temporary and most commonly occurs just after drug administration	Particular care should be taken in patients with unstable blood pressure values
Antipsychotics	First generation antipsychotics	Probably yes	Carefully, especially in patients treated with diuretics
	Second generation antipsychotics	Probably yes	Should be used with caution
Mood stabilizers	Carbamazepine, valproic acid	No	Seem safe
	Lithium carbonicum	No	Be careful due to interactions with diuretics
	Lamotrigine	No	The drug is cardiologically safe
Psychostimulants		Yes	Rather not recommended in patients with cardiac burden; they should be used with extreme caution

TCAs — tricyclic antidepressants; SSRIs — selective serotonin reuptake inhibitors; SNRIs — serotonin and norepinephrine reuptake inhibitors; SARI — serotonin antagonist and reuptake inhibitor; IMAOs — monoamine oxidase inhibitor; NDRI — norepinephrine-dopamine reuptake inhibitor

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