Psychiatric aspect of most common used cardiological drugs

Krystian Cholewa, Student Research Group of Applied Psychology, Medical University of Lublin Poland https://orcid.org/0000-0002-1310-1615

Olga Wysokińska, Student Research Group of Applied Psychology, Medical University of Lublin Poland, https://orcid.org/0000-0002-9679-9958

Michał Siwek, Student Research Group of Applied Psychology, Medical University of Lublin Poland, https://orcid.org/0000-0002-0930-9333

Magdalena Kozyra, Student Research Group of Applied Psychology, Medical University of Lublin Poland https://orcid.org/0000-0002-0260-4102

Gracjan Rudziński, Student Research Group of Applied Psychology, Medical University of Lublin Poland https://orcid.org/0000-0001-8911-9144

Joanna Milanowska, Department of Applied Psychology, Medical University of Lublin Poland, https://orcid.org/0000-0001-9741-1583

Uniwersytet Medyczny w Lublinie
Aleje Racławickie 1, 20-059 Lublin, Poland

Abstract

Introduction: The count of psychiatric patients is growing. The same trend it is observed among cardiovascular diseases and metabolic like diabetes. Many people take drugs which may affect on mental state. On the one hand that drugs could have pleotropic mechanism of action which are beginning to use in treatment of psychiatry. The other hand is showed undiscovered field of impact on brain working.

Methods and Aim: Shown the psychiatric aspect, like side effects and unusual use, of the most used cardiological drugs. To do this, research of articles was done with the help of data bases such as PubMed and Google Scholar.

Results: The most used cardiological drugs are beta blockers, calcium canal blockers, ACE inhibitors, ARBs, nitrates, cilostazol, amiodarone and clonidine In this article it was shown current known about those drugs like mechanism of action and a report of psychiatric clinical trials. Beta-blockers are the most commonly used group of cardiological drugs as the one that significantly affects mental health. Their therapeutic importance has been noted in diseases such as: PTSD or stage fright. It was also long believed that they could make depression worse, but the latest research strongly contradicts this. A positive effect in the treatment of depression can also be obtained by usage of inhibitors of the RAA. Calcium channel blockers are another group of cardiac drugs that are important in the regulation of mood in bipolar disorder. To sum up, a large proportion of cardiac drugs can influence the flow of psychiatric diseases, and the use of them may be clinically desirable in patients with both - cardiac and psychiatric problems.

Key words: cardiological drugs, mental disorders, side effects, mechanism of action

Epidemiology of cardiovascular disease

Cardiovascular disease (CVD) remains the leading cause of mortality and morbidity. There was over 17 million CVD-related deaths in 2016 which is 31% of all deaths worldwide. According to a 2014 study this number is expected to increase to more than 23,6 million by 2030. [1]

WHO estimated that 75% of CVD occurs in low- and middle- income countries and 85% of all CVD deaths are due to strokes and heart attacks. [2] In USA almost 1 of every 3 deaths was caused by CVD which is 840,678 deaths in 2016.

121,5 million American adults between 2013 and 2016 had some kind of CVD.

Chronic Lower Respiratory Disease all forms of cancer take less lives than CVD each year.

According to American Heart Association in 2016 Coronary Heart Disease was foremost (43,2%) cause of deaths linked with CVD in USA, accompanied by stroke (16.9%), High Blood Pressure (9.8%), Heart Failure (9.3%), diseases of the arteries (3.0%), and other cardiovascular diseases (17.7%). In the US every 40 seconds someone has a stroke on average. [1]

In European Union Cardiovascular disease is most deadly, it takes 1.8 million lives each constituted year and is responsible for 40% of all deaths in men and 49% of the deaths in woman. [3] which is main cause of death in woman in all except for two countries. [4]

  Ischemic heart disease is the most common cause of death from CVD in the EU followed by stroke. [3] European Cardiovascular Disease Statistics 2017 claims that CVD mortality is now falling in most European countries.

All of this is resulting in an increasing need for cardiovascular drugs. Data obtained from Clinical website have reported that the most prescribed drugs in the US based on systems were cardiovascular [5].

Atorvastatin, used to lower the cholesterol , was the top dispensed medication in England in 2018 with approximately 41.8 million items supplied. Among leading chemical drugs

dispensed in England eight of twenty are using in cardiology listing in order: Atorvastatin, Amlodipine, Ramipril, Simvastatin, Bisoprolol Fumarate, Aspirin, Furosemide, Bendroflumethiazide. [6]

Analyzing the types of drugs taken by citizens of Poland Polish Central Statistical Office have seen that 28,1 % medications was taken for CVD. Cardiovascular drugs was preceded only by a headache drugs (36,8%). [7]

In 2016 European Health network reported that DALYs due to CVD are showing a downward trend in most European countries over the last decade. Albeit CVD is still responsible for loss of more than 26 million DALYs in the EU (19%). Generally DALYs lost due to CVD is lower in Northern, Southern and Western Europe than in Central and Eastern Europe. [8]

CVD is estimated to cost economy of EU approximately €210 billion per year, around 53% is due to health care costs, 26% losses of productivity and 21% to the informal care of people with CVD. This contributes to 8% the total health care expenditure across the EU [9] In the US 14% of total health care expenses were accounted for CVD and strokes in 2014-2015 and it is expected that total direct medical costs of CVD will increase to 749$ in 2035.

For the plenty of cardiovascular diseases the most frequently administered drugs are: beta-blockers (Beta-Adrenergic Blocking Agents), Calcium Channel Blockers (CCBs), ACE Inhibitors (Angiotensin-Converting Enzyme Inhibitors), ARBs (Angiotensin II Receptor Blockers), vasodilators – especially Nitrates, Alfa-Adrenergic Blocking Agents such as Clonidine, antiarrhythmic agents especially Amiodarone, antiplatelet drugs for example Cilostazol.

Beta blockers

Beta-blockers are in use for more than fifty years and it would not be inappropriate to say they are essential in the treatment of cardiovascular diseases. Undoubtedly the discovery of this group of drugs was a great breakthrough and the one who did it was given the Nobel Prize in 1988. At the beginning they were used in hypertension therapy. Nowadays due to better knowledge of the pathophysiology of the chronic heart failure beta-blockers are also administered in this indication. Long term observations has shown positive effects of this drugs on mortality of the patients with heart failure as well as acute myocardial infarction.[10] Relating to treatment of high blood pressure beta blockers are most appropriate choose in young and middle-age group therapy, because the most common reason of hypertension in these patients is high sympathetic nerve activity.[11] On the other hand the latest researches have put in doubt using beta-blockers as first-line therapy without compelling causes. [10] The mechanism of action of these drugs is binding to beta-adrenoreceptors so norepinephrine and epinephrine could not stimulates them. As result the influence of the sympathetic system on the organism is decreased. There are three generation of beta-blockers. The first one include non-selective drugs – they block both beta-1 and beta-2 adrenoreceptors. Substances from the second generation are more cardio selective, which means they more specific for beta-1 receptors current in cardiac muscle. Finally the third group comprise drugs with characteristic vasodilator actions thanks to blocking of alpha-1-adrenoreceptors.

Beta blockers are diverse group of substances, which include beta-blockers with Intrinsic Sympathomimetic Activity (ICA) and beta-blockers with Membrane Stabilizing Activity (MSA). ICA is defined as ability to partial stimulating of beta-adrenoreceptors despite blocking them at the same time. This trait makes these drugs being both agonists and antagonists of beta-adrenoreceptors with the ascendancy of the first function. Substances with

MSA block myocyte sodium channels, which may increase toxicity of this kind of drugs by prolonging QRS duration and deteriorate cardiac conduction when used in higher then therapeutic doses. [12] Major effects of beta-blockers action from both of aforementioned groups are: reduction of cardiac output, hence reduction of arterial blood pressure; decrease heart rate as well as oxygen demand of the cardiac muscle and more effective oxygen supply; decrease contractility(negative intropy), relaxation rate (negative lusitropy), conduction velocity (negative dromotropy). In conjunction with all of mentioned above properties the main indications for beta-blockers administration are: hypertension, cardiac failure, angina pectoris, myocardial infarction and arrhythmia such as atrial fibrillation.

A preclinical study of double-blind propranolol showed that the usage of propranolol in post-traumatic stress disorder patients contributed to better and faster cognitive processes compared to the placebo group. Therefore, the study showed the possible usage of propranolol in stress diseases [13]. This possible application may be associated with a decrease in the recognition of objects and their location in an experiment conducted on mice [14].

Calcium Channel Blockers – CCBs
The another widely common cardiovascular drugs are calcium channel blockers. The latest researches has shown there is no evidence of prevalence of beta-blockers or CCBs in mortality and myocardial infarction or stroke among patients treated for stable angina. [15]

The mechanism of action of these drugs is blocking L-type (long-acting) voltage-gated calcium channels located on the smooth muscle wall of blood vessels, cardiac myocytes as well as on cardiac nodal tissue. L-type channels regulate the inflow of calcium ions into muscle cells, which leads to myocyte contraction. Thus CCBs dilate blood vessels, in particular arterioles. The hypotension influence on patients' cardiovascular system is induced by decrease peripheral vascular resistance with relatively minor impact on venous capacity and cardiac output. Among CCBs could be distinguished two categories in view of mechanism of action. The first one is more numerous and contains dihydrophyridine derivatives which are characterised by inconsiderable direct influence on cardiac muscle taken in therapeutic dose, nonetheless may trigger of reflex tachycardia. The major indications to use them are: hypertension, angina pectoris as well as Prinzmetal angina. The other group comprise verapamil and diltiazem - non-dihydropyridines medicines which impose significant effect on cardiac muscle through decrease heart rate and cardiac output. Due to reduction of conduction in atrioventricular (AV) node and elongation of refractory period of AV node, these two drugs form the fourth class of antiarrhythmic drugs. Werapamil may be indicated in angina pectoris treatment as well as in supraventricular arrhythmias, atrial fibrillation and rarely in ventricular arrhythmias, hypertrophic cardiomyopathy and hypertension.

Drugs from the group of calcium channel antagonists have been precisely studied in numerous studies on their usage in mental diseases such as bipolar disease (together with sleep and memory disorders, which are also components of this disease) and in self-injurious behaviors.

In bipolar disorder, drug therapy with calcium channel antagonists has been from long time attempted. It was caused by a calcium disfunction in the course of the disease. Numerous studies indicate that these drugs are not very significant in the treatment of bipolar disorder. A special problem occurs with older drugs from this group of cardiological drugs (e.g.

verapamil), which have limited flow through the blood-brain barrier, which may weakly penetrate the brain and not cause the intended blocking effect of calcium channels associated with bipolar disorder [16]. Newer drugs from this group no longer have such problems with crossing the blood-brain barrier. However, they act better on calcium channels located in the heart and blood vessels, and thus their effects can be mainly observed in cardiological diseases, and those related to mental health are side effects of drugs rather than their primary use [17]. Therefore, it is suggested to look for solutions that increase the blood-brain barrier permeability for calcium channel antagonists.

Nifedipine has been tested in animal models for use in the treatment of self-mutilation. Moreover, the mechanism, although not known, it is probably not associated with the calming effect of nifedipine and probably by its effect on the biological processes of the animal's body [18].

ACE-Inhibitors

Another worth mentioned group of medicines used in hypertension, cardiac failure and myocardial infarction treatment are Angiotensin-Converting Enzyme Inhibitors. These drugs indispose conversion angiotensin I to angiotensin II (ATII) by blocking the crucial enzyme. As result all of specific effects of angiotensin II activity are reduced. ATII stimulates AT1 receptors which are placed In smooth muscle tissue, therefore the direct effect of ATII is constriction of arterial blood vessels. The other outcomes of ATII activity in organism inhibited by ACEI are: stimulation adrenal cortex to exudation of aldosterone as well as higher reversible absorption of natrium ion from proximal; convoluted tube; increase of release of antidiuretic hormone (ADH) from pituitary gland and norepinephrine from sympathetic nerves; stimulation of growth factor in arteries and myocardium. Catalysis of decomposition reaction of endogenous vasodilation peptide – bradykinin is another worth mentioned function of ACE. It follows from the above mentioned features that ACEI medicines have positive effect on patients who suffer from cardiovascular diseases. Therefore ACEI act as vasodilators and thus decrease peripheral resistance; increase cardiac output, however do not cause consensual tachycardia; decrease preload and afterload; improve systolic and diastolic function of ventricles; result in regression of structural impairment of the cardiac muscle and blood vessels (remodeling). In addition ACEI have positive impact on reduction symptoms of congestive cardiac failure and decrease effort tolerance. Indirectly, due to decrease of concentration of bradykinin and synthesis of prostacyclin in the wall of blood vessels ACEI have vasodilators effect on blood vessels, especially on efferent arterioles.

ARBs - Angiotensin II Receptor Blockers

The general mechanism of action of ARBs is similar to aforementioned ACEI. Though ARBs block selectively AT1 receptors in diverse tissues and that is the difference. They may also substitute ACE – inhibitors in the case of side effect such aa characteristic, persevering cough. In addition researches have shown there is no difference in effectiveness, preventing risk of myocardial infarction or stroke and positive influence on cardiovascular mortality between ACEI and ARBs. [19,20]

It is said that the RAA system affects the development of depression. This happens under the influence of angiotensin II on the central nervous system. Angiotensin II acts on the AT1R receptor causing various responses to stress. Main pathway of creating stress by RAS is to stimulate AT1R by Angiotensin II to produce corticotrophin-releasing factor what then stimulate adrenocorticotropic hormone secretion and the reaction to the stress. That is why some studies were conducted to inhibit hypothalamic – pituitary – adrenal axis activation [21].

Many researches results indicate a reduction in the symptoms of depression in hypertensive patients who have been treated with angiotensin converting enzyme inhibitors (ACEI) compared to those who have been treated with beta-blockers or calcium channel inhibitors [22,23]. Similar observations were made by Norwegians who observed on 55,472 patients using ACEI a significant reduction in depression symptoms compared to those using beta-blockers [24].

However, some studies can be found, that indicate no effect of RAA inhibitors on mood, such as the one in which the lack of effects of captopril on euphoria was found [25].

The effect of RAA inhibitors on brain structure and therapeutic options in cognitive decline and Alzheimer's disease was also studied. It was found that ACEI did not affect these things, and in turn angiotensin receptor blockers (ARBs) therapy compared to ACEI resulted in a larger hippocampal volume, and a brain parenchymal fraction, and a smaller volume of white matter hyperintensive brain responsible for the development of AD. It can therefore be concluded that the use of ARBs can protect patients from developing AD compared to ACEI [26].

Nitrates

Unquestionably the most common example of nitrates is nitroglycerine. Since first usage in treatment angina pectoris in 1847 nitroglycerine has obtained wilder popularity among patients. However this substance is often used without any medical validation. It is estimated that averagely 32% of patients take this medicine for many different reasons other than angina chest pain. [27] Nitrates are specific group of medicines which imitates the action of endogenous NO inside of blood vessels. Drugs such as sodium nitroprusside release NO spontaneously. In spite of them, organic nitrates with the aforementioned one – nitroglycerine, form NO within tissues in enzymatic reaction. In myocytes of the wall of blood vessels NO activates guanylate cyclase which catalyses cGMP synthesis. In effect smooth muscle of blood vessels, especially venous vessels, dilate. In addition nitroglycerine reduce preload and afterload which results in reduction of myocardial oxygen consumption.

Nitrates have found their primary use in the treatment of angina pectoris, when they expand blood vessels through the NO molecules they contain. In 2015, a study was conducted in which the effect of compounds containing nitric acid esters in the treatment of schizophrenia was examined. The effect of such compounds as methylene blue, sodium nitroprusside and glyceryl trinitrate were tested on animal models. The last two are commonly used respectively as a medicine for sudden hypertensive crisis and for acute attacks of angina pectoris. First of all, the study showed a positive effect of sodium nitroprusside and glycerol triazotam on improving long-term memory in animal models of schizophrenia [28].

The usage of combinations of drugs such as diuretics, blockers of the RAA system and calcium channel antagonists in patients with Alzheimer's disease with concomitant hypertension caused that within three years of the first use of the combination of these drugs, no decrease in cognitive function was observed in patients. Separately used drugs, or in other combinations, caused that although the cognitive decline in patients did occur, it was much slower than in those without any treatment [29].

In terms of cognitive functions and episodic memory, it turns out that Angiotensin II receptor antagonists work well in improving them. In addition to their use in the treatment of hypertension, they can also help in these common diseases of older patients [30].

Cilostazol

Cilostazol is an phosphodiesterase type 3 (PDE3) inhibitor and leads to increase concentration of cAMP in platelets and smooth muscle tissue of blood vessels which in turn blocks platelets aggregation and dilate blood vessels.

Cilostazol - a phosphodiesterase type 3 (PDE3) inhibitor has been tested for antidepressant activity in an animal model. It has been discovered that it may have an effect on reducing in depression. Moreover, it was also found that cilostazol therapy resulted in the formation of many new cells that underwent differentiation into neurons in the hippocampus and ipsilateral striatum [31].

In turn, cilostazol and aripiprazole therapy on mice, that experienced chronic mild stress, resulted in a greater reduction in depression (including despair and anhedonia) than using the above-mentioned drugs alone. Moreover, the use of this therapy resulted in a reduction of atrophic changes in the striatum, dentate gyrus and hippocampus. There was also greater proliferation of nerve cells in the striatum, compared to the use of aripiprazole or cilostazol alone. The above study suggests that aripiprazole may increase the antidepressant effect of cilostazol [32].

Amiodarone

The most common medicine from the third class of antiarrhythmic drugs is amiodarone. It inhibits kalium channels and in effect blocks outflow of kalium ions from the cardiac cells which leads to elongation of the third phase of action potential. In addition amiodarone may also block natrium and calcium channels and beta-adrenergic receptors. This medicine is often administrated in cases of supraventricular as well as ventricular arrhythmia. Compering to plenty of other antiarrhythmic drugs this one has relatively minor inotropic activity and minimal risk of ventricular proarrhythmia. On the other hand amiodarone should be carefully prescribed due to high frequency of side effects. [33]

Most of the cardiological drugs described above have additional, positive usage in psychiatric conditions. However, amiodarone is an exception. The last case report from 2015 just indicates amiodarone as this drug, responsible for the onset of depression. The 71-year-old woman described has been receiving cardiological treatment for a long time. A new drug that she received 5 weeks before going to the hospital in a state of severe depression (symptoms included a lack of positive reactions, a lack of desire to live, a lack of desire to get out of the bed and constantly looking into empty space and refusing to eat) was amiodarone. She has been taking other medicines over the past few years. A week after starting to take a new medicine, her first symptoms appeared - a decrease in appetite, nausea, dizziness, sleep

disturbance. Within 4 weeks they only deepened. After stopping of use of an amiodarone, there was a sudden improvement in well-being and the symptoms of depression began to pass off. [32]. Interestingly, only cases of depression are described as a side effect of amiodarone only in people over 65 years of age [33,34,35].

Clonidine

Clonidine belongs to imidazoline antihypertensive drugs. This medicine stimulates alfa-2-adrenergic and imidazoline receptors in the central nervous system which leads to decrease the influence of vasomotor center In medulla oblongata on the sympathetic system. That is why clonidine is used in hypertension therapy. What is worth mentioning the stimulation of alfa-2-adrenergic receptors I central nervous system impose an calming effect.

There are strong links between the occurrence of mental and cardiovascular disorders, the relationship between them is bidirectional. Cardiovascular diseases such as hypertension and ischemic heart disease can increase the risk of mental disorders, so also the coexistence of depressive disorders, anxiety and even personality type have an impact on the development and course of coronary heart disease and hypertension.

Discussion:

Equally significant is the impact of drugs used in the treatment of diseases of one of the systems on the condition of the other, examples of both negative and positive effects of cardiological drugs on the mental state of patients are described.

The group of drugs most important in this aspect are beta blockers. They have, been recognized for long time as the drug of choice in situations requiring relief of anxiety, e.g. in public speaking [37] The importance of beta-blockers in the treatment of disorders related to traumatic memories has recently been known. Agents abel to overcome the blood-brain barrier, such as propranolol, given after injury reduce the degree of subsequent reaction of patients to trauma-related stimuli. Centrally acting beta blockers block the consolidation of long-term memory in the hippocampal CA1 region. Despite this, the agents was not found to affect declarative memory impairment. [38] For a long time, there have been suspicions linking beta-blockers with the risk of developing depression, and lipophilic beta-blockers have been associated with an increased risk compared to non-lipophilic ones. [39] In a recent published study on the subject from 2002, which included 15 studies with a total group of over 35,000 patients, Ko and colleagues proved that there is no significant effect of using β-blockers on the development of depression, and there is no relationship between the lipophilic profile and non-lipophilic agent and the risk of symptoms during therapy. [40]

In 2017, however, a study appeared in which Rebecka Ahl et al. have proved the effectiveness of β-blockers in the prevention of post-traumatic depression, to which up to half of patients who are injured are exposed [41] These conclusions were drawn after analyzing depressive symptoms in 596 patients who were injured in the period from four years to one year before the beginning of the test. 68 of them started treatment with β-blockers in the early post-traumatic period.

Until recently, the effect of reserpine on the risk of developing depressive disorders in patients treated for hypertension was controversial [42]. In a multi-center, cross-sectional study conducted in 2019, Zhu et al. after examining 787 pairs of patients receiving and not receiving

reserpine, they showed that the average depression score studied using the Chinese Zung Depression Scale was 40.4 for reserpine users and 40.6 for people not using reserpine (p = 0.7). Most subjects had a score of <53 (87.6% for reserpine users and 88.2%, respectively, for those who did not receive reserpine). Therefore, no significant differences were found in the incidence of mild, moderate or severe depression in reserpine users and non-reserpine users. [43]

Another group of cardiological drugs that have an effect on the mental state of patients are calcium channel blocker (CCB). A number of studies include verapamil, belonging to the CCB group compared with lithium, clonidine, placebo and benzodiazepines in the treatment of bipolar disorder. These studies led to the conclusion that CCBs have lower efficacy than lithium, however, they may be a therapeutic option in patients who do not use standard therapy with mood stabilizers, patients who want to avoid uncontrolled weight gain, and pregnant patients. Patients whose lithium was effective respond to verapamil therapies. [44]

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