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Review

Effects of psychopharmacological treatment with antidepressants on the vascular system

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ABSTRACT

Psychopharmacological treatment with antidepressants is an essential part of guideline-based treatment strategies in affective disorders, such as major depressive disorder, persistent depressive disorder, and bipolar disorder. Furthermore, antidepressants are frequently prescribed in patients with physical disorders, such as cardiovascular diseases, and comorbid depression. The type of association between physical diseases, particularly chronic diseases, and depression is bidirectional, meaning that affective disorders enhance the risk for the development of cardiovascular and metabolic disorders, and that cardiovascular/metabolic disorders enhance the risk for the development of depressive disorders. Therefore, knowledge of vascular side effects of psychopharmacological treatment is important for clinicians. This clinical orientated review article covers direct and indirect effects of commonly prescribed antidepressant drugs on the vascular system.

1. Introduction

Researchers are consistently reporting that patients with severe mental disorders (SMI) i.e., schizophrenia and other psychotic disorders, bipolar disorder, and moderate-to-severe depression have a significant higher morbidity and premature mortality compared to the general population [1–13]. Numerous studies showed that they die, on average, fifteen to twenty years earlier than people without SMI [3–12,14–19]. The mortality rate is more than two times higher than in the general population [12,14,20]. Furthermore, recent studies and meta-analyses found that the mortality gap between patients with mental disorders and the general population is widening in the last years [18,21–24].

The link between mental disorders and excess mortality is complex. About 60% of the premature mortality among patients with SMI are due to physical illness, especially cardiovascular disease, which includes coronary heart disease, atherosclerosis, hypertension and stroke [25–27]. Other leading causes of premature deaths among these patients are respiratory and infectious diseases, diabetes, hypertension, suicide, accidents, non-suicidal substance-induced deaths, mostly from alcohol or other drugs, and cancer [7,8,18,28,29]. Patients with SMI have a more than two-fold increased risk of cardiovascular death relative to persons without SMI [8,17].

Most patients with mental disorders have high rates of adverse health behaviors, including tobacco smoking, harmful levels of alcohol consumption, lack of exercise, excessive salt intake, and poor diet [30–32]. The WHO and the American Heart Association recommend that depression itself should be considered as an independent major cardiovascular risk factor similar to diabetes, hypertension, hyperlipidemia, and smoking [33–35]. Lack of emotional support/social networks and poverty can also increase the cardiovascular risk, even after adjusting for severity of coronary disease [12,22,25,36]. There are many other factors that may contribute to the early and frequent development of cardiovascular disease in this population, including genetic vulnerability [37], insufficient physical health care [38,39], and last but not least direct and indirect medication side effects [5,8,12,17,23,40]. As an example, many antipsychotics which are given as augmentation in antidepressive treatment, and to a more restricted degree antidepressants can exert orexigenic effects and can increase weight, nd promote dyslipidemia, lead to higher rates of diabetes and therefore indirect higher cardiovascular risk [26,41]. There are also direct associations between psychopharmacological treatment and the vascular system, such as increase or decrease of blood pressure, endothelial alterations, risk of thrombosis, and bleedings [42–49].

Therefore, it is highly recommended that health care practitioners are familiar with potential cardiovascular side effects of

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psychopharmacological treatments. Furthermore, monitoring and modifying cardiovascular risk factors is also recommended in patients with severe mental illness.

2. Methods

The purpose of this clinical orientated review article was to examine the link between antidepressant treatment and the vascular system.

We searched Pubmed (2000 – February 2017) for relevant data on the association between vascular system and direct and indirect effects of psychopharmacological treatments. We combined the MeSH terms of antidepressants, neuroleptics, antipsychotics, as well as substance names, with the different MeSH terms of increase or decrease of blood pressure, endothelial alterations, risk of thrombosis, bleedings, body-weight, blood glucose levels, or alterations in lipid profile. Reference lists of reviews and meta-analysis were also searched for additional relevant studies.

3. General aspects

Numerous studies report an association between depression and an increased risk of coronary artery disease, myocardial infarction, congestive heart failure, and isolated systolic hypertension [33,48,50–56]. There is strong evidence that there are pathophysiological mechanisms, particularly endothelial dysfunction, elevated systemic arterial pressure and blood viscosity, altered platelet aggregation, and hyperactivation of the thrombosis cascade, which coexist with hypothalamic-pituitary-adrenocortical axis dysfunction [57]. However, controversy exists as to whether antidepressants increase or decrease the risk [58]. This is highly relevant, taken into account; that antidepressants are one of the most commonly prescribed types of drugs worldwide with increasing numbers [59]. i.e., 23% of patients in UK primary care were prescribed an antidepressant on at least one occasion [60]. In the United States antidepressants are the most frequently used drug by persons aged 18–44 years [61]. It is therefore important to know the effects of antidepressants on the vascular system. The choice of treatment should be considered based on their purported mechanism of action and their related side effects.

3.1. Direct vascular side effects of antidepressants

One of the principal potential risks of antidepressants is their effect on slowing of intraventricular conduction, manifested by prolonged PR, QRS and QTc intervals on the standard ECG [62–77], and on orthostatic hypotension [78–86]. The cardiovascular toxicity of tricyclic antidepressants (e.g. imipramine, desipramine, and amitriptyline) is well established. Tricyclics inhibit cardiovascular Na +, Ca2 + and K + channels often leading to life-threatening arrhythmia [87–90]. New generation antidepressants, such as selective serotonin reuptake inhibitors SSRIs, may be also associated with an increased risk of arrhythmias, prolonged QTc interval, and orthostatic hypotension [58,62,91,92], even if they are only mild pronounced [93]. Another risk factor is the increased risk of bleedings and therefore intracranial hemorrhages or intracerebral hemorrhages because of the inhibiting effects on the serotonin transporter by antidepressants [46,94–97]. The risk of intracerebral hemorrhages is even higher when antidepressants were combined with NSAIDs compared to antidepressant use without NSAIDs and there were no differences between antidepressant drug classes [98,99].

3.2. Indirect vascular side effects of antidepressants

Furthermore, effects on body-weight may indirectly influence the vascular system, with tricyclics and mirtazapine being associated with the greatest weight gain, due to their pharmacodynamic properties [41,100]. This might predispose individuals to type 2 diabetes. A nested case-control analysis in a cohort of 165.958 patients with depression showed in a 15-year follow-up, that people who had used antidepressants for 2 years or more experienced almost a doubling of later diabetes risk compared with non-users for both tricyclic antidepressants and selective serotonin reuptake inhibitors [101]. Analysis of three cohorts of US adults confirmed a moderately elevated risk of type 2 diabetes mellitus in antidepressant users compared with non-users [102]. However, the risk of diabetes associated with the use of antidepressants is discussed controversially, with a few antidepressants linked to worsening glucose control, particularly with higher doses and longer duration, others linked with improved control, and yet more with mixed result [103–105]. Longitudinal data of a recent cohort study show that use of antidepressants is not associated with altered glucose metabolism, suggesting that the association between antidepressant use and diabetes reported by previous studies may not be causal [106,107].

3.3. Possible beneficial effects on the cardiovascular system

On the other hand, antidepressants can also have beneficial effects on the cardiovascular system, e.g. on heart rate and ECG values [108–110]. Platelet motility may decrease because of reduced intraplatelet serotonin concentrations [94]. Antidepressants, especially SSRI inhibit platelet aggregation, possibly leading to a reduction in cardiovascular mortality and morbidity [110,111].

Both beneficial and adverse cardiovascular events can be established following the chronic use of various antidepressants. Therefore, the cardiovascular effect of each antidepressant has to be carefully considered.

3.3.1. Selective serotonin reuptake inhibitors (SSRIs)

SSRI (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline) are the most commonly used antidepressants because of their acceptable safety profile and wider margins of nontoxic levels compared with tricyclic antidepressants. Cardiovascular adverse events are usually mild, but an increased risk of arrhythmias, prolonged QTc interval, and orthostatic hypotension can occur in higher than recommended dosage ranges [58,62,91–93]. Arrhythmia occurs in estimated 4% of cardiovascular patients, therefore ECG monitoring is recommended in SSRI treated patients [138]. Most cases of SSRI-induced QTc interval prolongation and subsequent arrhythmia were seen in patients > 60 years of age, low potassium, polypharmacy, or taking higher doses of citalopram and escitalopram [69,91,139].

Because of the risk for QTc prolongation, the US Food and Drug Administration (FDA) and also the European Medicines Agency issued a safety warning for citalopram in 2011 with a revised maximum dose of 40 mg/day [115,116]. Coupland et al. reported 2016 in a large population based cohort study that citalopram even at high doses (40 mg/day and over) was not associated with an increased risk of myocardial infarction, stroke or transient ischemic attack in a general population cohort of people with depression aged 20 to 64. In this study, risk of arrhythmia was not significantly increased in patients taking citalopram and es-citalopram [128]. Qirjazi et al. found that compared to paroxetine and sertraline, initiation of citalopram, but not escitalopram was associated with a small but statistically significant higher 90-day risk of a hospital encounter with ventricular arrhythmia [114]. A recent study observed no significant relationship between dosage of escitalopram and QTc-length even when recognized modulating factors of the QT-interval were controlled for [127].

The use of fluvoxamine and sertraline was also associated with QTc prolongation, although effect sizes were smaller than with citalopram and escitalopram [63]. Nevertheless, the prospective Rotterdam Study with 12,589 participants with a total of 26,620 ECGs observed no SSRI class effect on QTc prolongation [69]. The authors concluded, that for other SSRIs than citalopram there is, at most, moderate QTc prolongation, which is considered as minimally clinically relevant. Lam et al. summarized that the effects of SSRIs in therapeutic doses on QTc

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