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Cardiologic side effects of psychotropic drugs

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Abstract

Psychotropic drugs can produce cardiovascular side effects associated with a degree of cardiotoxicity. The coexistence of a heart disease complicates the management of mental illness, can contribute to a reduced quality of life and a worse illness course. The co-occurrence of psychiatric disorders in cardiac patients might affect the clinical outcome and morbidity. Moreover, the complex underlying mechanism that links these two conditions remains unclear. This paper discusses the known cardiovascular complications of psychotropic drugs and analyzes the important implications of antidepressive treatment in patients with previous cardiac history.

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1 Introduction

The World Health Organization has defined an adverse drug reaction as "a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function". Edwards provided a more recent definition: "an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product".[1] In general, adverse drug reactions are conditions that might depend on a sufficiently augmented administration (75%) or types of immunological reactions (25%).[2]

An extensive body of researches have reported cardiovascular mortality in patients suffering from psychiatric illness.[3] Some types of antidepressants and antipsychotic drugs have various cardiovascular side effects that can lead to cardiovascular complications, especially cardiac arrhythmias, which in some cases have resulted in death of people with no previous cardiac history. Furthermore, the fact that psychotropic drugs have various cardiovascular effects may also negatively affect clinical outcome of cardiac patients. Based on these arguments, it has been developed a novel line of antidepressants which produce fewer cardiovascular side effects.[3] Furthermore, a meta-analysis conducted by Mazza and coworkers suggests that patients with acute coronary syndromes show lower re-hospitalization rates when they receive treatment with selective serotonin reuptake inhibitors (SSRIs).[4] The SSRIs represent a promising, effective and tolerable treatment that could improve quality of life for patients with acute coronary syndromes and their families.

For managing depression attributed to adverse effects of medications, determining whether or not the agent in question is actually necessary and whether alternative approaches for treatment are available is important. In most, the initial step in managing depression thought to be related to adverse drug effects is withdrawal of the agent held to be the main cause.[3]

No drug can be completely safe and the estimation of the probability that a drug caused an adverse clinical event is usually entrusted to clinical judgment. The occurrence of adverse drug reaction is a price that a patient has to pay in order to obtain therapeutic advantages benefits. In this way

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the physician have to be very scrupulous in the prescription management, and it is necessary to pay attention to undesirable reaction ensuring that patients receive therapeutic benefits. The potential risk of unwanted and unexpected drug reactions can be so significant that caution should be exercised when patients receiving medications. The judgment of the physician is continuously needed, health professionals need to be aware of the evidence pertaining to differences in side effects, clinical characteristics of the patient should be evaluated withdrawing all unsuitable medications and attention should be paid to the knowledge of possible undesirable reaction in order to practice preventive strategies might help to reduce the risk of adverse drug reactions.

2 Cardiovascular disease: mortality and comorbidity

Cardiovascular disease indicates a wide class of disorders that involve the heart and, sometimes, the blood vessels. Cardiovascular disease includes conditions such as aneurysm, angina, atherosclerosis, cerebrovascular disease, congenital heart defects, coronary artery disease, heart attack, myocarditis, peripheral vascular disease and stroke. Risk factors for developing cardiovascular disease include alcohol intake, diet, dyslipidemia, hypertension, hyperglycemia, obesity, physical activity, psychosocial factors and smoking habits. Other non-modifiable risk factors are age, biological sex, genetic background and previously accumulated risks.[5] Most countries have to face high and increasing rates of cardiovascular disease, which represents a major cause of death and disability.[6] The prevalence of depression is between 8% and 12% in the world[7,8] and, by the year 2020, it is projected to reach the second place of the biggest disease burden following cardiovascular disease.[8,9] On the other hand, 20%–40% of cardiac patients were identified as being even more seriously affected by depression.[10,11] For patients who suffer from depression the risk of developing a myocardial infarction are quite common.[8,12] In 2009, according to the American Heart Association the socio-economic burden of healthcare resources for cardiovascular disease would amounts to $475.3 billion.

It has been reported a link between people affected by mental illness and increased levels of mortality. In case of people with schizophrenia, it is estimated that they are more likely to die with an increased mortality rate equal to an average loss of 25 years form the expected lifespan.[13–15] On the other hand, in bipolar patients established coronary heart disease signifies a higher risk for subsequent coronary heart disease mortality, in particular 1.9 times greater for men and 2.6 times greater for women in comparison with subjects without a comorbid cardiovascular disorder.[14,16] The key to face this question could be the presence of modifiable risk factors that contribute to cardiovascular disease, and a decline in cardiovascular burden across patients could be attributed to risk-factor modification. There is increasing awareness that people affected by mental illness tend to develop a cardiovascular disorder, thus the physician should carefully evaluate clinical conditions and provide a refine treatment to match the intensity of treatment to patients' risk for future adverse cardiovascular events.[14,16]

There is a growing body of evidence that people affected by psychiatric disorders are more likely to suffer from cardiovascular disease.[5,17–20] Among all the potential comorbidities, depression represents the psychiatric condition that is associated with cardiovascular disease at higher prevalence, because depression might have an etiological as well as a prognostic role.[5] The coexistence of a heart disease complicates the management of depression and can contribute to a reduced quality of life and a worse illness course. In depressed patients the identification of a comorbid disorder should trigger careful clinical assessment.

Moreover, the complex underlying mechanism that links these two conditions remains unclear. Although the association between depression and cardiovascular disease has been recognized, it is difficult to establish whether the illness is a real medical comorbidity, a harmful side effect of medications, or a combination of both, and the precise nature of the relationship among cardiovascular disease, mortality and mental illness is not clearly delineated. It is possible that an accumulation of risk factors may have a powerful impact on those patients with serious and persistent psychiatric disorders and, potentially, leading to the development of secondary diagnoses.[21] However, it has also been hypothesized that the co-occurrence of cardiovascular disease, mortality and mental illness might be worsened by the presence of other factors such as genetic predisposition, psychotropic drugs and healthcare system.[5] In clinical psychiatric practice, physicians should evaluate patients suffering from depression for the coexistence of heart disease. Like this, the correct diagnosis of a comorbid cardiovascular disease can prevent to expose a patient to the progression of the disorder using appropriate pharmacologic and psychological interventions in order to ensure the improvement of prognosis.

3 Sex differences in psychotropic drug-induced side effects

Few studies have examined how sex might affect side effects of psychotropic medications. Being female has been

identified as a risk factor in the development of side effects due to psychotropic drugs.[2] There are some studies suggesting that women show a higher prevalence (50%–75%) in the occurrence of adverse drug reaction which can jeopardize health.[2,22]

Body mass index, drug metabolism and body fluid constituents were shown to have an involvement in the development of side effects.[2,23] Different circumstances were studied prospectively for factors which might influence the side effects of psychotropic drugs such as gastric emptying rates and menstrual cycle,[24–26] hepatic drug metabolism,[27–32] and renal drug clearance.[33–36]

Beyond adverse drug reaction, patients experience with a low quality of life also contribute to patient adherence, thus tolerability profile was also examined. At present, most published studies have focused mainly on demonstrating both short- and long-term efficacy, whereas fewer studies have explored effectiveness in terms of other important outcomes such as compliance, quality of life and overall better subjective tolerability.[2,37–39] In a study by Barbui *et al.*[40] the authors investigated sex as the only variable accounting for all subjective tolerability of anti-psychotics and showed that men tend to have a less negative subjective tolerability than women. However, some researchers have also considered whether it could be a dose-related question, because they estimated a higher level of concentration in blood plasma among women, evaluating this condition as a potential indicator of the explanation of subjective tolerability.[2,41–43]

Time and continued research have revealed that cardiologic side effects of psychotropic drugs can presumably show a sex-dependence action.[44–49] Prolongation of the QT interval is a common and serious adverse effect, associated with high risk for ventricular arrhythmias, syncope and sudden death.[50] Women have a greater risk for a QT prolongation when compared with men.[51–53] Therefore, the female sex is a parameter that should not be overlooked. The occurrence of drug-induced QT prolongation presumably depends on the specific regulation of channel expression by sex hormones.[5] Whereas it has been reported an inverse expression pattern of predominance of drug-related sudden cardiac death, men are more likely to have a higher susceptibility to this adverse reaction.[2,54] Afterwards, the presence of cardiovascular disease is a clinical variable that negatively influence the prescription of psychotropic drugs. On the other hand, the prescription of psychotropic drugs requires a complex therapeutic approach, because it should be considered the potential risk for cardiovascular events taking into account the risk for having a severe mental illness untreated.[2]

4 Cardiac and circulatory adverse effects of antidepressants

Monoamine oxidase inhibitors (MAOIs**)** were the first type of antidepressant developed. They are effective, but because of their side effects and drug interaction, MAOIs have historically been reserved as a last line of treatment, used only if other classes of antidepressants, such as SSRIs and tricyclic antidepressants (TCAs), are not helpful.[55] Patients treated with MAOIs occasionally appeared to experience "spontaneous" hypertensive episode without eating foods rich in tyramine.[56] Sometimes this cardiovascular event was transient, but seldom the hypertensive episodes could lead to hypertensive crisis.[55,57,58]

TCAs are one of the oldest classes of antidepressant, most commonly prescribed as the standard treatment for depression before the introduction of SSRIs that cause fewer side effects. At present, TCAs are not considered first-line medications for psychiatric disorders. The question of using them is controversial because of the unresolved issue of possible sudden unexplained cardiac fatalities. Nevertheless, TCAs are still prescribed to people for whom SSRIs are ineffective or inappropriate.[3] TCAs have significantly high rate of serious cardiovascular side effects and toxicity in patients without previous cardiovascular disease.[3,59–62] The major side effects include heart rate increase, blood pressure abnormalities and slight prolongation of the intraventricular conduction time. Serious conduction alterations, including right and left bundle-branch block or partial or complete atrioventricular block, occur at high or toxic plasma levels and are reflected in electrocardiogram (ECG) as prolonged PR, QRS and QT intervals and T-wave flattening or inversion.[63–66] TCAs may slow electrical conduction inducing a prolongation of the electrical impulse[67,68] and therefore they have a higher risk of causing arrhythmias, especially in individuals with conduction disease.[67,68] It has been documented in literature that TCAs may also behave as class 1A antiarrhythmics reducing intraventricular conduction velocity and increasing collateral blood circulation.[69–71] This antiarrhythmic effect at therapeutic plasma level is responsible for extremely high plasma levels that cause arrhythmias and heart block as well as the high rate of mortality after TCAs' overdose. This case must be considered when patients are already taking type 1 antiarrhythmics, because the dosage may need to be changed. Moreover, patients following antiarrhythmic drug therapy would require a close ECG monitoring. The therapeutic role of TCAs for children needs to be seriously

weighed against lethality. There have been a number of case reports of sudden unexplained death occurring in children stable on TCAs.[72–74] Any suspected overdose should be treated as an emergency, it is a significant cause of fatal drug poisoning due to TCAs' cardiovascular toxicity.[3]

TCAs tend to cause a combination of troubling adverse effects that are more likely to affect cardiovascular parameters. Moreover, TCAs increase a potential cardiac risk and should be taken with great scrupulousness in individuals affected by cardiovascular disease. If physicians do prescribe TCAs, it is important to be fully informed of potential cardiovascular complications.[3]

5 Cardiac and circulatory adverse effects of new antidepressants

SSRIs have largely replaced TCAs as the drug of choice in the treatment of mental illness, mainly because of their favorable side effect profile. The antidepressants of this class are therapeutically similar, but important pharmacokinetic differences exist among these drugs in terms of metabolism and hepatic clearance. Despite a favorable clinical profile SSRIs still produce side effect with less frequency and intensity than other antidepressants. The major difference between SSRIs and TCAs is a significant anticholinergic effect as well as low cardiotoxicity.[3] In fact, SSRIs are now widely prescribed in preference to TCAs because of their lower side effect profile and reduced toxicity after overdose. To date, only two SSRIs overdose death have been reported in literature, one involved the ingestion of fluoxetine[75] and the other implied the use of citalopram.[76,77] Side-effects profile for the SSRIs shows greater similarities to each other than differences (Table 1). SSRIs induce significantly less anti-cholinergic, anti-histaminergic and cardiotoxic side effects than TCAs. The most common cardiac side effects are a mild bradycardia, orthostatic hypotension and abnormalities in the electrical activity of the heart such as QRS lengthening or prolonged QT interval.[77,78] SSRIs may also exert a direct vasoconstrictive effect leading to a myocardial ischemia known as Prinzmetal's angina.[77,79] Moreover, accounting for the vasoconstrictive effects of SSRIs, extreme caution should be exercised in the use of SSRIs treatment in patients who are at increased risk for hemorrhagic and vasoconstrictive diseases.

Table 1. Licensed indications, mechanism of action and comparative tolerability and side effects of SSRIs.[77]

	FDA approved year	FDA therapeutic indications	Mechanism of action	Cardiovascular profile
Citalopram	1998	Major depressive disorder	A highly selective and potent serotonin reuptake inhibitor	Uncommon (≥ 1/1000 to <1/100): bradycardia, orthostatic hypotension, tachycardia; Rare (≥ 1/10000 to <1/1000): atrial fibrillation, bundle branch block, cardiac arrest, hypertension, myocardial infarction, phlebitis, transient ischemic attacks, stroke
Escitalopram	2002	Major depressive disorder; generalized anxiety disorder	More selective serotonin reuptake inhibitor than citalopram	Uncommon (≥ 1/1000 to <1/100): tachycardia; Rare (≥ 1/10000 to <1/1000): bradicardia, orthostatic hypotension
Fluoxetine	1987	Bulimia nervosa; major depressive disorder; obsessive compulsive disorder; panic disorder; premestrual dysphoric disorder	Potent and selective inhibitor of serotonin reuptake with antidepressant, antiobsessional and antibulimic effects	Uncommon (≥ 1/1000 to <1/100): junctional rhytms, mild bradycardia, sinus tachycardia, ventricular trigeminy; Rare (≥ 1/10000 to <1/1000): ECG abnormalities, thrombophlebitis
Fluvoxamine	1993	Major depressive disorder; obsessive compulsive disorder	A selective serotonin reuptake inhibitor with affinity for the serotonin transporter over the norepinephrine transporter	Uncommon (≥ 1/1000 to <1/100): ST segment changes, atrioventricular and supraventricular blockade; Rare (≥ 1/10000 to <1/1000): coronary heart disease, embolus, pericarditis, phlebitis, pulmonaty infarction, stroke
Paroxetine	1992	Generalized anxiety disorder; major depressive disorder; obsessive compulsive disorder; panic disorder; post-traumatic stress disorder; premestrual dysphoric disorder; social anxiety disorder	The most potent inhibitor of the reuptake of serotonin	Uncommon (≥ 1/1000 to <1/100): hypertension, syncope, tachycardia; Rare (≥ 1/10000 to <1/1000): angina pectoris, bradycardia, congestive heart failure, hypotension, myocardial infarction, thrombophlebitis, vascular headache

Sertraline	1991	Major depressive disorder; obsessive compulsive disorder; panic disorder; post-traumatic stress disorder; premestrual dysphoric disorder; social phobia	Selective inhibitor of the reuptake of serotonin and a weak activity in inhibiting the reuptake of dopamine	Uncommon (≥ 1/1000 to <1/100): hypertension, postural hypoternsion, tachycardia; Rare (≥ 1/10000 to <1/1000): angina pectoris, bradycardia, myocardial infarction, stroke

SSRIs: Selective serotonin reuptake inhibitors; FDA: Food and Drug Administration; ECG: Electrocardiogram.

SSRIs interfere with serotonin accumulation in platelets and SSRI treatment (but not TCAs' treatment) normalizes elevated indices of platelet activation and aggregation in patients with depression and ischemic heart disease. The antiplatlet effect of SSRIs is neither associated with antidepressant effect nor does resolution of depression immediately normalize increased platelet activity.[80-82] The antiplatelet effect of SSRIs may reduce risk of future ischemic cardiovascular events. SSRI-treated patients have a significantly low rate of myocardial infarction than the non-SSRI-treated patients.[82] This lower myocardial infarction rate may not simply be due to reduced psychiatric symptoms; for instance, patients whose anxiety is reduced by anxiolitic medications do not have a reduced rate of myocardial infarction.[80-82]

In conclusion, the use of TCAs and structurally related antidepressants should be limited in cardiac patients because of the myriad of side effects of these medications on the cardiovascular system, including orthostatic hypotension, tachycardia, reduction in heart rate variability and slowing of intraventricular conduction. These antidepressants should never be prescribed for patients with bundle branch block. As might be expected, examination of prescription has revealed an increased risk of myocardial infarction with administration of TCAs in comparison to SSRIs and atypical antidepressants. MAOIs are generally free of effects on cardiac conduction, but, like TCAs, may cause postural hypotension. Because of their fewer potential adverse effects on the cardiovascular system and the lack of lethality from an overdose, pharmacotherapeutic treatments with SSRIs may offer significant advantages in depressed or anxious patients affected by cardiovascular disease.[77,82]

6 Cardiac and circulatory adverse effects of antipsychotics

Antipsychotic medications are used to treat psychotic symptoms and other mental and emotional conditions. The first class of these drugs was introduced in the 1950s and was known as typical antipsychotics. The early antipsychotic medications often have unpleasant side effects, thus researchers continue their search for better drugs and developed the second generation called atypical antipsychotics. Important antipsychotic-induced cardiovascular effects include cardiac arrhythmia and cardiac arrest, whereas orthostatic hypotension is more common in elderly patients.[3,83] The combination of antipsychotic-induced orthostatic changes and age-related loss of postural reflexes leads to an increased risk of falls in older adults. Therefore, orthostatic hypotension episodes are particularly dangerous at night, when the older patients awakens to urinate and gets out of bed quickly.[3, 83]

A further adverse health outcome in the profile of antipsychotic drugs is tachycardia that seems to occur primarily as result of the anticholinergic properties of antipsychotics.[84,85] Epidemiological studies provide evidence that antipsychotics increase the risk of sudden cardiac death.[3,84,85] Specifically, certain antipsychotics can induce prolongation of the QT interval, that can potentate a lethal ventricular arrhythmia.[3,84,85] Among the antipsychotic drugs, ziprasidone is associated with the greatest QT prolongation.[3,86]

In addition to their effect on cardiac conduction, antipsychotic medications do not have extremely negative effects in case of overdose: clozapine induces tachycardia,[3] olanzapine and quetiapine do not determine sudden death,[3] and risperidone shows no significant symptoms in the 66% of the cases, but could provoke sudden death.[3,87,88]

However, patients with pre-existing cardiovascular disease should be carefully evaluated before they begin any antipsychotic treatment. In particular, extreme caution is required in prescribing drugs with anticholinergic properties or those that produce orthostatic hypotension.[3,83]

7 Behavioral cardiology: the impact of the psychological on cardiovascular well-being

Psychological stress can have serious negative effects on well-being and plays a large role in several diseases such as diabetes, cancer, immunological disorders,[89,90] and cardiovascular diseases are another areas where stress could have a negative effect. In this context, expressive and overwhelmingly significant body of evidences have been provided by the INTERHEART study that has measured whether psychosocial stress can be considered as a risk factor associated with myocardial infarction. In this analysis, psychosocial stress has placed in the third place among cardiovascular risk factor and one-third of the total risk is attributable to this modifiable factor.[90,91] It has been shown

there is a distinct connection between depression and increased risk of cardiovascular disease. Depression may be considered a prognostic factor in patients affected by cardiovascular disorders and could be useful in risk stratification, with the fact that the presence of depression is threefold higher among cardiovascular patient.[90,92–97] Milani and Lavie conducted a study to evaluate the effect of cardiac rehabilitation on depression.[98] All patients who received cardiac rehabilitation experienced a sensible reduction of depressive symptoms severity (from 17% to 6%) and mortality.[98] In 2009, Milani and Lavie found that, in the context of a structured cardiac rehabilitation, the exercise training improves levels of psychosocial stress and has a strong influence on the incidence of heart disease and overall mortality, that is 60% lower compared with control subjects.[99] In a more recent study, Milani *et al.*[100] performed a research to examine the influence on exercise training in patients suffered from coronary heart disease. They identified positive changes in depression status with a symptom reduction by 40% associated with a decrease in mortality by 59% in comparison with patients not undergoing rehabilitation.

Although the importance of psychological stress in the development of cardiovascular disease has been mainly valued in presence of depressive symptoms, other behavioral factors including anxiety and hostility have provided clear and convincing evidence that contribute significantly to the expression of cardiovascular disorders.[90,93,101–103] Among patients with heart disease, anxiety syndromes appear to be associated with a higher risk of cardiovascular disorders.[90,104–109] Anxiety and cardiovascular disease frequently coexist, and there is evidence to suggest that anxiety may be an independent risk factor for cardiac morbidity and mortality, in addition to leading to poorer outcomes.[90] Cardiac rehabilitation and exercise training significantly improve anxiety's levels up to half their rate.[106] In a recent meta-analytic review, Herring *et al.*[110] individuated that patients who exercise reported fewer anxiety symptoms, lower levels of stress and improved their prognosis. On the other hand, hostility may be an indirect cause of the high rate of cardiovascular problems, because leads to a fivefold increased risk of developing cardiovascular disease.[90,111–115] Studies have reported that cardiac patients with high levels of hostility subsequently showed significant improvement in cardiac efficiency after exercise training.[90,115,116]

To date, a causal relationship and the pathophysiological mechanisms underlying psychological stress and cardiovascular health have not yet well delineated, whereby psychosocial conditions personality factors and character traits contribute to a higher frequency of adverse health behavior, such as poor diet, physical activity, height weight and smoking, and direct pathophysiological mechanisms, such as imbalance in the autonomic nervous system, neuroendocrine activation, endothelial dysfunction, vasoconstriction and stimulation of platelet function.[90] Therefore, cardiac rehabilitation program brings advantages to cardiovascular health involving mechanisms not entirely identified, but likely multifactorial.[90]

Although SSRIs appear to be the safest antidepressant medication for use in cardiac patients, there is data suggesting that exercise training is associated with reduced morbidity and mortality.[90] The effectiveness of behavioral intervention for cardiac patients needs to be evaluated in clinical setting and, maybe, an exercise training program should be recommended for cardiac patients with depression and high psychological distress prior to going on a treatment with psychotropic drugs.

8 Conclusions

Antidepressants are one of the most-prescribed class of drugs in the United States.[117] MAOIs, TCAs and antipsychotics could be both effective for the treatment of mental illness, but their cardiovascular side effects and sometimes toxicity in overdose show many disadvantages. On the basis of a cardiovascular profile with fewer adverse reactions, the SSRIs are generally well-tolerated agents and should therefore be the preferred choice of the treatment of most patients with comorbid cardiovascular disease.

An important topic is related to the diagnosis of psychiatric disorders in the face of significant comorbidity from medical conditions such as cardiovascular disease. Depression occurs in most cases as a component, complication or consequence of comorbid medical disease. Depression itself could represent a risk factor for cardiovascular events as well as stroke, coronary heart disease and early death.[12,77,117–121] Therefore, it has also been addressed the issue of determining whether a condition is related to the nature of the underlying illness or to the nature of the treatment given.

"The right drug for the right patient"[122,123] is the assertion to whom health professionals should be inspired in their learning motives, their comprehensive ability and their clinical activity. Clinicians should be vigilant in conducting a rigorous assessment for the development of adverse effects and providing monitoring recommendations before beginning psychopharmacological treatment. Physicians have to take into account their knowledge about cardiovascular profile of psychotropic drugs when screening a patient for physical or mental problems. In case of medical

comorbidity, clinician should provide a plan for alternative treatment and monitoring of the patient's well being and should determine the most effective approach developing indications for drug prescription on the basis of predictive risk profile and potential adverse drug effects.[3,77] Moreover, clinicians have also to pay a particular attention to psychotropic drugs combination when patients are affected by cardiovascular disease. Drugs interaction can lead to cardiovascular complications, thus the physician has to focus attention on assessing and monitoring cardiac status in patients treated with psychotropic drugs.[77]

Additional studies to explore the cellular and molecular basis of the cardiac profile of psychotropic drugs in the etiology or clinical manifestations as well as others are warranted. These may lead to new forms of prevention as well as treatment.[3, 77]

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