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Review

Cardiovascular risk and major depression linked to antidepressive pharmacotherapy at adolescent age

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ABSTRACT

It is well known that depressive disorder is associated with an increased risk of cardiovascular diseases; however, the pathophysiological mechanisms illuminating the relationship between depression and cardiovascular risk still remain unclear. Notably, adolescence represents a critical and vulnerable age period for potential depression-induced cardiovascular complications due to developmental and brain maturational changes; thus, adolescent major depression could represent an important risk factor for cardiovascular adverse outcomes that manifest in adulthood. This aspect seems crucial in terms of prevention. Therefore, the aim of this review is to characterize the main regulatory mechanisms involved in the onset and progression of cardiovascular illnesses associated with depressive disorder at adolescent age, from a pathophysiological and clinical point of view. This review is focused on the description of the unique role of allostasis-linked systems such as autonomic nervous system in depressive disorder and inflammatory regulation/dysregulation whose interaction is mediated through the extensively discussed "*cholinergic anti-inflammatory pathway*". Further insight into the mechanisms underlying both vagal regulation and the cholinergic anti-inflammatory pathway may lead to effective new treatments for major depression, especially at the adolescent age.

KEYWORDS: depressive disorder, cardiovascular risk, adolescent age, autonomic nervous system, inflammation, pharmacotherapy.

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1. Introduction

Major depressive disorder (MDD) is a serious social and health problem not only in adults but also in children and adolescents with increasing prevalence. Previous studies have reported a prevalence rate of up to 3% in children and 8% in adolescents [1], and the lifetime prevalence rate for depression in youths aged 15 to 18 years has been estimated to be 14 to 15% [2]. Recently, depressive disorder has been a common mental health problem in adolescents worldwide, with an estimated 1 year prevalence of 4-5% during mid to late adolescence [3, 4], and a recent review indicated that the worldwide prevalence of depressive disorder in children and adolescents is 2.6% [5]. Moreover, depressive disorder in adolescents is a major risk factor for suicide, serious social and educational impairments, or psychoactive substance addiction [6-8].

Furthermore, depressive disorder has been suggested as a risk factor for development of cardiovascular disorders which are a major cause of morbidity and mortality worldwide. In this aspect, cardiovascular illnesses seem to have a bidirectional relationship

with depression: depressive disorder seems to increase cardiovascular risk, and *vice versa* – cardiovascular disorders are associated with increased rates of depression [9]. Although an increased rate of cardiovascular diseases is a common finding in adult patients with depression [10], there are only a few studies in children and adolescents with depressive disorder in spite of the importance of adolescence as a critical and vulnerable age period for potential depression-induced cardiovascular risk due to developmental and brain maturational changes [11, 12]. This makes early adolescence an interesting period for studying the interaction between depression and indicators of cardiovascular risk such as hypertension. Moreover, adolescent major depression could represent an important risk factor for cardiovascular adverse outcomes that manifest in adulthood; thus, this aspect is crucial in terms of prevention. However, the exact pathomechanisms leading to depression-linked cardiovascular morbidity at the adolescent age-period are still unclear and extensively discussed. In this context, antidepressant treatment may also contribute to increased cardiovascular risk in depression, but this observation is still uncertain. Further, there is a lack of high-quality studies focusing on the treatment of depression in children and adolescents [13-15] and the question of whether the increased cardiovascular risk associated with depression is the consequence of the depressive disorder itself or the antidepressant medication is still under extensive debate.

This review focuses on the role of potential pathophysiological regulatory mechanisms illuminating the pathway between depressive disorder and cardiovascular complications with respect to pharmacotherapy during adolescent age-period. It seems that this issue is crucial for the prevention and early diagnosis of clinically asymptomatic signs of cardiovascular risk as well as for monitoring of pharmacotherapy effect in adolescents.

2. Pathomechanisms leading to depression-linked cardiovascular risk

2.1. Cardiac autonomic regulation

The autonomic nervous system (ANS) represents an important physiological allostatic mechanism regulating the main organ functions in the same way as "main leader keeps the orchestra in symphony". Both the divisions of the autonomic nervous system (sympathetic and parasympathetic nervous system) play a crucial role in stress response. In other words, the shift of sympathovagal balance characterized by parasympathetic withdrawal associated with sympathetic overactivity to stress and *vice versa,* increased parasympathetic activity ("vagal rebound") and sympathetic underactivity after stress (recovery phase) represents a complex physiological "stress" response indicating the adaptive functioning of the autonomic nervous system. Thus, autonomic imbalance - sympathetic overactivity associated with parasympathetic underactivity - could indicate one of the potential mechanisms leading to cardiovascular complications.

The resting heart rate (HR) itself, determined by complex sympathetic and parasympathetic interplay, represents a strong predictor of cardiovascular mortality [16, 17]. For example, HRs of 74 bpm or less were associated with half of the 2-year cardiovascular event rates compared to those with HRs greater than 74 bpm [18]. Although our studies revealed significantly higher HR (tachycardia) in adolescent major depression, the exact mechanisms by which HR may affect cardiovascular illnesses remain speculative [19, 20]. It is assumed that increased HR intensifies the pulsatile motion of the heart affecting the coronary arteries´ geometry leading to structural and functional changes of the endothelial cells. The abnormalities may be driven by increased sympathetic activity [20, 21].

Recently, the evaluation of cardiovascular autonomic regulation has been considered as an important index of sophisticated central-peripheral interaction. Benarroch (1993) described the central autonomic network (CAN) as an integrated component of an internal regulation system through which the brain controls visceromotor, neuroendocrine, and behavioural responses that are critical for goal-directed behaviour and adaptability. Structural components of the central autonomic network are found at the level of the forebrain (anterior cingulate; insular and ventromedial prefrontal cortices; central nucleus of the amygdala; paraventricular and related nuclei of the hypothalamus), midbrain (periaqueductal grey matter), and hindbrain (parabrachial nucleus, nucleus of the solitary tract, nucleus ambiguus, ventrolateral and ventromedial medulla, medullary tegmental field) [22]. The primary output of the

CAN is mediated through the sympathetic and parasympathetic neurons innervating the heart *via* the stellate ganglia and the vagus nerve [23]. In this context, the interplay of sympathetic and vagal inputs to the sino-atrial node of the heart produces the complex "beat-to-beat" heart rate variability (HRV), i.e. HR oscillations around its mean value. Therefore, the CAN output is linked to the HRV as an index of central-peripheral neural feedback, and central nervous system-autonomic nervous system integration indicating a healthy organism [23-25]. Specifically, internalizing psychopathology such as depression is characterized by an imbalance between positive and negative feedback loops in the neurocardiac integrative system. Thayer and Lane (2009) emphasize the inhibitory influence of the prefrontal cortex on lower sympathoexcitatory regions; thus, the prefrontal hypoactivity associated with depression can contribute to autonomic imbalance resulting in vagal withdrawal and sympathetic overactivity [25]. Furthermore, the short-term HRV is considered as an index of parasympathetic nervous functioning whose reduction reflects poor physiological, emotional, cognitive, and behavioural regulation associated with numerous risk factors for adverse health outcomes including cardiovascular complications [25-27].

It is questionable whether these discrete abnormalities in complex neurocardiac and cognitive/emotional network are already present at adolescent age. Several studies have referred to impaired complex neurocardiac regulation already in adolescents with major depression [19, 28, 29].

2.2. Inflammation

Recently, scientific research has been focused on inflammatory variables as potential markers of the causes/consequences of depressive disorder from a complex point of view (*cytokine hypothesis of depression*). Cytokines and interleukins are immunomodulatory signalling molecules that have been increasingly implicated in the development of major depression. The "*inflammatory response system activation theory of depression*" described by Maes *et al.* [30-32] is based on the fact that depression could be a result of stress-related increased production of pro-inflammatory cytokines leading to increased oxidative and nitrosative brain damage and to indoleamine 2,3 dioxygenase (IDO) induction, with production of tryptophan catabolites along the IDO pathway and consequent reduced availability of tryptophan and serotonin [33-35]. Thus, the cell-mediated immune activation linked to depression could result in the serotonergic disturbances characterizing depressive disorder [20].

These pro-inflammatory cytokines are under tonic inhibitory control *via* the vagus nerve (*anti-inflammatory cholinergic pathway*): peripheral inflammatory mediators generate sensory input to the brain *via* afferent vagus nerve fibres and circumventricular organs. Then, the peripheral signal is processed by the nucleus tractus solitarii (NTS). On the efferent side, the NTS provides input to the nucleus ambiguus and nc. dorsalis n. vagi and, consequently, the acetylcholine, as a neurotransmitter of vagus nerve endings, interacts with nicotinic α7 subunit receptor on macrophages in the reticuloendothelial system resulting in deactivation of macrophages and inhibition of cytokine release [36-39]. From this perspective, the vagal modulation is inversely associated with inflammatory processes: if vagal activity is lower, the inhibitory influence on inflammation will be disturbed resulting in a pro-inflammatory state characterized by increased cytokine levels. Thus, according to the neurovisceral model, the prefrontal cortex and amygdala are important central nervous system structures linked to the regulation of the inflammatory system through the inhibition mediated by the vagus nerve and this inhibitory function may have important implications for health and disease [25, 39].

Nowadays, depression is recognized as a major risk factor for coronary heart disease with a substantially increased risk of developing new cardiovascular diseases or worsening the already existing pathological conditions [40]. Potential causes of this adverse effect include endocrine changes potentiating hyperglycaemia and elevated blood pressure, stimulation of platelets and formation of blood clots, greater risk of unhealthy lifestyle involving smoking, diminished physical activity, fatty diet, and lower medication compliance [40]. All these risk factors, together with a systemic pro-inflammatory state, are associated with endothelial dysfunction, which reflects the total risk burden predisposing depressive individuals to atherosclerotic cardiovascular disease [41].

It seems that the investigation of the interaction of pro-inflammatory markers, allostatic load, cardiovascular regulation/dysregulation, and depression is very important because of the potentially increased risk of cardiovascular complications due to the depression-evoked pro-inflammatory state already in young people. With regard to this aspect, several studies concluded that depression, autonomic dysfunction, and inflammation are additive and independent risk factors for long-term cardiovascular mortality [9, 42]. Further insight into the mechanisms underlying the cholinergic anti-inflammatory pathway may lead to effective new treatments for major depression, especially at the adolescent age.

Importantly, the effect of depressive disorder-linked complex therapeutic approach including pharmacotherapy during adolescent age is still unclear. This important issue is discussed in the following section.

3. Cardiovascular risk and depression-linked therapy at adolescent age

MDD in children and adolescents is often unrecognized and untreated due to the variation in its symptoms from that of adults [43]. In this context, about 1 in 5 young people will experience an episode of major depression characterized by a high recurrence rate, persistent psychosocial impairment and increased risk of suicide [44]. Thus, the issue regarding antidepressant treatment in children and adolescents seems crucial. Therapeutic procedure depends on the severity of depressive symptoms. Treatment of mild and moderate depressive symptoms includes non-pharmacological approaches such as psychotherapy, whereas in moderate to severe symptomatology a combination of psychotherapy and antidepressant medications is needed [43].

3.1. Pharmacotherapy

It is well-known that antidepressant treatment recommended for adolescent patients suffering from moderate to severe depression is focused on the re-establishment of normal balance of the brain monoamine neurotransmission whose discrepancies are associated with depression [45]. Importantly, antidepressant treatment in adolescents is associated with several specifics such as maturation changes, with the serotoninergic system maturing faster than other monoaminergic systems [46]. Because of the antidepressant treatment-linked potential increase in behavioural activation, moodiness and suicidality [47], the application of antidepressant medications in adolescent age would require giving proper knowledge to the patients and their family about the treatment, careful assessment and precise monitoring [48].

3.2. Antidepressants of choice for adolescent major depressive disorder treatment

Nowadays, clinical guidelines for the management of moderate to severe major depressive disorder in adolescents recommend the prescription of selective serotonin reuptake inhibitors (SSRIs), with *fluoxetine* as the medication of first choice due to its efficacy as substantiated by randomized-controlled studies [49-51]. *Fluoxetine* is approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) for the treatment of depressive patients aged 8 years and older, with an initial dose of 5-10 mg/day depending on the patient age and weight. This dosage can be increased every 5-7 days by 5-10 mg, whereas dosage for sufficient response for most children and adolescents is 20 mg in the morning. In the case of ineffective response, the dosage might be increased to 40-60 mg/day [52].

Importantly, SSRI therapy for young people suffering from depression is characterized by high placebo response rates [1, 44]. For example, twelve small double-blinded controlled studies published in the mid-1990s demonstrated no effect of tricyclic antidepressants (TCAs) or *fluoxetine* compared to placebo in childhood and adolescent depression (according to [44]). Contrarily, two recent meta-analyses revealed a small therapeutic effect for all antidepressants, with *fluoxetine* as the only medication with a significantly higher effect than placebo for depression treatment [53, 54]. Furthermore, a Cochrane review concluded that *fluoxetine* was the only agent with consistent evidence of its effectiveness in decreasing depressive symptoms [55].

Of note, antidepressant medication should not be the only form of adolescent depression treatment, but it should also be combined with psychotherapy. In this context, the Treatment of Adolescent

Depression Study (TADS) compared *fluoxetine*, cognitive behavioural therapy (CBT), combination treatment (*fluoxetine* + CBT) and placebo in 439 depressive adolescents and concluded that the combination of *fluoxetine* with CBT offered the most favorable tradeoff between benefit and risk for adolescent major depressive disorder [15]. However, the study by authors Goodyer *et al.* with 208 adolescents suffering from moderate to severe major depressive disorder not responding to a brief initial intervention concluded that SSRIs (in particular, *fluoxetine*) combined with CBT did not provide any additional benefit compared to SSRI alone at the end of 12 and 28 week-lasting treatment [56].

Importantly, heart rate and blood pressure should be measured, as well as routine blood tests should be performed at specific time periods: before SSRI treatment initiation, in the first month of the treatment, and subsequently every 6 months. Moreover, in cases with pre-existing cardiac problems or positive cardiac family history, ECG monitoring is necessary during SSRI treatment [52].

Although SSRI toxicity is low, in rare cases serotonin syndrome occurs with potentially life-threatening arrhythmia, seizures, and coma. In such cases, SSRI has to be immediately discontinued and intensive care may be needed [52].

In the case of non-response to *fluoxetine* monotherapy at a sufficient dose over 4-6 weeks, the second-choice in depression treatment management is to switch to another SSRI (i.e. *escitalopram*, *citalopram*, *sertraline*) or an antidepressant with a different profile such as selective noradrenalin reuptake inhibitor (SNRI) *venlafaxine*. In controlled studies the positive effect of *venlafaxine* in depressive adolescents was observed [57, 58]; however, it is not a first choice antidepressant due to its lack of approval and potentially increased suicidal thoughts [52]. In addition, the Treatment of Resistance Depression in Adolescents (TORDIA) study with 334 adolescents treated with a second SSRI (e.g. *paroxetine, citalopram*) or *venlafaxine* with or without CBT revealed that combination treatment was superior to antidepressant monotherapy [14]. TCAs and α_2-adrenoreceptor antagonists may be used as alternatives, but they are not medications of first or second choice because of their potential severe side effects. Tricyclic antidepressants (i.e. *imipramine*, *desipramine*, *amitryptiline*), introduced for depression treatment in the late 1950s, are associated with cardiovascular adverse effects (orthostatic hypotension, reduced HRV, QT interval prolongation, greater risk of hypertension) as well as over-dose mortality leading to their greatly limited use in clinical practice [52]. With respect to adolescent age, the studies revealed limited efficacy of TCAs in comparison to placebo [59], and their use is considerably restricted due to the association with cardiac adverse events. The α_2-adrenoreceptor antagonists (*mirtazapine and mianserin*) are recommended in anxious and agitated depressive patients with sleeping problems [60, 61].

Lastly, augmenting agents such as *lithium, bupropion* (noradrenaline and dopamine reuptake inhibitor) or *quetiapine* (second-generation antipsychotic medication), despite their limited evidence, are used in the pharmacotherapy of adolescent treatment-resistant depression [62]. The precise antidepressant treatment duration in adolescent patients has not been established. The general consensus is that once symptom remission is achieved, treatment should be continued for 6-12 months before initiating a slow taper off the medication [63]. General guidelines for adolescent depression treatment are summarized in Table 1.

3.3. Antidepressant treatment-linked impact on heart rate variability

As noted above, cardiac regulation is extremely sensitive to autonomic regulatory inputs. From this perspective, oscillations of heart rate around its mean value - HRV is considered as a noninvasive index of cardiac autonomic regulation. It is important to note that antidepressant treatment impacts HRV although the precise effect is not yet known.

In adults, the TCAs decrease HRV indicating reduced cardiovagal modulation associated with higher cardiovascular risk due to their anticholinergic effects [64, 65]. However, the effect of SSRI on HRV is still unresolved. Kemp *et al.* concluded that SSRI treatment has a benign effect on HRV [64]. Udupa *et al.* found reductions in time and frequency HRV parameters indicating abnormal cardiac autonomic regulation associated with higher cardiovascular risk when using TCAs, whereas SSRIs were associated with no HRV changes [66]. Another study revealed that HRV measures

Table 1. Guidelines for adolescent major depressive disorder treatment (according to [43]).

Major depressive disorder severity	Recommendations for treatment
Mild to moderate	Cognitive behavioural therapy Interpersonal therapy Family interventions
Moderate to severe	Pharmacotherapy (SSRIs - *fluoxetine*, *escitalopram*, *citalopram*, *sertraline*; SNRIs - *venlafaxine*, *duloxetine*) Combination therapy (pharmacotherapy + psychotherapy) Antidepressant augmentation (lithium or antipsychotic) Antidepressant combination Repetitive transcranial magnetic stimulation Electroconvulsive therapy

SSRIs – selective serotonin reuptake inhibitors, SNRIs – selective noradrenaline reuptake inhibitors.

decreased during *venlafaxine* or *mirtazapine* treatment, while the heart rate (HR) increased [67]. In a large cohort study, Kemp *et al.* reported that use of almost all antidepressants (i.e. TCAs, SNRIs, SSRIs) suppressed HRV with TCAs having the greatest effect, followed by SNRIs and SSRIs with the least effect [68]. Additionally, a longitudinal study revealed that all antidepressants (TCAs, SSRIs, SNRIs) cause a decrease in cardiac vagal control and that antidepressant discontinuation was associated with cardiac autonomic function recovery suggesting that the unfavorable effects of antidepressants are partially reversible [69].

Finally, a recent study suggested that SSRI antidepressants may reduce the risk of depression-linked major adverse cardiovascular events [70]. In this context, SSRI treatment is associated with dampening of platelet aggregability potentially leading to reduced cardiovascular risk [71]. On the other hand, SSRI medication in adult patients with major depressive disorder is shown to be associated with elevated levels of inflammatory markers such as C-reactive protein [72].

In adolescents, studies regarding antidepressant treatment impact on HRV are rare. The most recent exploratory study found that antidepressant medication (*fluoxetine*, *sertraline*, *citalopram*, *mirtazapine*) is associated with reduced HR but, without significant changes in HRV parameters [73]. This finding contrasts with the lower HRV measures and increased HR observed in adults taking antidepressants indicating that SSRIs in adolescent patients may be associated with HR and HRV changes contrary to that of adults.

Notably, Park *et al.* revealed significantly higher low frequency (LF) measures of HRV in adolescent depressive patients at baseline with its significant reduction after treatment suggesting that depression treatment using SSRIs may reduce sympathetic activity and enhance parasympathetic activity [74]. However, it is important to note that it is unclear whether this change is due to the medication itself or mood improvement.

Previous study that included adolescent females with anxiety disorders and/or major depressive disorder concluded that psychiatric patients show reduced HRV compared to healthy subjects which can be partially explained by the antidepressant treatment (SSRI) effect. Moreover, these findings do not support the idea that decreased HRV in depressive patients can be explained by the hyperarousal of co-morbid anxiety [28]. It seems that the question related to depressive disorder-antidepressant treatment-cardiovascular risk is crucial and needs further research, especially in adolescent age.

3.4. Other treatments

A better understanding of the unique role of vagus nerve in both inflammation and cardiovascular regulation may contribute to the development of successful therapeutic approaches in MDD. While electrical vagus nerve stimulation is a basic approach in the experimental studies of the cholinergic anti-

inflammatory pathway, the alternative, non-invasive and non-pharmacological methods potentially leading to increased vagal activity as a protective mechanism against cardiovascular complications, such as psychotherapy and cognitive-behavioural therapy, should be explored in the treatment of adolescent depressive disorder [75]. For example, our study revealed the cardiovagal regulation improvement after a non-pharmacological complex approach (dietary regimen, physical regular activity, autogenic training) in obese children and adolescents [76], and we also reported the positive effect of cognitive behavioural therapy on neurocardiac dysregulation indexed by HRV [77]. It is important to note that depression-induced modifiable lifestyle changes, *e.g.* physical inactivity, could also be of interest in therapy; therefore, targeting reduced vagal activity in depressed children and adolescents (*i.e.* by increasing physical activity) may add to current treatment options. In addition, the use of vagus nerve stimulation may offer a promising treatment for depressive children and adolescents not responding to pharmacotherapy or psychotherapy [27].

4. Conclusion

We hypothesize that higher cardiovascular risk already present in adolescent major depression could reflect a combination of all or some of the biological/non-biological mechanisms (prefrontal dysfunction, inflammation, autonomic and hypothalamic–pituitary–adrenal axis dysfunction, life-style modifications, etc.) and other unknown pathomechanisms [78] that are important for early diagnosis, prevention and therapeutic interventions in children and adolescents, as well as in adults. Furthermore, longitudinal studies need to address the causal pathways linking depression and cardiovascular risk in children and adolescents [27].

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

ABBREVIATIONS

ANS - autonomic nervous system
CAN - central autonomic network
CBT - cognitive behavioural therapy
EMEA - European Medicines Agency
FDA - Food and Drug Administration
HR - heart rate
HRV - heart rate variability
IDO - indoleamine 2,3 dioxygenase
LF - low frequency
MDD - major depressive disorder
n. - nervus
nc. - nucleus
NTS - nucleus tractus solitarii
SNRI - selective noradrenalin reuptake inhibitor
SSRI - selective serotonin reuptake inhibitor
TCAs - tricyclic antidepressants

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