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Antidepressant Pharmacotherapy and Structured Physical Activity in Major Depressive Disorder: Implications for Functional Capacity and Cardiometabolic Health

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Abstract

Major depressive disorder (MDD) is a multidimensional condition associated not only with affective symptoms but also with reduced physical activity, impaired functional capacity, and increased cardiometabolic risk. Beyond mood disturbance, depression is frequently accompanied by decreased cardiorespiratory fitness, altered body composition, and autonomic dysregulation. While antidepressant pharmacotherapy remains a cornerstone of treatment, structured physical activity has emerged as a clinically relevant intervention within sports and lifestyle medicine.

Evidence from recent meta-analyses and network meta-analyses demonstrates moderate antidepressant effects of aerobic and resistance-based exercise interventions. Comparative analyses suggest similar efficacy of exercise and pharmacotherapy in mild-to-moderate depression, with structured training providing additional benefits for cardiovascular performance, metabolic regulation, and functional recovery. The bidirectional relationship between depression and metabolic syndrome further underscores the importance of addressing systemic risk factors alongside psychiatric symptoms.

Antidepressant agents differ in their metabolic, autonomic, and endocrine profiles, with potential implications for weight regulation, insulin sensitivity, and exercise adherence. Overlapping biological mechanisms between pharmacotherapy and physical training include monoaminergic modulation, neuroplasticity enhancement through brain-derived neurotrophic factor pathways, and attenuation of systemic inflammation. However, direct randomized comparisons of combined pharmacotherapy and structured exercise remain limited.

An individualized treatment model integrating pharmacological stabilization with progressive physical training may optimize both psychological recovery and long-term physiological resilience in patients with major depressive disorder.

Methods

Study Design

This study was designed as a narrative review synthesizing current evidence on the interaction between antidepressant pharmacotherapy and structured physical activity in the treatment of major depressive disorder (MDD). The primary objective was to integrate findings from psychiatry, sports medicine, and metabolic research to provide a clinically relevant perspective on functional capacity and cardiometabolic outcomes.

Literature Search Strategy

A structured literature search was conducted using PubMed and relevant clinical guideline repositories. The search covered publications from January 2000 to February 2026. Emphasis was placed on contemporary evidence from the past decade, while earlier landmark studies were included when mechanistically relevant.

Search terms included combinations of the following keywords: “major depressive disorder,” “antidepressants,” “exercise,” “physical activity,” “resistance training,” “aerobic exercise,” “cardiometabolic,” “metabolic syndrome,” “insulin resistance,” “neuroplasticity,” “BDNF,” “inflammation,” and “autonomic dysfunction.”

In addition, reference lists of selected articles were manually screened to identify further relevant studies.

Eligibility Criteria and Selection Process

Priority was given to systematic reviews, meta-analyses, network meta-analyses, randomized controlled trials, large cohort studies, and contemporary clinical guidelines. Articles published in English were considered.

Given the narrative design of this review, no formal risk-of-bias assessment tool was applied. Study selection was guided by methodological rigor, clinical relevance, and consistency of findings across the literature. Discrepancies in interpretation were resolved through discussion among the authors.

Keywords

Major depressive disorder; Antidepressants; Physical activity; Exercise therapy; Cardiometabolic health; Functional capacity; Neuroplasticity; Metabolic syndrome;

Content

1. Introduction

Major depressive disorder (MDD) is one of the leading contributors to global disability and disease burden worldwide [1]. Beyond its core affective symptoms, depression is associated with psychomotor slowing, fatigue, cognitive impairment, and reduced motivation, all of which directly influence daily functioning and participation in physical activity. Functional decline in MDD often manifests not only as impaired occupational performance but also as diminished cardiorespiratory f itness, decreased muscular strength, and progressive physical deconditioning.

The relationship between depression and physical inactivity appears bidirectional. Prospective cohort studies demonstrate that low levels of physical activity increase the risk of incident depression [2], while sedentary behavior independently correlates with greater depressive symptom severity [3]. Reduced movement and impaired fitness may contribute to systemic inflammation, autonomic dysregulation, and metabolic disturbance—mechanisms increasingly recognized as central components of depressive pathophysiology [4-6]. This interaction positions depression not only as a psychiatric disorder but also as a condition with significant physiological and cardiometabolic dimensions.

Antidepressant pharmacotherapy remains the cornerstone of treatment for moderate to severe MDD and is widely recommended in international clinical guidelines [7,8]. Contemporary pharmacological strategies primarily target monoaminergic neurotransmission, with downstream effects on neuroplasticity and stress-response regulation [9]. While antidepressants effectively reduce depressive symptom severity in many patients, their physiological impact extends beyond mood regulation and may include alterations in body weight, metabolic parameters, autonomic balance, and endocrine function [10-13]. These systemic effects are particularly relevant when considering long-term functional recovery and overall physical resilience.

In parallel, structured physical activity has gained increasing recognition as an evidence-based intervention in depression treatment. Accumulating data from randomized controlled trials and meta-analyses demonstrate moderate antidepressant effects of aerobic and resistance-based exercise, with efficacy comparable to pharmacotherapy in selected populations with mild-to moderate depression [14-17]. Importantly, beyond symptom reduction, exercise interventions consistently improve cardiorespiratory fitness, muscular strength, metabolic regulation, and

overall functional capacity. These physiological adaptations may directly counteract the deconditioning and metabolic vulnerability frequently observed in individuals with MDD.

Despite growing evidence supporting both pharmacotherapy and physical training, these treatment domains are often discussed separately within psychiatric and sports medicine literature. Limited attention has been devoted to their physiological overlap, potential synergistic effects, and implications for long-term functional recovery. Therefore, the aim of this narrative review is to synthesize current evidence regarding the systemic effects of antidepressant pharmacotherapy and structured physical activity in MDD, with particular emphasis on functional capacity and cardiometabolic health. By integrating perspectives from psychiatry and exercise science, we seek to outline a clinically relevant framework for individualized and performance-oriented care.

2. Antidepressant Pharmacotherapy and Physical Function

2.1 Differential Profiles Across Antidepressant Classes

Antidepressant pharmacotherapy constitutes a central component of treatment in moderate-to severe major depressive disorder and remains strongly recommended in international clinical guidelines [7,8]. Although primarily prescribed to alleviate affective and cognitive symptoms, antidepressants exert systemic physiological effects that may influence body composition, metabolic regulation, autonomic balance, and exercise tolerance.

Selective serotonin reuptake inhibitors (SSRIs) are commonly used as first-line agents due to their overall tolerability and favorable safety profile. Nevertheless, weight gain, gastrointestinal disturbances, sexual dysfunction, and emotional blunting have been consistently reported [10,18,19]. Among these, sexual dysfunction represents a clinically significant factor influencing long-term adherence and overall quality of life [19]. While not universally present, these effects may indirectly affect motivation for physical activity and engagement in structured exercise programs.

Serotonin–norepinephrine reuptake inhibitors (SNRIs) provide additional noradrenergic modulation, which may contribute to improved energy and psychomotor activation in some patients. However, mild elevations in heart rate and blood pressure have been documented [12]. Although typically clinically manageable, these cardiovascular changes may warrant monitoring in individuals participating in high-intensity training or endurance sports.

2.2 Metabolic and Endocrine Considerations

Certain antidepressant classes, particularly mirtazapine and tricyclic antidepressants, are more frequently associated with sedation and appetite stimulation, which may contribute to clinically relevant weight gain [10-13]. Iatrogenic weight increase can, in selected patients, promote reduced exercise tolerance and decreased motivation for physical activity. In this context, obesity management strategies and lifestyle interventions should be considered when clinically indicated [20].

The relationship between depression and metabolic syndrome is bidirectional and multifactorial. Shared mechanisms include chronic low-grade inflammation, hypothalamic–pituitary–adrenal

axis dysregulation, and behavioral factors such as reduced physical activity [5,21]. Large meta-analytic data further demonstrate increased insulin resistance in individuals with depressive disorders, even prior to pharmacological treatment [6]. Therefore, cardiometabolic risk in MDD cannot be attributed solely to medication exposure.

Antidepressant agents may differentially influence metabolic parameters, including lipid profiles and glucose regulation [11]. Importantly, cardiometabolic effects vary substantially across antidepressant classes, reinforcing the need for individualized risk–benefit assessment, particularly in patients with pre-existing metabolic vulnerability. Although these effects are typically modest and agent-specific, they are clinically relevant in patients with pre-existing metabolic vulnerability or limited baseline fitness. Routine monitoring of body weight, waist circumference, lipid profile, and fasting glucose is advisable during long-term pharmacotherapy.

Endocrine modulation represents an additional layer of complexity. Evidence suggests that certain antidepressants may alter testosterone and estrogen pathways [22]. While the clinical magnitude of these hormonal changes varies and remains incompletely characterized, potential implications for energy levels, body composition, and recovery capacity warrant further investigation—particularly in physically active populations.

2.3 Activating Antidepressants and Functional Profile

In contrast to sedative or appetite-stimulating agents, bupropion demonstrates a comparatively activating pharmacological profile. Due to its dopaminergic and noradrenergic mechanisms, it is generally considered weight-neutral and has been associated in some studies with modest weight reduction [10]. Its lower incidence of sexual dysfunction compared to serotonergic agents may further support treatment adherence in selected patients [19].

From a functional perspective, the activating properties of bupropion may be advantageous in individuals experiencing pronounced fatigue, psychomotor slowing, or reduced physical drive. However, individual response variability remains substantial, and pharmacological selection should be guided by overall clinical presentation rather than presumed performance benefits alone.

2.4 Adherence and Functional Remission

Long-term treatment success in major depressive disorder depends not only on symptom reduction but also on sustained adherence and functional recovery. Adverse effects such as sexual dysfunction, weight gain, sedation, and gastrointestinal disturbances are among the most common reasons for treatment discontinuation [18,19]. Even when depressive symptoms improve, unresolved side effects may impair quality of life and reduce engagement in physical and social activities.

Increasing attention has been devoted to the concept of functional remission, defined as the restoration of occupational functioning, social participation, and physical performance capacity beyond symptomatic improvement alone.However, functional endpoints remain underrepresented in many antidepressant trials, which primarily rely on psychometric scales. In patients with comorbid medical conditions, the balance between antidepressant efficacy and systemic safety becomes particularly important, as highlighted in recent umbrella meta-analytic evidence [23].

From a sports and lifestyle medicine perspective, medication tolerability directly influences exercise consistency, training progression, and overall physical resilience. Therefore, pharmacological decision-making should incorporate not only mood symptomatology but also functional goals, metabolic profile, and patient-specific lifestyle factors.

3. Structured Physical Activity as a Core Therapeutic Strategy

3.1 Evidence from Randomized Trials and Meta-Analyses

A substantial body of evidence supports structured physical activity as an effective intervention for depressive symptoms. Meta-analyses and network meta-analyses consistently demonstrate moderate antidepressant effects of aerobic exercise, resistance training, and mixed modalities [14-17]. A recent large-scale network meta-analysis reported that walking or jogging, yoga, and strength training were associated with particularly robust reductions in depressive symptom severity, with effect sizes comparable to established first-line treatments in selected populations [15].

Comparative analyses further indicate that, in individuals with mild-to-moderate depression, exercise may demonstrate efficacy similar to antidepressant pharmacotherapy, while combined treatment approaches may yield additional benefits [16,33]. In a recent comparative study, running therapy and antidepressant treatment demonstrated comparable effects on depressive symptoms, with differential impact on physical health parameters [33]. These findings support a complementary rather than competitive model of care, in which structured physical training is integrated with pharmacological management when clinically appropriate.

Importantly, treatment effects appear proportional to prescribed intensity, with moderate-to vigorous interventions demonstrating greater symptom reduction compared to low-intensity protocols [15]. These results emphasize the importance of structured, progressive, and supervised exercise programs rather than unsystematic increases in general activity. It should be noted that exercise intensity recommendations should be individualized, particularly in patients with severe depressive episodes, cardiovascular comorbidities, or marked deconditioning, and may require interdisciplinary supervision to ensure safety and adherence.

3.2 Functional and Cardiometabolic Adaptations

Beyond symptom reduction, structured physical training produces measurable physiological adaptations that directly address the systemic consequences of major depressive disorder. Aerobic and resistance-based interventions have been shown to improve cardiorespiratory fitness, muscular strength, and overall functional capacity in individuals with depressive disorders [17,24]. These improvements are clinically relevant, as reduced physical fitness is independently associated with higher cardiometabolic risk and poorer long-term health outcomes.

Regular exercise exerts beneficial effects on insulin sensitivity, lipid metabolism, and body composition—mechanisms particularly important in the context of the established bidirectional relationship between depression and metabolic syndrome [5,6]. Improvements in glucose regulation and reductions in visceral adiposity may partially counteract both disease-related and medication associated metabolic burden. In contrast to pharmacotherapy, which may differentially influence metabolic parameters depending on the agent used [11], structured physical activity consistently demonstrates favorable effects across cardiometabolic domains.

Exercise also positively influences autonomic nervous system balance, contributing to improved heart rate variability and reduced sympathetic overactivity [25]. Given that autonomic dysregulation has been observed in depressive disorders and may be further modulated by psychotropic medications [25], physical training represents a non-pharmacological strategy capable of restoring physiological equilibrium.

From a functional standpoint, improvements in physical capacity may translate into enhanced daily performance, increased self-efficacy, and greater engagement in social and occupational roles. These adaptations extend beyond psychometric symptom scales and align closely with the concept of functional remission.

From a functional standpoint, improvements in physical capacity may translate into enhanced daily performance, increased self-efficacy, and greater engagement in social and occupational roles. These adaptations extend beyond psychometric symptom scales and align closely with the concept of functional remission.

Nevertheless, exercise interventions should be individualized and appropriately supervised, particularly in patients with significant comorbid medical conditions or reduced baseline fitness, to ensure safety and long-term adherence.

4. Mechanistic Overlap and Biological Convergence

Depression is increasingly conceptualized as a disorder involving neuroplastic, inflammatory, autonomic, and neuroendocrine dysregulation rather than solely monoaminergic deficiency. Antidepressant pharmacotherapy primarily targets serotonergic and noradrenergic pathways, yet downstream effects include enhancement of neuroplasticity, modulation of stress-response systems, and normalization of synaptic signaling [9].

Physical activity appears to influence many of the same biological pathways. Both aerobic and resistance exercise have been associated with increased expression of brain-derived neurotrophic factor (BDNF), promotion of hippocampal neurogenesis, and improved synaptic plasticity [26,27]. These adaptations may contribute not only to mood improvement but also to cognitive restoration and stress resilience, supporting the neurotrophic model of depression.

Inflammation represents another shared pathway. Elevated pro-inflammatory cytokines have been implicated in depressive symptomatology, and certain antidepressants demonstrate anti inflammatory properties [4]. Regular physical activity similarly reduces systemic inflammation and improves immune regulation, potentially reinforcing pharmacological effects through complementary mechanisms [4,26].

Dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis, reflected in altered cortisol secretion and impaired stress adaptation, is a well-established feature of major depressive disorder. Antidepressant treatment has been associated with partial normalization of HPA axis function over time, while regular physical training improves stress reactivity and neuroendocrine flexibility. Through these overlapping effects on stress-response systems, both interventions may contribute to restoration of physiological homeostasis [26,28].

Autonomic nervous system imbalance, characterized by reduced heart rate variability and increased sympathetic tone, has been observed in depressive disorders [25]. While psychotropic

medications may variably influence autonomic parameters, structured exercise consistently promotes improved autonomic regulation and cardiovascular adaptability [25]. These converging mechanisms suggest that pharmacotherapy and exercise are not mechanistically antagonistic but may operate along complementary biological pathways.

A comparative summary of the systemic effects of antidepressant pharmacotherapy and structured physical activity is presented in Table 1.

Table 1. Comparative Overview of Antidepressant Pharmacotherapy and Structured Physical Activity in Major Depressive Disorder

Domain	Antidepressant Pharmacotherapy	Structured Physical Activity
Primary Mechanism	Monoaminergic modulation (serotonin, norepinephrine, dopamine) [9]	Multisystem activation via neuromuscular and metabolic stimulation
Neuroplasticity	↑ BDNF, synaptic remodeling [9]	↑ BDNF, hippocampal neurogenesis, enhanced plasticity [26,27]
Inflammation	Partial anti-inflammatory effects [4]	Reduction of systemic inflammatory markers [4,26]
HPA Axis	Gradual normalization of stress-response systems	Improved stress reactivity and neuroendocrine flexibility [26,28]
Autonomic Regulation	Variable effects depending on agent [25]	↑ Heart rate variability, improved autonomic balance [25]
Metabolic Impact	Agent-specific; potential weight gain and metabolic alterations [10,11]	Improved insulin sensitivity, lipid profile, body composition [5,6]
Functional Capacity	Indirect improvement via symptom reduction	Direct improvement in VO_2max, strength, endurance [17,24]
Adherence Factors	May be limited by side effects [18,19]	Influenced by supervision, motivation, and program design
Role in Treatment	Core treatment in moderate-to-severe MDD [7,8]	Evidence-based adjunct or alternative in mild-to-moderate MDD [16]

Abbreviations: BDNF – brain-derived neurotrophic factor; HPA – hypothalamic–pituitary–adrenal axis. Pharmacological effects are agent-specific and may vary across antidepressant classes.

5. Integrative Model and Clinical Implications

The accumulated evidence suggests that antidepressant pharmacotherapy and structured physical activity should not be conceptualized as competing interventions but rather as complementary components of a multidimensional treatment model. Pharmacological stabilization may facilitate engagement in exercise by reducing acute symptom burden, while structured training may enhance physiological resilience, improve metabolic regulation, and support long-term functional recovery.

In clinical practice, treatment selection should consider symptom severity, baseline physical capacity, metabolic profile, comorbid medical conditions, and patient preferences. Individuals presenting with pronounced psychomotor retardation or severe depressive symptoms may initially require pharmacological intervention to enable subsequent behavioral activation. Conversely, patients with mild-to-moderate depression and preserved functional capacity may benefit substantially from early integration of supervised exercise programs, either as monotherapy or in combination with medication [16].

From a cardiometabolic perspective, integrating structured physical activity into standard psychiatric care may mitigate both disease-related and medication-associated metabolic risk. This is particularly relevant in patients with elevated body mass index, insulin resistance, or features of metabolic syndrome [5,6]. Collaboration between psychiatry, primary care, and exercise professionals may therefore represent an important step toward comprehensive lifestyle-oriented management.

Importantly, individualized programming is essential. Exercise prescriptions should be tailored in terms of intensity, modality, and progression, taking into account cardiovascular risk, baseline f itness, and personal goals. Similarly, pharmacological regimens should consider metabolic and endocrine profiles alongside psychiatric efficacy. Such an integrative and personalized framework aligns with emerging perspectives in sports psychiatry and lifestyle medicine, emphasizing restoration of functional capacity and long-term health rather than symptom reduction alone.

6. Limitations

Several limitations should be acknowledged. First, this study was conducted as a narrative review rather than a formal systematic review with predefined registration and quantitative synthesis. Although a structured literature search was performed, study selection was not guided by a standardized risk-of-bias tool. Consequently, the findings should be interpreted as an integrative synthesis of current evidence rather than a comprehensive meta-analytic evaluation.

Second, heterogeneity across exercise trials—including differences in modality, intensity, supervision, and participant characteristics—limits direct comparison between studies. Variability in antidepressant dosing strategies and treatment duration further complicates cross-study interpretation. As a result, precise conclusions regarding optimal treatment combinations or sequencing remain provisional.

Third, most clinical trials prioritize symptom reduction measured by psychometric scales, while long-term functional, cardiometabolic, and performance-related outcomes are less frequently assessed. Therefore, the integration of physiological and psychiatric endpoints remains incomplete in the current literature.

Finally, direct randomized controlled trials explicitly comparing combined pharmacotherapy and structured exercise against monotherapies are relatively limited. Although mechanistic overlap suggests potential synergy, high-quality longitudinal trials with standardized functional endpoints are needed to clarify additive or interactive effects.

7. Conclusion

Major depressive disorder is increasingly recognized as a condition extending beyond affective symptomatology, encompassing neuroplastic, inflammatory, autonomic, and metabolic dysregulation. Contemporary treatment approaches must therefore move beyond isolated symptom control toward restoration of functional capacity and long-term physiological resilience [29,30].

Antidepressant pharmacotherapy remains an essential component of care, particularly in moderate to-severe presentations, as reflected in international clinical guidelines [7,8,31]. At the same time, structured physical activity represents a biologically coherent and clinically meaningful intervention capable of improving both depressive symptoms and systemic health parameters [30]. Rather than conceptualizing these strategies as alternatives, an integrated model—combining pharmacological stabilization with progressive, individualized exercise programming—may offer the most comprehensive therapeutic framework.

Given the established association between depression, metabolic syndrome, and obesity, long-term management strategies should incorporate cardiometabolic monitoring and lifestyle-based interventions [20,32]. Such an approach may reduce both disease-related and treatment-related metabolic burden.

Future research should prioritize longitudinal trials incorporating standardized functional, cardiometabolic, and performance-related endpoints to better define optimal sequencing and combination strategies. As psychiatry increasingly interfaces with sports and lifestyle medicine, personalized interventions targeting both mental and physiological domains may redefine recovery not only as symptom remission but as restoration of adaptive capacity and sustainable health.

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Conflicts of Interest

The authors declare no conflict of interest.

Declaration on the Use of Artificial Intelligence

AI-assisted tools were used exclusively for linguistic refinement and structural editing of the manuscript. The authors take full responsibility for the scientific content, interpretation of the data, and final version of the manuscript.

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