



PSYCHOPHARMACOLOGICAL OPTIMIZATION IN DRUG-RESISTANT MOOD DISORDERS AND MUSCLE METABOLISM

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ABSTRACT

Skeletal muscle has a significant impact on drug distribution and can influence pharmacokinetics and drug resistance due to myokines that are produced during muscular activity. The activity of muscle interacts with the central nervous system (CNS), influencing metabolism and modulating drug-resistant mood disorders by affecting neuroendocrine signaling. Antidepressant medications have often proven treatment-resistant in patients with mood and anxiety disorders. Optimal clinical psychopharmacological therapy can achieve maximum efficacy with minimal side effects. Individualized therapy can produce rapid and effective antidepressant effects in patients with mood and anxiety disorders, where some medications have often proven treatment-resistant. It can be concluded that both psychopharmacological therapy and the application of strategies that include dosage optimization, the study of pharmacokinetic factors, and individualized treatment with personalized clinical practice can improve various pathologies, including those of the CNS.

KEYWORDS: *Muscle metabolism, depression, drug-resistance, mood disorder, pharmacokinetic*

INTRODUCTION

The role of muscle in drug resistance has been little discussed in the biomedical literature (1). The link between skeletal muscle, muscle mass, metabolism, and drug-resistant mood disorders, such as drug-resistant depression, is an important, recent topic (2). Skeletal muscle can influence pharmacokinetics and therefore, drug resistance (3). Muscles represent approximately 45% of human body weight and have a significant impact on drug distribution, metabolism, and clearance.

DISCUSSION

Muscle is an endocrine organ that secretes cytokines and myokines, molecules with systemic effects on various organs including the central nervous system (CNS) (4). Muscle can intervene in the local perfusion, absorption, metabolism, distribution, and elimination of ingested drugs (5). Muscle mass and blood flow are important because they can affect the effective drug concentration and pharmacokinetic resistance (6).

The myokines released by muscle during its activity include interleukin (IL)-6, IL-1, irisin (which derives from FNDC5), and cathepsin. IL-6 improves glucose and lipid metabolism, IL-1 causes inflammation, and irisin promotes neurogenesis, while cathepsin B promotes the formation of new neurons (7). Aerobic exercise increases brain-derived neurotrophic factor (BDNF), which enhances the antidepressant effect, induces neurogenesis and the production of

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serotonin and dopamine, and regulates the hypothalamic-pituitary-adrenal (HPA) axis, reducing hypercortisolaemia (4). Muscle cross-talks with the CNS, and muscle activity and metabolism modulate drug-resistant depression by acting on inflammation, neuroplasticity, and neuroendocrine signaling (8).

In patients with drug-resistant depression, the psychiatric history can be supplemented with parameters such as muscle strength and muscle metabolism (9). In clinical practice, psychopharmacological optimization can achieve maximum therapeutic efficacy with minimal side effects (10). This treatment may reduce therapeutic doses of drugs, and therapy is also individualized (11). Drugs that produce rapid and robust antidepressant effects in patients with mood and anxiety disorders have often proven resistant to treatment (12,13). At times, treatment ineffectiveness and the lack of long-term efficacy data have led to an increase in the use of unapproved off-label medications (14,15).

The goal of personalized pharmacological treatment is to tailor therapy to the biological, genetic, and clinical characteristics of each individual, as occurs in precision psychiatry. Pharmacogenomics and pharmacogenetics are involved in drug metabolism, identifying metabolizers, which are elements necessary to predict drug efficacy and toxicity. Personalized clinical treatment must take into account certain patient characteristics, such as age, weight, medical and psychiatric comorbidities, gender, patient preferences, and previous response to medications. The choice of antidepressants should be based on the CYP enzyme profile, and the dosage of antipsychotics should be personalized based on plasma levels.

While certain medications may be beneficial for some patients with mood disorders, it is important to consider the potential risks associated with the drug when considering treatment (16). Clinicians should recommend evidence-based use of the drug to ensure patient safety. The goals are to improve symptoms, reduce side effects, facilitate individual therapy, prevent relapse, and integrate treatment with psychological therapies (17). To achieve these goals, specific strategies must be implemented for each individual being treated. Each patient requires dose adjustment based on the response, tolerability, and kinetics of the drug being used (18). Flexibility in using a different drug that targets different receptors is essential, as is the use of multiple drugs with complementary mechanisms.

The most important strategies to implement must involve reducing or discontinuing unnecessary or harmful medications (19). Several factors must be considered, such as the precise diagnosis, significant symptoms and organic and psychiatric comorbidities, metabolism, such as CYP450 variants, and drug interactions (20). The patient's age, gender, and lifestyle, the use of clinical scales, regular interviews, and dosages must also be considered. In these cases, useful tools to consider are international guidelines (APA, NICE, CANMAT, WPA), personalized therapies based on "precision psychiatry", and pharmacogenetics such as CYP2D6 and CYP2C19.

The American Psychiatric Association (APA) guidelines (USA) refer to APA Practice Guidelines, which focus primarily on the diagnosis and treatment of mental disorders (21). Their key features are evidence-based. They are a systematic framework with recommendations for diagnosis, pharmacological treatment, and psychotherapeutic interventions. They also place great emphasis on personalized treatment, comorbidity, and continuity of care.

The National Institute for Health and Care Excellence (NICE) guidelines (UK) focus primarily on integrated clinical treatment (medication, psychotherapy, and social support) (22). These treatments include extremely detailed guidelines geared toward daily clinical practice, and consider not only efficacy, but also cost-effectiveness, social impact, and quality of life.

The Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines primarily address mood and anxiety disorders, which are widely used in psychiatry for the management of major depressive disorder and bipolar disorder (23).

The World Psychiatric Association (WPA) Practice Guidelines & Position Statements focus primarily on global standards of psychiatric care, adaptable to different cultural and resource contexts, promoting international harmonization of psychiatric practice and paying attention to cultural, ethical, and human rights factors (24). The guidelines are often developed in collaboration with the World Health Organization (WHO) (25).

CONCLUSIONS

In summary, psychopharmacological optimization should improve symptoms, reduce side effects, facilitate therapeutic adherence, prevent relapse, and integrate psychotherapeutic interventions. A systematic approach including dosage optimization, switching, augmentation, and therapeutic combinations, leads to the identification and discontinuation of medications and targeted prescription, personalized clinical practice, pharmacokinetic factors, and patient characteristics.

Conflict of interest

The authors declare that they have no conflict of interest.

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