psychoactives

MDPI

Review

Unlocking the Potential of Meldonium: From Performance Enhancement to Therapeutic Insights

Val Bellman

Department of Psychiatry, University of Missouri Kansas City, Kansas City, MO 64108, USA; vvzzw8@umkc.edu

Abstract: Meldonium, a promising pharmacological agent initially developed for cardiovascular indications, has sparked considerable interest in recent years due to its potential performance-enhancing effects. This review manuscript delves into the multifaceted roles of meldonium, examining its pharmacological mechanisms, therapeutic applications, and controversial implications in medicine. Beyond its cardiovascular applications, emerging research has shed light on meldonium's neuroprotective properties and its potential for mitigating various psychiatric conditions. Moreover, recent investigations have explored meldonium's potential in treating neurodegenerative disorders, alcohol use disorder, and even enhancing cognitive function. However, meldonium's journey extends beyond the realm of medicine, as its use among athletes has stirred debates surrounding performance enhancement and fair competition. The substance's inclusion in the World Anti-Doping Agency's (WADA) prohibited list has intensified scrutiny and raised ethical considerations regarding its use in sports. This manuscript aims to provide a comprehensive resource for researchers, clinicians, and enthusiasts alike, fostering a deeper understanding of meldonium's complex biological interactions and its potential contributions to psychiatry.

Keywords: meldonium; mildronate; doping; psychopharmacology; psychiatry

Citation: Bellman, V. Unlocking the Potential of Meldonium: From Performance Enhancement to Therapeutic Insights. *Psychoactives* **2024**, *3*, 235–247. https://doi.org/10.3390/psychoactives3020015

Academic Editor: Kabirullah Lutfy

Received: 23 March 2024
Revised: 27 April 2024
Accepted: 3 May 2024
Published: 6 May 2024

1. Introduction

Meldonium, a small synthetic compound initially developed in the 1970s, has garnered significant attention in recent years, both for its controversial use as a performance-enhancing substance in competitive sports and for its promising therapeutic applications [1]. Meldonium was first synthesized by a team of researchers at the Latvian Institute of Organic Synthesis in Riga [2]. Initially developed as a growth-promoting agent for livestock and poultry, its cardioprotective properties were quickly recognized, leading to its approval for human use in the late 1980s [2]. While meldonium gained traction as a cardioprotective and anti-ischemic drug, its alleged performance-enhancing effects in athletes sparked controversy. In 2016, the World Anti-Doping Agency (WADA) added meldonium to its list of banned substances, citing concerns over its potential to increase endurance and aid in recovery [3]. This decision sparked a heated debate and led to several high-profile doping cases involving elite athletes.

Despite the controversies surrounding its use in sports, the unique pharmacological properties of meldonium have prompted extensive research into its therapeutic potential [4]. Investigations have explored its role in various medical conditions, such as cardiovascular diseases, neurological disorders, and metabolic disorders, among others [4]. This review aims to provide a comprehensive overview of meldonium, delving into its history, pharmacological properties, and the ongoing debate surrounding its use in athletics. Additionally, we will explore the emerging therapeutic insights that have propelled meldonium into the spotlight of medical research, highlighting its potential applications across various medical specialties. By examining the current state of knowledge and the latest scientific evidence, this review seeks to unlock the full potential of meldonium, offering a balanced perspective on its role in performance enhancement while shedding light on its therapeutic prospects in neurology and psychiatry.

2. Materials and Methods

A comprehensive literature search was conducted in PubMed, PsycINFO, the Universal Database of Russian Newspapers (UDB-COM), Web of Science, Scopus, CyberLeninka, Mendeley, ProQuest, Google Scholar, Scholar.ru, and eLibrary to identify peer-reviewed articles published between 2000 and 2023. The search terms included "meldonium" and "mildronate" in combination with keywords such as "pharmacology", "pharmacokinetics", "therapeutic uses", "clinical trials", "performance enhancement", and "doping". The search was not restricted by language. Articles were included if they met the following criteria: (1) reported findings related to the pharmacology, pharmacokinetics, therapeutic applications, or performance-enhancing effects of meldonium; (2) were conducted in vitro, in vivo (animal models), or on human subjects; and (3) were published in peer-reviewed journals or conference proceedings between 2000 and 2023. Studies were excluded if they did not provide sufficient information relevant to the scope of this review or if they were deemed to be of low quality based on established criteria for scientific rigor and reporting.

The author screened the titles and abstracts of the retrieved studies against the inclusion and exclusion criteria. Full-text articles were then obtained and assessed for eligibility. Data from the included studies were extracted and organized into relevant categories, such as pharmacokinetic parameters, mechanisms of action, therapeutic indications, performance enhancement, safety and adverse effects, and regulatory aspects. Every Russian article was translated, and the data from these articles were incorporated into the review. Given the author's fluency in Russian, they personally undertook the task of translating the articles, ensuring that the meaning and context of the original text were accurately conveyed during the translation process. As this was a narrative review, no formal quality assessment of the included studies was performed. The extracted data were synthesized narratively, with a focus on providing a comprehensive overview of the current state of knowledge regarding meldonium.

3. Discussion

3.1. Pharmacology of Meldonium

Meldonium, chemically known as 3-(2,2,2-trimethylhydrazinium) propionate dihydrate, is a small synthetic compound with a relatively simple molecular structure. It consists of a trimethylhydrazinium cation and a propionate anion, forming a zwitterionic inner salt [5]. This unique structure contributes to its water solubility and distinct physicochemical properties. The lack of comprehensive research and the presence of confusing or conflicting data on meldonium's pharmacokinetic properties have made it challenging to establish clear guidelines regarding its use in clinical practice [6–8]. Table 1 summarizes pharmacokinetic properties of meldonium based on published data.

Table 1. Pharmacokinetic properties of meldonium.

Pharmacokinetic Aspect (s)	Description	References
Absorption	After oral intake, it is rapidly absorbed, with a bioavailability of 78%, and the Tmax in plasma is 1–2 h. Food intake prolongs the time to reach maximum concentration (Tmax) but does not impact the maximum concentration (Cmax).	[9]
Distribution	Meldonium concentration in the blood plasma peaks within 1 to 2 h after administration. Cmax and AUC rise with dose proportionality.	[9]
Biotransformation	Meldonium undergoes hepatic metabolism primarily through gamma-butyrobetaine hydroxylase (BBOX), leading to the formation of various metabolites, including succinic acid, the main metabolite detected in plasma.	[5,9]
Elimination	Renal excretion is vital for removing meldonium and its metabolites, showing two distinct phases in elimination curves: an initial phase of rapid excretion, with a half-life estimated to be between 5 and 15 h, followed by a subsequent, more prolonged elimination phase with a half-life exceeding 100 h.	[9,10]

Notably, the half-life varies with the dosage administered, indicating dose-dependent kinetics [11–13]. Trace amounts of meldonium persist in the systemic circulation and blood components for a long time [14]. It is important to note that the pharmacokinetic properties of meldonium can be influenced by factors such as age, renal and hepatic function, and potential drug–drug interactions, which may necessitate dose adjustments or close monitoring in certain patient populations.

Meldonium exerts its mechanism of action primarily through inhibiting γ-butyrobetaine hydroxylase (BBOX), a 2-oxoglutarate (2OG) oxygenase involved in the final step of carnitine biosynthesis [15]. By inhibiting this enzyme, meldonium decreases L-carnitine levels, leading to an increase in peroxisome activity in the cytosol [16]. This inhibition of carnitine biosynthesis aims to prevent the accumulation of cytotoxic intermediate products of fatty acid beta-oxidation in ischemic tissues, thereby reducing tissue damage [16]. Moreover, meldonium has been shown to compete with organic cation transporter 2 (OCTN2), leading to the elimination of carnitine through urine and a subsequent decrease in tissue carnitine content [17]. This competition for OCTN2-mediated transport plays a crucial role in the elimination of carnitine from the body due to meldonium administration [17]. Furthermore, studies have indicated that meldonium's mechanism of action involves regulating platelet-type phosphofructokinase (PFKP)-mediated glycolysis, which contributes to alleviating hypoxia-induced lung injury under hypobaric hypoxic conditions [18]. By modulating glycolysis through PFKP, meldonium can mitigate oxidative stress and lung injury caused by hypoxia [18].

3.2. Clinical and Therapeutic Applications

3.2.1. Performance Enhancement Effects

While some studies have questioned the direct performance-enhancing effects of meldonium, citing limited evidence in certain populations like older adults with angina pectoris [19], the overall body of research suggests that meldonium's influence on various metabolic and physiological pathways could potentially lead to enhanced physical performance in athletes. The use of meldonium among healthy athletes has been associated with mild adverse effects and the belief in its potential to enhance performance [4]. One speculated mechanism behind meldonium's performance-enhancing potential is its ability to decrease myocardial oxygen requirements, which could contribute to improved athletic performance [20]. Moreover, meldonium's impact on mitochondrial function and oxidative stress has been linked to potential performance benefits. Studies have shown that meldonium can improve mitochondrial dysfunction in conditions like Huntington's disease, leading to enhanced motor function and increased survival rates [21]. Additionally, meldonium's regulation of glycolysis through platelet-type phosphofructokinase has been suggested to alleviate hypoxia-induced lung injury, further indicating its potential in enhancing physical performance [18]. Furthermore, meldonium's effects on metabolic pathways, such as inhibiting fatty acid beta-oxidation and enhancing glucose utilization, may contribute to its performance-enhancing properties [22]. Memory performance, particularly visual memory, showed enhancement after therapy initiation, indicating meldonium's potential efficacy in memory processes. Attention volume and switching also significantly increased throughout the observation period, suggesting improved cognitive function [23].

The use of meldonium by athletes raises ethical concerns regarding fair competition and the potential risks to their health. The World Anti-Doping Agency (WADA) banned meldonium in 2016 due to the widespread use of the drug among elite athletes without reasonable health justifications [24]. This decision was influenced by the observation of meldonium's extensive use by athletes from Russia and other eastern European countries, raising suspicions of state-supported doping practices [24]. The ban on meldonium was part of WADA's efforts to address the misuse of performance-enhancing substances in sports, reflecting concerns about the potential abuse of substances like meldonium to gain an unfair advantage [25]. While proponents argue that meldonium may provide a legal and ethical advantage by improving recovery and endurance, opponents contend that its use

violates the principles of fair play and could potentially lead to unknown long-term health consequences. Some athletes have claimed to have unknowingly consumed meldonium, highlighting the need for better education and transparency within the sporting community. Additionally, the lack of clear scientific consensus on meldonium's performance-enhancing effects has fueled debates about the ethical implications of banning a substance without definitive evidence of its efficacy as a doping agent [19].

3.2.2. Neuroprotective Effects and Other Indications

Meldonium, a drug known for its anti-ischemic and cardioprotective properties, has garnered attention for its potential neuroprotective effects in various neurological disorders. The drug's ability to inhibit ß-oxidation and activate glycolysis contributes to its neuroprotective mechanisms [4]. Additionally, meldonium has been recognized for its antioxidant, neuroprotective, and vasodilatory effects, further supporting its potential in treating age-related cardiovascular and neurological pathologies [26]. Furthermore, lipidomics studies have shed light on the neuroprotective effects of meldonium, particularly in the context of ischemia–reperfusion injury [27]. Clinical trials have also confirmed the neuroprotective benefits of meldonium in the treatment of acute ischemic stroke [28]. The drug's efficacy in relieving allodynia in rat models of neuropathic pain underscores its potential in addressing neurological conditions associated with pain [22].

Preclinical studies have suggested that meldonium may exert neuroprotective effects by modulating cellular energy metabolism, reducing oxidative stress, and inhibiting apoptosis in neuronal cells. These neuroprotective mechanisms could potentially contribute to cognitive enhancement or delay neurodegeneration, but clinical evidence in humans is still lacking [29]. Research by Cristo et al. (2018) highlights meldonium's ability to improve mitochondrial dysfunction in Huntington's disease by restoring the expression of peroxisome proliferator-activated receptor γ coactivator 1α [21]. Other authors have discussed the potential future applications of meldonium in neurological disorders such as Parkinson's disease, diabetic neuropathies, stroke, chronic fatigue syndrome, and conditions involving cognitive impairment like neurodegenerative diseases and schizophrenia [4,30]. Furthermore, Tretzel et al. (2016) mention ongoing clinical trials focusing on meldonium's anti-ischemic and cardioprotective properties, as well as its potential applications in diabetes, neurodegenerative disorders, and bronchopulmonary diseases [31]. Table 2 summarizes all clinical indications and contraindications for meldonium use [9,32–36].

Table 2. Clinical indications and contraindications for meldonium use.

Indications	Contraindications
Comprehensive therapy of ischemic heart disease (angina, myocardial infarction)	Hypersensitivity to the components of the medication
Chronic Heart Failure and cardiomyopathies	Increased intracranial pressure (in cases of venous outflow disorders and intracranial tumors)
Comprehensive therapy of acute and chronic cerebrovascular disorders	Age under 18 years (efficacy and safety not established)
Hemophthalmos and retinal hemorrhages of various etiologies, thrombosis of the central retinal vein and its branches, and retinopathies of various etiologies (diabetic, hypertensive).	Pregnancy
Reduced performance; mental and physical overloads (including in athletes).	Breastfeeding period
Withdrawal syndrome in alcohol use disorder	Unstable liver and/or kidney diseases

Due to the potential development of an excitatory effect, it is recommended to administer the medication in the first half of the day. The method of administration, dosage, and

duration of treatment are established individually, depending on the indications, severity of the condition, and other factors. Table 3 summarizes these methods of administration and dosage as recommended by the manufacturers [9,37–39].

Table 3. Methods of administration and dosage.

Indication(s)	Administration and Dosage
Ischemic heart disease (myocardial infarction)	IV bolus of 0.5–1.0 g per day
Stable angina (chronic heart failure) and cardiomyopathy	IV bolus of 0.5–1.0 g per day or IM at a dose of 0.5 g 1–2 times a day for 10–14 days, followed by oral administration. The total course of treatment is 4–6 weeks.
Cerebral Circulatory Disorders	In the acute phase: IV bolus of 0.5 g once a day for 10 days, then switching to oral administration of 0.5–1 g. The total course of treatment is 4–6 weeks. In chronic cerebral circulatory insufficiency: IM/IV once a day for 10 days, then orally. The total course of treatment is 4–6 weeks.
Hemophthalmos, retinal hemorrhages, thrombosis of the central retinal vein and its branches, and various etiologies of retinopathies (diabetic, hypertensive)	Parabulbarly at a dose of 0.05 g for 10 days.
Mental and Physical Exhaustion of various etiologies	IM/IV once a day at a dose of 0.5 g. The course of treatment is 10–14 days. Treatment may be repeated every 2–3 weeks if necessary.
Alcohol Use Disorder	IM/IV twice a day at a dose of 0.5 g. The course of treatment is 7–10 days.

3.2.3. Psychiatric Benefits and Potential Treatment for Mental Health Conditions

Despite the intriguing preclinical findings and its theoretical potential, the use of meldonium in psychiatry remains largely unexplored in clinical settings. European researchers have hypothesized that meldonium's proposed neuroprotective and metabolic effects could potentially translate into cognitive enhancement or improved cognitive function [32,34,40]. In animal studies, meldonium demonstrated superior stress-relieving effects compared to diazepam, enhancing survival rates under chronic stress conditions, positively impacting behavioral activity, and reducing damage to the gastroduodenal mucous membranes. Additionally, meldonium prevented the suppression of nonspecific immune cells and activated their protective functions, suggesting its potential as a stress protector in clinical settings [41].

Preliminary studies have suggested that meldonium may possess anxiolytic and antidepressant-like properties, possibly due to its modulation of neurotransmitter systems and its ability to reduce oxidative stress in the brain [42,43]. For example, continuous therapy with meldonium at a daily dose of 500 mg proved to be the sole therapeutic regimen that significantly enhanced all cognitive function parameters and improvements in both anxiety and depression levels among older patients suffering from arterial hypertension and cognitive impairment [44]. The administration of Mildronate at a dosage of 1000 mg per day led to a statistically significant decrease in depression levels in patients with ischemic stroke, while also eliminating reduced activity levels, general fatigue, and mental exhaustion [45]. Similarly, the administration of meldonium to relatively young patients (up to 45 years old) with post-stroke depression led to a notable reduction in depressive episodes, with a significant correlation found between the severity of depressive symptoms and patients' motivation to recover from the stroke, which is crucial for rehabilitation [46]. This suggests that meldonium can be potentially used in various patients with post-stroke depressive symptoms and cognitive impairment.

Over the duration of Mildronate treatment, patients demonstrated a notable reduction in levels of reactive anxiety, which refers to the temporary state of heightened anxiety or tension stemming from a particular situation or stressor [29]. Additionally, there was an observed decline in personality-related or trait anxiety, which is the predisposition to perceive many situations as threatening and to experience anxiety more frequently and intensely than others [29]. The amelioration of anxiety symptoms, in conjunction with improvements in depressive symptoms previously reported, point to Mildronate's broader psychotropic capabilities beyond its primary cardiovascular indications. However, further investigation is warranted to elucidate the mechanisms underpinning these neuropsychiatric effects and to establish the appropriate dosing and patient populations that may benefit from Mildronate as an adjunct or alternative intervention for anxiety and depressive disorders.

Other findings suggest that meldonium may be useful in the treatment of attention deficit hyperactivity disorder (ADHD). Russian authors also reported that the intake of the beta-adrenoreceptor sensitizer meldonium at a dose of 250 mg enhanced the effectiveness of beta-adrenoceptor activation, improving attention and concentration processes [47]. Meldonium therapy is associated with improvements in visual memory performance, as well as increased attention span and cognitive flexibility, suggesting potential benefits for enhancing memory and cognitive functions. Certain athletes have demonstrated heightened mental productivity, while others noted a decrease in mental activation and comfort levels but exhibited heightened interest or motivation, resembling the effects observed in individuals using stimulants over an extended duration [23].

Preliminary research has explored the potential use of meldonium in the treatment of substance use disorders, particularly alcohol use disorder [48]. Preclinical studies indicate that meldonium improves the deterioration of behavioral reactions, decreased productivity, disruption of blood clotting, and imbalance in ionic levels associated with prolonged alcohol consumption [49]. Its administration significantly reduces the blood alcohol concentration in individuals consuming alcohol at both low and high altitudes [50]. Meldonium, administered at a dosage of 0.5 grams four times a day (2000 mg per day) for three weeks following the completion of standard anti-alcohol withdrawal therapy, allows for a reduction in the number of relapses immediately after the completion of the main therapy. It also helps to alleviate asthenic manifestations that persist during the remission phase more rapidly. The proposed mechanisms involve the modulation of neurotransmitter systems and improvements in cellular energy metabolism in the brain, which may help to alleviate withdrawal symptoms and promote recovery [51].

Overdosing on meldonium can lead to a range of symptoms, including lowered blood pressure, headaches, rapid heart rate, dizziness, and general weakness [37–39]. Treatment for overdose is typically symptomatic [9]. Notably, meldonium is relatively non-toxic and does not typically provoke adverse reactions that are hazardous to patients' health, suggesting that the risk of severe harm from overdose is low [37–39]. Larger-scale, well-designed clinical trials are necessary to establish the therapeutic efficacy, optimal dosing, and safety profiles of meldonium in various psychiatric conditions before it can be considered as a viable treatment option.

3.2.4. Understanding the Safety Profile of Meldonium

Meldonium is associated with various side effects and safety concerns. According to some authors, rare adverse reactions may include allergic reactions (redness, rash, itching, and swelling), dyspeptic symptoms, tachycardia, and fluctuations in blood pressure, as well as agitation [52,53]. Very rare reactions may include eosinophilia and general weakness.

Other potential side effects of meldonium include cardiovascular issues like arrhythmias, low blood pressure, and bradycardia, as well as neurological and gastrointestinal effects [5]. There is a notable lack of English-language research on how meldonium affects exercise tolerance or cardiovascular function in both healthy individuals and trained athletes. This scarcity of data suggests a gap in our understanding of meldonium's impact on these parameters in diverse populations, warranting further investigation to elucidate

its potential effects. Major side effects and studies regarding the safety of meldonium are summarized in Table 4 below.

Table 4. Research studies and reviews on the safety of meldonium use.

Authors	Description of Findings
Jargin, 2019 [54]	Considering the reduced accessibility of ATP as an energy source due to decreased carnitine levels, meldonium could potentially lead to cell damage and diminished heart function in cases of heart failure and myocardial infarction.
Berlato and Bairros, 2020 [5]	There have been no documented cases of acute or chronic meldonium toxicity in humans.
Vilskersts et al., 2021 [55]	Meldonium treatment prevents RV and LV systolic dysfunction by improving mitochondrial function in models resembling cardiovascular issues seen in COVID-19 patients.
Zhu et al., 2013 [56]	The administration of meldonium via injection is equally effective and safe as using Cinepazide injections in treating acute stroke.
Schobersberger et al., 2017 [4]	Meldonium has proven beneficial in cardiovascular, neurological, and metabolic diseases for its anti-ischemic and cardioprotective properties, without major side effects.
Zhao et al., 2016 [57]	The medication is safe and well-tolerated within a dosage range from 250 to 750 mg.
Heuberger et al., 2022 [53]	Use of meldonium is associated with stomach or esophageal burning, muscle spasms, dizziness, tension-induced discomfort, depression, sedation or drowsiness, rapid heart rate, vision disturbances, appetite loss, and increased appetite, which are among the potential side effects.
Adami et al., 2022 [52]	Athletes have reported adverse effects such as allergic reactions (skin redness, itching, hives, rash, or angioedema), digestive issues, rapid heartbeat, and changes in blood pressure (either increase or decrease).
Arduini and Zammit, 2016 [58]	WADA added meldonium to the list of banned substances due to its real danger for athletes who may overdose and lower intracellular carnitine to pathological levels.

RCT: Randomized controlled trials.

Studies on meldonium toxicity indicate a gender discrepancy in susceptibility, with female rats exhibiting lower non-lethal doses compared to males. This suggests that females may be more vulnerable, potentially due to differences in excretion rates [59]. However, Kirimoto et al. also noted a lethal meldonium dose exceeding 5000 mg/kg for both rats and male dogs, with no discernible gender-related variations [59]. Human studies similarly suggest higher plasma concentrations and lower excretion rates in females, indicating an increased toxicity susceptibility [8]. Despite a study showing no sex differences in meldonium toxicity in Chinese volunteers, discrepancies in the dosage and administration route suggest potential limitations in these findings [13]. The lack of awareness among athletes about the dangers of meldonium exacerbates the risks associated with its use [5]. Additionally, there are concerns about drug interactions, the risk of overdose, and the potential for misuse [2,60,61] and dependence [62]. Furthermore, the long-term effects of meldonium use, particularly in healthy individuals, are not well-studied, highlighting the need for more

research and caution regarding its safety profile. Table 5 summarizes the potential drug–drug interactions associated with meldonium, providing a comprehensive understanding of its pharmacological interactions and implications, based on the published literature.

Table 5. Meldonium's interactions with other medications.

Drug–Drug Interactions	Description
Glyceryl trinitrate	Meldonium could potentially enhance the effect [9].
Nifedipine	Meldonium could potentially enhance the effect [9]. Potential additive hypotensive effect
Beta-blockers	Meldonium could potentially enhance the effect [9]. Potential additive hypotensive effect
Other hypotensive agents and peripheral vasodilators	Meldonium could potentially enhance the effect [9].
Anticoagulants	Synergistic therapeutic combination comprising meldonium acetylsalicylate and warfarin sodium for use as an anticoagulant agent [63]. Potential increased risk of bleeding due to additive effects.
Antidiabetic agents (e.g., insulin, metformin)	Possible additive hypoglycemic effect, requiring dose adjustments [64].
HIV medications	Meldonium exhibits a protective effect against efavirenz-induced cardio- and neurotoxicity [65].
Other agents	An overdose of meldonium may exacerbate the cardiotoxicity of cyclophosphamide [65].

Upon the cessation of prolonged meldonium administration, individuals may experience asthenia, diminished self-assurance, and reduced energy levels. This phenomenon could be attributed to the body's adaptation to a consistent supply of requisite oxygen to the tissues, particularly during intense physical exertion, such as that encountered by athletes in the preparatory stages of competition. After the discontinuation of meldonium use, the body reverts to the preferential metabolic pathway for energy production—lipolysis. However, the tissues may not receive an equivalent amount of oxygen as that during meldonium administration, resulting in a disequilibrium between the consumption and supply of molecular oxygen [66]. To minimize these discontinuation symptoms, it is recommended to taper off meldonium gradually rather than stopping it abruptly [66].

3.3. Regulatory Challenges and Limitations in Clinical Research

Meldonium has widely varying approval statuses globally. In Russia and the Baltic states of Latvia, Lithuania and Estonia, it remains an approved and commonly used medication [5,20]. Meldonium is also registered as a cardioprotective medication in other countries like Azerbaijan, Belarus, Georgia, Kazakhstan, Kyrgyzstan, Moldova, Ukraine, and Uzbekistan [67]. However, in major Western nations like the United States, Canada, Australia, and the European Union, meldonium is not approved for therapeutic use [68]. These countries consider it a prohibited substance, particularly in sports, due to concerns over its potential performance-enhancing effects [67,68].

Outside of its historical usage in the former Soviet sphere, most countries have either not approved meldonium or have banned it, especially after the World Anti-Doping Agency added it to the prohibited list in 2016 following positive tests from high-profile athletes [69]. These disparate policies reflect meldonium's limited clinical evaluation and lack of approval through major international regulatory bodies. Its status remains a source of controversy regarding anti-doping rules and appropriate medical usage.

In 1984, clinical studies were conducted in the USSR according to the standards at the time, as the concept of evidence-based medicine trials was not yet established [70]. With Latvia's entry into the European Union, it became necessary to conduct full-scale clinical trials in three phases, following European standards rooted in evidence-based medicine principles. These trials began in Riga in 2006, but were prematurely terminated [71]. The second-phase trial, aiming to assess the drug's safety, effectiveness, and optimal dosage, was abruptly stopped by its sponsor—the drug manufacturer. This action violated clinical trial regulations, leaving unanswered questions about meldonium's safety, effectiveness, and appropriate dosage. Currently, the standard daily dosage is typically 500–1000 mg, with treatment courses usually lasting from 10 days to three weeks, although therapeutic doses may differ [5,20,72].

At the same time, there are a lack of sufficient data regarding the usage of meldonium among athletes. The limited studies conducted many years ago on small sample sizes, without meeting the necessary conditions for using dietary supplements, fall into the "D" category (the lowest level) in terms of evidence-based medicine. Despite its long history of use as a cardioprotective agent, there is a relative paucity of large-scale, well-designed clinical trials investigating the therapeutic potential of meldonium in various medical conditions. This lack of robust clinical data presents a significant challenge in understanding the true efficacy, optimal dosing, and safety profiles of meldonium for different indications. The review also highlights gaps in our understanding of meldonium's complex mechanisms of action, including an incomplete elucidation of its biological pathways and potential off-target effects. While meldonium has generally been considered safe and well-tolerated, its full spectrum of potential off-target effects and adverse events has not been thoroughly characterized. While off-label use aims to benefit individual patients [73], it poses ethical and regulatory challenges, particularly in competitive sports and doping control [74]. Cultural and geographical differences in research practices, regulatory frameworks, and access to information also pose limitations in synthesizing a comprehensive understanding of meldonium. As meldonium continues to be investigated for its therapeutic potential, there is a need for rigorous scientific research adhering to the ethical principles of transparency, objectivity, and scientific integrity, which is hard to achieve in certain countries [75]. Potential conflicts of interest, such as industry funding or personal biases, must be addressed to ensure the credibility and reliability of research findings.

4. Conclusions

The future of meldonium research holds promise for unlocking its therapeutic potential across various medical domains. While its performance-enhancing effects in competitive sports remain controversial, the multifaceted pharmacological properties of meldonium warrant further investigation into its clinical applications. Specifically, the preliminary findings on meldonium's anxiolytic and antidepressant-like properties open up intriguing prospects in the field of mental health. As a metabolic modulator with potential effects on neurotransmitter systems, meldonium could contribute to the development of novel therapeutic approaches for anxiety, depression, and other psychiatric disorders.

However, to fully harness the potential of meldonium, rigorous scientific research adhering to the highest ethical and methodological standards is paramount. Well-designed, large-scale clinical trials are necessary to establish its safety profiles, optimal dosing regimens, and efficacy across various indications. Collaboration among researchers, clinicians, and regulatory bodies is crucial to ensure the responsible exploration of meldonium's therapeutic potential while addressing any potential risks or ethical concerns.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: All information and data utilized in this review are sourced from publicly available literature and cited accordingly.

Conflicts of Interest: The author declares no conflicts of interest.

References

1. Dambrova, M.; Makrecka-Kuka, M.; Vilskersts, R.; Makarova, E.; Kuka, J.; Liepinsh, E. Pharmacological effects of meldonium: Biochemical mechanisms and biomarkers of cardiometabolic activity. *Pharmacol. Res.* **2016**, *113*, 771–780. [CrossRef] [PubMed]
2. Lippi, G.; Mattiuzzi, C. Misuse of the metabolic modulator meldonium in sports. *J. Sport Health Sci.* **2017**, *6*, 49–51. [CrossRef] [PubMed]
3. Oliveira, D.; de Araújo, A.; Ribeiro, W.; Silva, D.; Duarte, A.C.; de Sousa, V.; Pereira, H.G. Screening method of mildronate and over 300 doping agents by reversed-phase liquid chromatography-high resolution mass spectrometry. *J. Pharm. Biomed. Anal.* **2021**, *195*, 113870. [CrossRef]
4. Schobersberger, W.; Dünnwald, T.; Gmeiner, G.; Blank, C. Story behind meldonium-from pharmacology to performance enhancement: A narrative review. *Br. J. Sports Med.* **2017**, *51*, 22–25. [CrossRef]
5. Berlato, D.G.; Bairros, A.V.D. Meldonium: Pharmacological, toxicological, and analytical aspects. *Toxicol. Res. Appl.* **2020**, *4*, 239784732091514. [CrossRef]
6. Liu, F.; Sui, X.; Wang, Q.; Li, J.; Yang, W.; Yang, Y.; Xiao, Z.; Sun, Y.; Guo, X.; Yang, X.; et al. Insights into the pharmacodynamics and pharmacokinetics of meldonium after exposure to acute high altitude. *Front. Pharmacol.* **2023**, *14*, 1119046. [CrossRef] [PubMed]
7. Knych, H.; Stanley, S.; McKemie, D.; Arthur, R.; Bondesson, U.; Hedeland, M.; Thevis, M.; Kass, P. Pharmacokinetics and pharmacodynamics of meldonium in exercised thoroughbred horses. *Drug Test. Anal.* **2017**, *9*, 1392–1399. [CrossRef]
8. Rabin, O.; Uiba, V.; Miroshnikova, Y.; Zabelin, M.; Samoylov, A.; Karkischenko, V.; Semyonov, S.; Astrelina, T.; Razinkin, S. Meldonium long-term excretion period and pharmacokinetics in blood and urine of healthy athlete volunteers. *Drug Test. Anal.* **2018**, *11*, 554–566. [CrossRef]
9. The Health Products Regulatory Authority (HPRA). Summary of Product Characteristics. 15 December 2023. Available online: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA22992-025-001_15122023133518.pdf (accessed on 22 March 2024).
10. WADA. NOTICE—MELDONIUM. 11 April 2016. Available online: https://www.wada-ama.org/sites/default/files/resources/files/wada-2016-04-12-meldonium-notice-en.pdf (accessed on 22 March 2024).
11. Pidpruzhnykov, Y.V.; Sabko, V.E.; Iurchenko, V.V.; Zupanets, I.A. UPLC-MS/MS method for bioequivalence study of oral drugs of meldonium. *Biomed. Chromatogr.* **2012**, *26*, 599–605. [CrossRef]
12. Peng, Y.; Yang, J.; Wang, Z.; Wang, J.; Liu, Y.; Luo, Z.; Wen, A. Determination of mildronate by LC-MS/MS and its application to a pharmacokinetic study in healthy Chinese volunteers. *J. Chromatogr. B Anal. Technol. Biomed. Life Sci.* **2010**, *878*, 551–556. [CrossRef]
13. Zhang, J.; Cai, L.J.; Yang, J.; Zhang, Q.Z.; Peng, W.X. Nonlinear pharmacokinetic properties of mildronate capsules: A randomized, open-label, single- and multiple-dose study in healthy volunteers. *Fundam. Clin. Pharmacol.* **2013**, *27*, 120–128. [CrossRef] [PubMed]
14. Forsdahl, G.; Jančić-Stojanović, B.; Anđelković, M.; Dikić, N.; Geisendorfer, T.; Jeitler, V.; Gmeiner, G. Urinary excretion studies of meldonium after multidose parenteral application. *J. Pharm. Biomed. Anal.* **2018**, *161*, 289–295. [CrossRef] [PubMed]
15. Islam, M.; Markoulides, M.; Chowdhury, R.; Schofield, C. Structural analysis of the 2-oxoglutarate binding site of the circadian rhythm linked oxygenase jmjd5. *Sci. Rep.* **2022**, *12*, 20680. [CrossRef] [PubMed]
16. Statsenko, M.; Turkina, S.; Lopushkova, Y. New data on well-known drug: Focus on meldonium. *Meditsinskiy Sov.* **2021**, *14*, 110–117. [CrossRef]
17. Liepinsh, E.; Makarova, E.; Sevostjanovs, E.; Hartmane, D.; Cirule, H.; Zharkova-Malkova, O.; Grinberga, S.; Dambrova, M. Carnitine and γ-butyrobetaine stimulate elimination of meldonium due to competition for octn2-mediated transport. *Basic Clin. Pharmacol. Toxicol.* **2017**, *120*, 450–456. [CrossRef] [PubMed]
18. Wang, D.; Liu, F.; Yang, W.; Sun, Y.; Wang, X.; Sui, X.; Yang, J.; Wang, Q.; Song, W.; Zhang, M.; et al. Meldonium ameliorates hypoxia-induced lung injury and oxidative stress by regulating platelet-type phosphofructokinase-mediated glycolysis. *Front. Pharmacol.* **2022**, *13*, 863451. [CrossRef] [PubMed]
19. Bezuglov, E.; Talibov, O.; Butovskiy, M.; Khaitin, V.; Ачкасов, E.; Waśkiewicz, Z.; Lazarev, A. The inclusion in WADA prohibited list is not always supported by scientific evidence: A narrative review. *Asian J. Sports Med.* **2021**, *12*, e110753. [CrossRef]
20. Greenblatt, H.; Greenblatt, D. Meldonium (mildronate): A performance-enhancing drug? *Clin. Pharmacol. Drug Dev.* **2016**, *5*, 167–169. [CrossRef]
21. Cristo, F.; Finicelli, M.; Digilio, F.; Paladino, S.; Valentino, A.; Scialò, F.; D'Apolito, M.; Saturnino, C.; Galderisi, U.; Giordano, A.; et al. Meldonium improves huntington's disease mitochondrial dysfunction by restoring peroxisome proliferator-activated receptor γ coactivator 1α expression. *J. Cell. Physiol.* **2018**, *234*, 9233–9246. [CrossRef]
22. Fulas, O.; Laferrière, A.; Stein, R.; Bohle, D.; Coderre, T. Topical combination of meldonium and n-acetyl cysteine relieves allodynia in rat models of crps-1 and peripheral neuropathic pain by enhancing no-mediated tissue oxygenation. *J. Neurochem.* **2020**, *152*, 570–584. [CrossRef]
23. Chaynikov, P.N.; Cherkasova, V.G.; Solomatina, N.V.; Kulesh, A.M. The effectiveness of Mildronate® in enhancing mental performance and correcting psychoemotional status in young ice hockey league players. *Ural Med. J.* **2015**, *131*, 56–61. Available online: http://elib.usma.ru/handle/usma/14012 (accessed on 8 March 2024).

24. Watson, C.; Stone, G.; Overbeek, D.; Chiba, T.; Burns, M. Performance-enhancing drugs and the olympics. *J. Intern. Med.* **2022**, *291*, 181–196. [CrossRef] [PubMed]
25. Vlad, R.; Hancu, G.; Popescu, G.; Lungu, I. Doping in sports, a never-ending story? *Adv. Pharm. Bull.* **2018**, *8*, 529–534. [CrossRef] [PubMed]
26. Bezrukov, V.; Sykalo, N.; Kuprash, L.; Panteleymonova, T. Treatment optimization of the age-related cardiovascular and neurological pathology using known metabolic, cytoprotective, vasodilatory action substances. *Rev. Ageing Longev.* **2022**, *4*, 114–129. [CrossRef]
27. Todorović, Z.; Đurašević, S.; Stojković, M.; Grigorov, I.; Pavlović, S.; Jasnić, N.; Tosti, T.; Macut, J.B.; Thiemermann, C.; Đorđević, J. Lipidomics provides new insight into pathogenesis and therapeutic targets of the ischemia—Reperfusion injury. *Int. J. Mol. Sci.* **2021**, *22*, 2798. [CrossRef] [PubMed]
28. Novikov, V.; Levchenkova, O.; Ivantsova, E.; Vorobieva, V. Mitochondrial dysfunctions and antihypoxants. *Rev. Clin. Pharmacol. Drug Ther.* **2020**, *17*, 31–42. [CrossRef]
29. Tanashyan, M.M.; Maksimova MYu Shabalina, A.A.; Fedin, P.A.; Medvedev, R.B.; Bolotova, T.A. Chronic cerebrovascular diseases and neuroprotection: The clinical efficacy of meldonium (Mildronat). *Zhurnal Nevrol. i Psikhiatrii Im. SS Korsakova* **2020**, *120*, 14–21. (In Russian) [CrossRef]
30. Filippova, A.V.; Pereverzev, A.P.; Ebzeeva, E.Y.; Ostroumova, O.D. Mildronate. Chronic fatigue syndrome. *Med. Alph.* **2020**, *7*, 15–20. (In Russian) [CrossRef]
31. Tretzel, L.; Görgens, C.; Geyer, H.; Thomas, A.; Dib, J.; Guddat, S.; Pop, V.; Schänzer, W.; Thevis, M. Analyses of meldonium (mildronate) from blood, dried blood spots (dbs), and urine suggest drug incorporation into erythrocytes. *Int. J. Sports Med.* **2016**, *37*, 500–502. [CrossRef]
32. Sjakste, N.; Gutcaits, A.; Kalvinsh, I. Mildronate: An Antiischemic Drug for Neurological Indications. *CNS Drug Rev.* **2005**, *11*, 151–168. [CrossRef]
33. Mytrokhina, O.; Kuryata, O. AB0828 Effects of meldonium for chronic heart failure after miocarditis in patients with connective tissue disease. *Ann. Rheum. Dis.* **2013**, *71* (Suppl. S3), 686. [CrossRef]
34. Beitnere, U.; van Groen, T.; Kumar, A.; Jansone, B.; Klusa, V.; Kadish, I. Mildronate improves cognition and reduces amyloid-β pathology in transgenic Alzheimer's disease mice. *J. Neurosci. Res.* **2014**, *92*, 338–346. [CrossRef] [PubMed]
35. Zvejniece, L.; Svalbe, B.; Makrecka, M.; Liepinsh, E.; Kalvinsh, I.; Dambrova, M. Mildronate exerts acute anticonvulsant and antihypnotic effects. *Behav. Pharmacol.* **2010**, *21*, 548–555. [CrossRef] [PubMed]
36. Turkina, S.V.; Poletaeva, L.V.; Inozemtseva, M.A. Use of Meldonium in Comprehensive Treatment of Patients with Type 2 Diabetes Associated with Peripheral Neuropathy. Role of Insulin Resistance. *J. Volgogr. State Med. Univ.* **2015**, *12*, 120–123. Available online: https://www.volgmed.ru/uploads/journals/articles/1467893551-vestnik-2015-2-2425.pdf (accessed on 10 March 2024).
37. Federal Medical-Biological Agency. *Formulary Guide on the Use of Medications in Youth Sports*; MBP-Agency: Luton, UK, 2014. Available online: http://centralsportschool.ru/f/formulyarnoe_rukovodstvo_dlya_vrachej_sportivnyh_uchrezhdenij.pdf (accessed on 22 March 2014).
38. Ministry of Health of the Russian Federation. *Instructions for the Use of the Medication Meldonium Organica*; AO "Organica"; Ministry of Health of the Russian Federation: Moscow, Russia, 2021. Available online: https://organica-nk.ru/wp-content/uploads/2019/04/Izmneniya-v-instruktsii-ot-29.09.21-250mg.pdf (accessed on 22 March 2024).
39. РЛС®. Мельдоний (Meldonium). Available online: https://www.rlsnet.ru/drugs/meldonii-35454 (accessed on 14 March 2024).
40. Pupure, J.; Rumaks, J.; Isajevs, S.; Korzakova, O.; Puncule, J.; Svirskis, S.; Kalviņš, I.; Kluša, V. Mildronate's protective effects in the peripheral nervous system: Stavudine-induced neuropathy and formalin-induced inflammation. *Proc. Latv. Acad. Sciences. Sect. B. Nat. Exact Appl. Sci.* **2010**, *64*, 114–118. [CrossRef]
41. Frantsuzova, T.I.; Chistyakov, S.I.; Balashov, V.P.; Ovsyannikova, L.A. Pharmacological methods of preventing stress-induced conditions in experiments. Proceedings of Higher Educational Institutions. *Volga Reg. Med. Sci.* **2010**, *4*, 26–35. Available online: https://cyberleninka.ru/article/n/farmakologicheskie-sposoby-profilaktiki-stress-indutsirovannyh-sostoyaniy-v-eksperimente (accessed on 12 March 2024).
42. Stoenica, L.; Senkov, O.; Gerardy-Schahn, R.; Weinhold, B.; Schachner, M.; Dityatev, A. In Vivo Synaptic Plasticity in the Dentate Gyrus of Mice Deficient in the Neural Cell Adhesion Molecule NCAM or Its Polysialic Acid. *Eur. J. Neurosci.* **2006**, *23*, 2255–2264. [CrossRef]
43. Klusa, V.; Beitnere, U.; Pupure, J.; Isajevs, S.; Rumaks, J.; Svirskis, S.; Dzirkale, Z.; Kalvinsh, I. Mildronate and its neuroregulatory mechanisms: Targeting the mitochondria, neuroinflammation, and protein expression. *Medicina* **2013**, *49*, 301–309. [CrossRef] [PubMed]
44. Statsenko, M.E.; Nedogoda, S.V.; Turkina, S.V.; Tyshchenko, I.A.; Poletaeva, L.V.; Chumachok, E.V.; Ledyaeva, A.A.; Tsoma, V.V. Possibilities of mildronate in the correction of cognitive impairment in elderly patients with arterial hypertension. *Russ. J. Cardiol.* **2011**, *4*, 91–95. Available online: https://cyberleninka.ru/article/n/vozmozhnosti-mildronata-v-korrektsii-kognitivnyh-narusheniy-u-patsientov-s-arterialnoy-gipertenziey-pozhilogo-vozrasta (accessed on 11 March 2024).
45. Tynterova, A.M.; Belousova, Y.D.; Reznik, E.Y. Clinical characteristics and metabolic therapy of fatigue in the acute and early recovery periods of ischemic stroke. *Zhurnal Nevrol. i psikhiatrii Im. SS Korsakova* **2023**, *123*, 94–100. (In Russian) [CrossRef]

46. Chukhlovina, M.L. The use of mildronate in ischemic stroke in young individuals. *Med. Perspect.* **2008**, *13*, 52–56. Available online: https://cyberleninka.ru/article/n/primenenie-mildronata-pri-ishemicheskom-insulte-u-lits-molodogo-vozrasta (accessed on 11 March 2024).
47. Popova, O.V.; Nureev, I.T.; Trukhina, S.I.; Shushkanova, E.G.; Trukhin, A.N.; Tsirkin, V.I.; Zlokazova, M.V. Features of higher mental functions, electrical brain activity, and learning success in adolescents and students with signs of ADHD. *Vyatka Med. Bull.* **2009**, *6*, 77–81.
48. Shorikova, A.I.; Filippova, E.V. The Use of Various Medicinal Preparations in the Therapy of Chronic Alcoholism. In *Current Issues in Modern Medical Science and Healthcare: Proceedings of the VI International Scientific and Practical Conference of Young Scientists and Students Dedicated to the Year of Science and Technology, Ekaterinburg, Russia, 8–9 April 2021*; Ural State Medical University: Ekaterinburg, Russia, 2021; Volume 2, pp. 1164–1169. Available online: http://elib.usma.ru/handle/usma/6069 (accessed on 12 March 2024).
49. Petrov, V.M.; Zakharov, A.G.; Zamuraeva, L.V. Changes in some physiological indicators with prolonged alcohol consumption and their correction by mildronate. *Bull. KRSU* **2011**, *11*, 109–113. Available online: http://lib.krsu.edu.kg/uploads/files/public/3262.pdf (accessed on 10 March 2024).
50. Petrov, V.M.; Proshchenko, D.A.; Kabonina, O.A. The Influence of Alcohol and Mildronate on the Blood Coagulation System under Low- and High-Altitude Conditions. *Bull. Ural. State Med. Univ.* **2017**, *4*, 66–70. Available online: http://elib.usma.ru/bitstream/usma/419/1/usmu_vestnik_2017_4_022.pdf (accessed on 10 March 2024).
51. Axmedov, S.J. Effects of the drug Mildronate. *Innov. Dev. Educ. Act.* **2023**, *2*, 40–59. [CrossRef]
52. Adami, P.E.; Koutlianos, N.; Baggish, A.; Bermon, S.; Cavarretta, E.; Deligiannis, A.; Furlanello, F.; Kouidi, E.; Marques-Vidal, P.; Niebauer, J.; et al. Cardiovascular effects of doping substances, commonly prescribed medications and ergogenic aids in relation to sports: A position statement of the sport cardiology and exercise nucleus of the European Association of Preventive Cardiology. *Eur. J. Prev. Cardiol.* **2022**, *29*, 559–575. [CrossRef] [PubMed]
53. Heuberger, J.A.A.C.; Henning, A.; Cohen, A.F.; Kayser, B. Dealing with doping. A plea for better science, governance and education. *Br. J. Clin. Pharmacol.* **2022**, *88*, 566–578. [CrossRef] [PubMed]
54. Jargin, S. Drugs and dietary supplements with unproven effects in research and practice. *J. Complement. Med. Res.* **2019**, *10*, 27. [CrossRef]
55. Vilskersts, R.; Kigitovica, D.; Korzh, S.; Videja, M.; Vilks, K.; Cirule, H.; Skride, A.; Makrecka-Kuka, M.; Liepinsh, E.; Dambrova, M. Protective Effects of Meldonium in Experimental Models of Cardiovascular Complications with a Potential Application in COVID-19. *Int. J. Mol. Sci.* **2021**, *23*, 45. [CrossRef]
56. Zhu, Y.; Zhang, G.; Zhao, J.; Li, D.; Yan, X.; Liu, J.; Liu, X.; Zhao, H.; Xia, J.; Zhang, X.; et al. Efficacy and safety of mildronate for acute ischemic stroke: A randomized, double-blind, active-controlled phase II multicenter trial. *Clin. Drug Investig.* **2013**, *33*, 755–760. [CrossRef]
57. Zhao, Z.; Chen, J.; Peng, W.; Wang, X.; Chen, Z.; Tang, H.; Liang, Y.; Ma, Z.; Chen, J.; Chen, X.; et al. Single- and Multiple-dose Pharmacokinetic, Safety and Tolerability Study of Mildronate Injection in Healthy Chinese Subjects Pharmacokinetic of Mildronate Injection. *Drug Res.* **2016**, *66*, 251–256. [CrossRef] [PubMed]
58. Arduini, A.; Zammit, V.A. A tennis lesson: Sharp practice in the science behind the Sharapova case. *Postgrad. Med. J.* **2016**, *92*, 429–430. [CrossRef] [PubMed]
59. Kirimoto, T.; Asaka, N.; Hayashi, Y.; Maeda, T.; Irimura, K.; Matsuura, N. MET-88: SR Ca2+-Uptake Stimulator for Treating Chronic Heart Failure. *Cardiovasc. Drug Rev.* **2006**, *17*, 75–86. [CrossRef]
60. Görgens, C.; Guddat, S.; Dib, J.; Geyer, H.; Schänzer, W.; Thevis, M. Mildronate (Meldonium) in Professional Sports—Monitoring Doping Control Urine Samples Using Hydrophilic Interaction Liquid Chromatography—High Resolution/High Accuracy Mass Spectrometry. *Drug Test. Anal.* **2015**, *7*, 973–979. [CrossRef]
61. Stuart, M.; Schneider, C.; Steinbach, K. Meldonium Use by Athletes at the Baku 2015 European Games: Table 1. *Br. J. Sports Med.* **2016**, *50*, 694–698. [CrossRef] [PubMed]
62. What Are the Dangers of Meldonium? Available online: https://www.mngz.ru/russia-world-sensation/3825443-chem-opasen-meldoniy.html (accessed on 26 April 2024). (In Russian)
63. Kalinin, D. Factor XII(a) inhibitors: A review of the patent literature. *Expert Opin. Ther. Pat.* **2021**, *31*, 1155–1176. [CrossRef]
64. Liepinsh, E.; Skapare, E.; Svalbe, B.; Makrecka, M.; Cirule, H.; Dambrova, M. Anti-diabetic effects of mildronate alone or in combination with metformin in obese Zucker rats. *Eur. J. Pharmacol.* **2011**, *658*, 277–283. [CrossRef]
65. Ministry of Health of the Republic of Belarus. State Institution "Center for Expertise and Testing in Healthcare". Instructions for Use of Meldonium Farmland. 21 September 2020. Available online: https://www.rceth.by/NDfiles/instr/20_09_2389_s.pdf (accessed on 26 April 2024).
66. Ryashentseva, A.; Gorbunov, A.; The Negative Influence of Meldonium on the Human Body. Center for Scientific Cooperation "Interactive Plus". 2016, pp. 1–5. Available online: https://interactive-plus.ru/e-articles/303/Action303-80823.pdf (accessed on 14 March 2024). (In Russian)
67. Cordiner, R. Meldonium. *Pract. Diabetes* **2016**, *33*, 330–331a. [CrossRef]
68. Hughes, D. Comment: Meldonium and the WADA Prohibited List. *Aust. Prescr.* **2016**, *39*, 102. [CrossRef]
69. Pitsiladis, Y.; Wang, G.; Lacoste, A.; Schneider, C.; Smith, A.D.; Di Gianfrancesco, A.; Pigozzi, F. Make sport great again: The use and abuse of the therapeutic use exemptions process. *Curr. Sports Med. Rep.* **2017**, *6*, 123–125. [CrossRef]

70. Geltzer, A. When the standards aren't standard: Evidence-based medicine in the Russian context. *Soc. Sci. Med.* **2009**, *68*, 526–532. [CrossRef] [PubMed]
71. Chirkova, A.; Petrenko, A.; Vasilyev, P. Testing Meldonium: Assessing Soviet pragmatic alternatives to the randomized controlled trial. *Clin. Trials* **2021**, *18*, 269–276. [CrossRef] [PubMed]
72. Dzerve, V.; MILSS I Study Group. A dose-dependent improvement in exercise tolerance in patients with stable angina treated with mildronate: A clinical trial "MILSS I". *Medicina* **2011**, *47*, 544–551. [CrossRef] [PubMed]
73. Ruan, X.; Kaye, A. Response to "off-label drug use. *Am. J. Med. Qual.* **2016**, *32*, 109. [CrossRef]
74. Meher, B.; Das, S.; Mohanty, R. Meldonium: Drug which brought disrepute to sport. *Int. J. Basic. Clin. Pharmacol.* **2017**, *6*, 1841. [CrossRef]
75. Butrina, L.V. Optimization of Pharmacotherapy for Asthenic Syndrome in Patients with Somatic Pathology. Doctoral Dissertation, Volgograd State Medical University, Volgograd, Russia, 2004. Available online: https://freereferats.ru/advanced_search_result.php?keywords=01004297681 (accessed on 26 April 2024).