Exploring the Comprehensive Effects of Psychoactive Substances and Therapeutic Agents on Mind and Mood

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DEREK H. SUITE, M.D.

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Derek H. Suite, MD, MS, is a board-certified psychiatrist and an academic leader in the field of neuro-psychopharmacology. As an Assistant Clinical Adjunct Professor with Columbia University's Teachers College since 2015, Dr. Suite has been instrumental in shaping the understanding of psychopharmacology of tomorrow's leaders in mental health, bringing over 25 years of clinical experience to his role as an educator and mentor.

Dr. Suite's academic journey began with obtaining his undergraduate and Master of Science degrees from Columbia University, and medical degree from Drexel University College of Medicine, followed by a residency in psychiatry at Montefiore Medical Center/Albert Einstein College of Medicine, where he selected as a Chief Resident.

Throughout his career, Dr. Suite has demonstrated exceptional leadership in multidisciplinary settings, spearheading initiatives that bridge the gap between clinical practice and academic research. His scholarly work, published in peer-reviewed journals, has significantly contributed to the understanding of critical issues in psychiatry, including, trauma, racial health disparities, and the psychological dimensions of urban mental health.

Dr. Suite's dedication to advancing the field is further exemplified by his pioneering the Student Journal of Mind, Mood, and Medications. This academic, student-driven publication serves as a platform for emerging scholars to engage with cutting-edge research and clinical perspectives in psychopharmacology and mental health.

Dear Esteemed Readers,

It is with great pleasure that I welcome you to the inaugural issue of the Journal of Mind, Mood & Medications, a scholarly publication dedicated to advancing our understanding of psychopharmacology and its profound impact on mental health and human cognition.

This journal represents the culmination of rigorous academic inquiry and clinical insights, born from the collaborative efforts of faculty and exceptional graduate students in Clinical Psychopharmacology at Teacher's College, Columbia University. Our mission is to bridge the gap between cutting-edge research and practical application, providing a platform for the exploration of the intricate interplay between psychiatric medications, neurobiological processes, and psychological well-being.

In this debut issue, we present a carefully curated selection of articles that delve into the multifaceted realm of psychopharmacology. From groundbreaking research on novel therapeutic agents to critical analyses of current treatment paradigms, our contributors offer nuanced perspectives that challenge conventional wisdom and push the boundaries of our field.

We have strived to create a publication that not only meets the highest standards of academic rigor but also remains accessible to a diverse readership. Whether you are a seasoned clinician, a researcher at the forefront of neuroscience, or a student embarking on your journey in mental health, you will find content that informs, challenges, and inspires.

The launch of this journal comes at a pivotal time in the field of mental health. As we grapple with unprecedented global challenges, the need for innovative approaches to understanding and treating mental health disorders has never been more urgent. It is our hope that the Journal of Mind, Mood & Medications will serve as a catalyst for new ideas, fostering interdisciplinary dialogue and driving forward the frontiers of psychopharmacological knowledge.

I extend my heartfelt gratitude to our distinguished editorial board, and our dedicated contributors who have made this endeavor possible. Your commitment to excellence and passion for advancing mental health care are the cornerstones of this publication.

As we embark on this scholarly journey together, I invite you to engage deeply with the content, question assumptions, and contribute to the ongoing discourse in our field. The pages that follow are not merely a collection of articles, but a testament to our collective pursuit of knowledge in service of better mental health outcomes for all.

Thank you for your readership and your commitment to the advancement of psychopharmacology and mental health care.

With warmest regards,

Derek H. Suite, MD, MS
Editor-in-Chief
Journal of Mind, Mood & Medications

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Exploring the Therapeutic Potential of Psilocybin:
A Review of Clinical Trials for Treatment-Resistant Depression

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May 3, 2024

Abstract

This paper reviews recent clinical trials investigating psilocybin as a treatment for treatment- resistant depression (TRD). Traditional treatments often fail to adequately address TRD, necessitating novel therapeutic options. Synthesizing systematic reviews and comparative studies, we explore psilocybin's efficacy, safety, and dose-response relationships. Studies consistently show rapid and sustained reductions in depressive and anxiety symptoms following psilocybin treatment, particularly in patients with life-threatening illnesses. Psilocybin's serotonin 2A receptor activation may reset dysfunctional brain circuits associated with depression. Secondary outcomes include improvements in existential distress and quality of life. However, the absence of control conditions in some studies necessitates cautious interpretation.Future research should refine therapeutic models, elucidate mechanisms, and conduct well-controlled trials. Despite limitations, evidence supports psilocybin as a promising treatment for TRD.

Introduction

Depression, characterized by persistent sadness, loss of interest, and a range of debilitating psychological and physical symptoms, stands as a foremost challenge in global mental health. Affecting over 264 million individuals of all ages worldwide, its impacts stretch across personal, social, and economic realms, making it a significant public health concern. The World Health Organization ranks depression as a leading cause of disability, underscoring its profound influence on global productivity and quality of life.

Traditional pharmacological treatments for depression, primarily antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), along with psychotherapies like cognitive behavioral therapy (CBT) and interpersonal therapy (IPT), have been the cornerstone of managing this pervasive disorder. However, a substantial portion of the patient population—approximately one-third—do not adequately respond to these interventions, a condition termed as treatment-resistant depression (TRD). TRD poses significant treatment challenges, often requiring alternative therapeutic strategies and leading to increased risks of morbidity and long-term disability.

The limitations of current treatment options have stimulated considerable interest in exploring novel therapeutic avenues. Among these, psilocybin, a naturally occurring psychedelic compound found in specific varieties of mushrooms, has emerged as a particularly promising candidate. Recent clinical research and systematic reviews have begun to highlight the potential of psilocybin not only to alleviate symptoms but also to modify the underlying psychopathological mechanisms of depression.

This literature review aims to synthesize the findings from these studies, critically evaluating psilocybin's efficacy, safety, and the mechanisms through which it may exert therapeutic effects, with a specific focus on its potential to manage and treat TRD.

In exploring the potential of psilocybin, this review will consider multidimensional aspects of its application: the direct impact on depressive symptoms, the psychological experiences induced during psilocybin sessions that may contribute to its long-term effectiveness, and the broader implications of incorporating a psychedelic into mainstream

psychiatric practice.

The synthesis of current research will provide a comprehensive overview of psilocybin's therapeutic potential, guiding future research directions and potential clinical applications in the ongoing struggle against depression.

Carhart-Harris et al. (2018) adds substantial weight to the growing body of evidence supporting the use of psilocybin with psychological support for treatment-resistant depression (TRD). Building upon previous findings, this study demonstrates the safety and efficacy of psilocybin in alleviating depressive and anxiety symptoms, with a notable fast and sustained response observed in many patients. The results corroborate earlier research by Griffiths et al. (2016), Ross et al. (2016), and Carhart-Harris et al. (2016), highlighting the consistent therapeutic potential of psilocybin across various studies.

The study underscores the feasibility of treating major depressive disorder (MDD) with psilocybin alongside psychological support, with promising results observed even in patients with severe depressive symptoms. Moreover, the findings suggest a potential shift in the treatment paradigm for depression, with psilocybin offering rapid and enduring antidepressant effects, contrasting with the delayed onset of action seen with traditional antidepressants.

However, the absence of a control condition in this trial limits the ability to draw definitive conclusions regarding efficacy, emphasizing the need for larger, better-controlled trials to validate these findings.

Current Understanding and Limitations of Depression Treatments

Psiuk et al. (2022) underscore the limitations of traditional depression treatments, particularly in addressing the needs of individuals with treatment-resistant depression (TRD). Despite the widespread use of pharmacological interventions such as selective serotonin reuptake inhibitors (SSRIs) and psychotherapeutic modalities like cognitive-behavioral therapy (CBT), a significant proportion of patients, approximately 30%, fail to achieve remission or experience only partial symptom relief.

This gap in treatment effectiveness highlights the critical need for innovative therapeutic options that can offer rapid and sustained relief from depressive symptoms. The challenges associated with TRD extend beyond clinical considerations to encompass socioeconomic burdens, including increased healthcare utilization, work impairment, and

diminished quality of life for affected individuals.

Psilocybin as an Emerging Therapeutic Option

Psiuk et al. (2022) present recent explorations into psilocybin as a potential solution for treatment-resistant depression (TRD). As a serotonin receptor agonist, psilocybin holds promise in rapidly reducing depressive symptoms, particularly in individuals who have not responded to conventional treatments like SSRIs or psychotherapy.

The systematic review conducted by Psiuk et al. (2022) compares the effects of psilocybin with esketamine, another emerging treatment for TRD. Both substances demonstrate potential in providing rapid relief from depressive symptoms, offering hope for individuals who have exhausted traditional treatment options.

Psilocybin's mechanism of action, primarily involving the serotonin 2A (5-HT2A) receptor, suggests a novel approach to addressing the underlying neurobiological dysfunction associated with depression. By modulating serotonin signaling and inducing profound alterations in consciousness, psilocybin therapy may facilitate the reorganization of dysfunctional brain circuits implicated in mood regulation.

However, despite its promising therapeutic potential, the clinical use of psilocybin faces regulatory and logistical challenges. Legal and ethical considerations surrounding the use of psychedelic substances necessitate careful navigation, and the intense nature of the psychedelic experience requires specialized clinical settings and trained professionals to ensure patient safety and well-being.

Ross et al.'s (2016) randomized controlled trial further illuminates the therapeutic potential of psilocybin in the treatment of anxiety and depression, particularly in patients facing life-threatening cancer diagnoses. The study demonstrated that a single moderate dose of psilocybin, in conjunction with psychotherapy, led to rapid and sustained clinical benefits, including significant reductions in anxiety and depression. These findings are particularly noteworthy as they highlight the novelty of a single dose of medication producing immediate and enduring anti-depressant and anxiolytic effects, lasting for weeks to months. The results also align with prior research indicating sustained anti-depressant effects of psilocybin in patients with treatment-resistant depression (Carhart-Harris et al., 2016), underscoring the potential of psilocybin as a breakthrough treatment for mood disorders.

Moreover, Ross et al. (2016) observed substantial anti-

depressant response rates associated with psilocybin, reaching as high as approximately 80% at 6.5 months follow-up. This is in stark contrast to meta-analyses of placebo-controlled trials investigating the efficacy of antidepressants in cancer-related depression, which have generally failed to demonstrate clear effects over placebo. The study's secondary outcomes also revealed significant improvements in cancer-related demoralization, hopelessness, spiritual well-being, general life satisfaction, and quality of life following psilocybin treatment. These findings underscore the potential of psilocybin not only to alleviate psychiatric symptoms but also to address existential and spiritual distress, offering a holistic approach to improving overall well-being in patients facing life- threatening illnesses.

Synthesis of Systematic Reviews and Meta-Analyses

Haikazian et al. (2023) contribute to the growing body of evidence supporting the efficacy of psilocybin in the treatment of major depressive disorder (MDD) and depression associated with life-threatening conditions. Their systematic review highlights significant reductions in depressive symptoms following psilocybin therapy, corroborating findings from previous research by Goldberg et al. (2020).

Goldberg et al. (2020) reported large and sustained decreases in depression and anxiety symptoms with psilocybin treatment. These findings underscore the potential of psilocybin as a therapeutic intervention for mood disorders, particularly when combined with psychotherapy. Both studies emphasize the synergistic effect between psilocybin and psychotherapy, suggesting that the integration of psychological support may enhance the therapeutic impact of psilocybin treatment.

The convergence of evidence from multiple systematic reviews and meta-analyses underscores the robustness of the findings regarding psilocybin's antidepressant effects. The consistent demonstration of symptom reduction across diverse patient populations and clinical settings strengthens the case for psilocybin as a promising treatment option for depression, warranting further exploration through well-designed clinical trials.

Comparative Studies and Clinical Trials

Goodwin et al. (2023) provide insights from clinical trials demonstrating the rapid and sustained efficacy of psilocybin in reducing

depressive symptoms, particularly in individuals with treatment-resistant depression (TRD). These trials offer compelling evidence of psilocybin's potential as a breakthrough treatment in the landscape of depression care, addressing the urgent need for novel therapeutic options for individuals who do not respond to conventional treatments.

Moreover, Carhart-Harris et al. (2021) conducted a comparative study evaluating the efficacy of psilocybin versus escitalopram, a commonly prescribed antidepressant. While primary outcomes were comparable between the two treatments, secondary outcomes favored psilocybin, indicating broader benefits in emotional and existential well-being. This suggests that psilocybin therapy may offer advantages beyond symptom reduction, potentially addressing existential distress and improving overall quality of life in individuals with depression.

The findings from comparative studies and clinical trials provide valuable insights into the relative efficacy and safety of psilocybin compared to conventional antidepressants. The favorable outcomes observed with psilocybin support its potential as a novel and transformative treatment option for depression, warranting further investigation through rigorous and well- controlled research studies.

Dose-Response Relationships and Safety Considerations

Perez et al. (2023) contribute valuable insights into dose-response relationships and safety considerations in the context of psilocybin therapy. Their dose-response meta-analysis highlights the nuanced relationship between psilocybin dosing and therapeutic outcomes, emphasizing the importance of optimizing dosing regimens to maximize efficacy while minimizing potential risks.

The findings from Perez et al. (2023) underscore the complexity of dosing considerations in psilocybin therapy, suggesting that the optimal dose may vary depending on individual patient characteristics, such as severity of symptoms, treatment history, and sensitivity to psychedelic effects. Tailoring psilocybin doses to individual patient needs may be crucial for achieving optimal therapeutic outcomes and mitigating potential adverse reactions.

While the customization of dosing regimens adds complexity to the clinical application of psilocybin, it also offers a pathway for personalized treatment strategies that can optimize treatment response and enhance patient safety. By considering factors such as patient demographics, clinical presentation, and treatment goals, clinicians can develop

individualized dosing protocols that balance therapeutic efficacy with safety and tolerability.

Interestingly, the dose-response meta-analysis conducted by Perez et al. (2023) provides important insights into the safety considerations associated with psilocybin therapy. By identifying dose-related trends in adverse events and risk profiles, clinicians can make informed decisions regarding dosing strategies and risk mitigation strategies to ensure patient safety during psilocybin treatment.

Overall, the findings from Perez et al. (2023) highlight the need for careful dosing considerations and safety monitoring in the clinical use of psilocybin. While optimizing dosing regimens may present challenges, personalized treatment approaches guided by dose-response relationships can maximize therapeutic benefits and minimize risks, ultimately improving outcomes for individuals undergoing psilocybin therapy.

Discussion

The landscape of depression treatment is evolving rapidly, driven by a growing recognition of the limitations of traditional approaches and the emergence of novel therapeutic options. Traditional modalities, including pharmacological interventions like SSRIs and psychotherapies such as CBT, provide relief for many individuals, but approximately 30% of patients remain resistant to these treatments. This treatment gap underscores the critical need for innovative solutions that offer rapid and sustained effectiveness. Recent research has highlighted psilocybin as a promising candidate in this regard, particularly in addressing treatment-resistant depression (TRD). Psilocybin's mechanism of action, involving serotonin receptor agonism and the potential to reset dysfunctional brain circuits associated with depression, offers a unique approach to symptom relief.

Systematic reviews and meta-analyses, such as those conducted by Haikazian et al. (2023) and Goldberg et al. (2020), provide robust evidence supporting the efficacy of psilocybin in reducing depressive symptoms, particularly when combined with psychotherapy. Comparative studies, such as those reviewed by Goodwin et al. (2023) and Carhart-Harris et al. (2021), further underscore the potential of psilocybin to rapidly reduce symptoms and sustain improvements over time, potentially offering advantages over conventional antidepressants. However, the clinical application of psilocybin is not without challenges. Dose-response meta-analyses, like the one conducted by Perez et al. (2023), emphasize

the importance of tailoring dosing regimens to individual patient needs to maximize therapeutic outcomes while minimizing risks. Regulatory barriers, ethical considerations, and the intense nature of the psychedelic experience also pose significant hurdles to widespread adoption. Despite these challenges, the growing body of evidence supporting the efficacy and safety of psilocybin therapy offers hope for individuals with treatment-resistant depression and highlights the potential for paradigm shifts in depression treatment.

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Medications For Challenging Behaviors in ASD

Research into the Psychopharmacological Interventions for the Challenging Behaviors Observed in Autism Spectrum Disorder (ASD): A Literature Review

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Abstract

Autism Spectrum Disorder (ASD) is a developmental condition marked by repetitive behaviors and deficits in social interaction. Autism can present in any combination of a vast variety of symptoms and, in severe cases, can be coupled with topographies of challenging behaviors such as aggression, Self-Injurious Behavior (SIB), and pica. While the treatment of ASD comes mainly in the form of psychotherapies, research has shown some medications to be effective in alleviating various symptoms of the condition. The present literature review summarizes the medications that have been studied for their potential to provide therapeutic benefits towards the more severe presentations of the external symptomologies of ASD. For the treatment of aggression and SIB, studies testing the effects of antipsychotics such as Haloperidol (Anderson et al., 1989; Campbell et al., 1997), Risperidone (McCracken et al., 2002; Troost et al., 2005), and Aripiprazole (Owen et al., 2009; Ichikawa et al., 2017) account for the majority of the pharmacological research available. However, some researchers have found other medications such as the opiate antagonist Naltrexone (Symons, Thompson, & Rodriguez, 2008) to yield positive results as well. Researchers also speculate that medications may reduce other challenging behaviors associated with ASD such as pica (Hergüner, 2016; Günes et al., 2016). A major limitation of the literature discussed here is the lack of insight into the long-term side effects of pharmacological treatments. Ultimately, medication therapies should only be implemented for challenging behaviors in a case of ASD after extensive consideration of their side effects and their impact on the progress of coinciding behavioral interventions.

As research into psychopathological disorders and their treatment continues to expand, one condition under constant scrutiny, for its symptom variety, the equifinality of its onset, and its potential for severe impairment, is Autism Spectrum Disorder (ASD). Progressions made in our understanding of the disorder are reflected in part in the changes made to the Diagnostic and Statistical Manual of Mental Disorders in its fifth edition. Four diagnoses once independent from one another in the DSM-IV— autistic disorder, Asperger syndrome, pervasive developmental disorder, and childhood disintegrative disorder— are combined into one overarching spectrum in the DSM-V. Conditions existing on this spectrum are characterized by two groups of behavioral symptoms: repetitive behaviors and deficits in social interaction. While dichotomous in their classifications, these symptoms can vary immensely in their manifestation and severity across individuals. Many behavioral interventions, such as applied behavioral analysis (ABA) have been effective in both reinforcing functional communication behavior and reducing undesirable, socially impairing behavior in ASD clients (Lindgren et al., 2020). However, the severe topographies that an individual with ASD may display such as aggression, self-injury, and other challenging behaviors, may require more fast-acting interventions due to the immediate danger that may be inflicted on oneself or others. In these cases, fast-acting intervention protocols may ensure short-term health and safety.

Challenging behaviors in ASD are a collection of high-intensity, case-specific topographies that are impairing and pose a danger to oneself or others (Sigafoos, Arthur, & O'Reilly, 2003). While the antecedents to these behaviors can often be difficult to discern, particularly in nonverbal individuals, they can nonetheless be categorized by their nature and repercussions. For example, behaviors that result in harm or an attempt to harm others are broadly coined as aggression, while behaviors that inflict harm on oneself are coined self-injurious behaviors (SIB) (Review: Fung et al., 2016). Practitioners of ABA will often create operational definitions of specific target behaviors for treatment, which allow for progress in therapy to be quantitatively measured and for effective intervention plans to be replicated.

Clinicians often demonstrate high inter-rater reliability in their operational definitions of a behavior, as well as their description of the function the behavior serves to the client (Hong et al., 2018). While ABA has thus been effective in treating some cases of ASD that are coupled with these topographies, benefits are limited in part to the lack of empirical research into effective treatment strategies and assessment methods

for these cases (Review: Matson & Nebel-Schwalm, 2007). Outside of behavioral interventions, some research into drug efficacy for treating cases of challenging behavior has yielded promising results, and has even led to FDA approval of a few multi-purposed medications.

Before the 21st century, the only drug that had been proven effective in treating disruptive behavior in ASD, potentially in its more severe cases, was Haloperidol. Developed in the late 1950s, Haloperidol is a dopamine receptor antagonist that falls into the class of first-generation antipsychotics; its original use is in the treatment of the positive symptoms of psychotic disorders (Preston et al., 2021).

A study conducted by Anderson et al., (1989) compared behavioral and learning outcomes between groups of children with a diagnosis of autistic disorder: one group received treatment of Haloperidol, and the other received a placebo. The treatment group had significantly more reduction in disruptive behaviors such as tantrums and hyperactivity than the control group. However, Haloperidol treatment did not provide any improvement in the facilitation of learning tasks, suggesting that it would not be an effective moderator of skill acquisition in behavioral therapies. Additionally, the sample of this study ranged from mild to severe cases of the behavioral topographies listed and its findings, thus, cannot be specified to severe cases of challenging behavior. Haloperidol is associated with a variety of side effects yet, remarkably, children in the experimental condition did not experience any of them. Only when a longitudinal study was conducted by Campbell et al. (1997) were the long-term effects of the use of Haloperidol for autism revealed. In their sample of 118 children, about 40% developed a drug-related dyskinesia; the majority of these cases were that of a withdrawal dyskinesia, and were positively associated with prescriptions of larger doses of Haloperidol. In light of potential long-term damage, the use of Haloperidol in the treatment of challenging behavior in ASD poses a great risk. Luckily, more medications that produce less drastic side effects have since been realized to decrease challenging behaviors.

In the early 2000s, efficacy studies were conducted on the benefits and safety of Risperidone for the treatment of severe cases of autism. Risperidone is considered a second-generation antipsychotic, as its mechanism of action is thought to mainly involve serotonergic blockade, as well as dopaminergic blockade secondarily. It is also associated with extrapyramidal side effects, yet perhaps less so than Haloperidol. Outside of its main function as a medication for psychotic disorders, Risperidone has also been implemented in treatments for bipolar and

obsessive-compulsive disorders (Preston et al., 2021). To test its potential as a medication for challenging behavior in autism, and also compare its therapeutic outcome to that of Haloperidol, McCracken et al. (2002) empirically tested Risperidone's effects on a sample of 101 children with any one of the four diagnoses in the DSM-IV (autism spectrum disorders) that were later combined into the ASD diagnosis in the DSM-V. Challenging behaviors observed in the sample ranged from tantrums to aggression and SIB. The dosage of Risperidone varied on a case-by-case basis from 0.5 to 3.5 mg in the experimental group. The authors reported a significantly better reduction (56.9%) in problem behavior in the experimental group compared to the control group. The side effects observed were mild— fatigue, drowsiness, and drooling being the most common— and tended to resolve after a few weeks. However, as this study only monitored behaviors in the short-term, it could not make inferences on whether medication-induced dyskinesias occurred in the long term.

Subsequent research into Risperidone treatment for severe cases of autism provided reassuring reports on its long-term effects. Troost et al. (2005) observed outcomes of long-term Risperidone use in children with autism spectrum disorders. Children in the experimental condition experienced significant reductions in problem behavior (aggression, SIB, and tantrums) after eight weeks of treatment compared to controls. Furthermore, those children who had continued treatment of Risperidone after 24 weeks showed significantly fewer instances of relapse, and only mild to moderate side effects: increased appetite, weight gain, fatigue, and anxiety, notably. As no medication-induced dyskinesias were observed, and the therapeutic effects of Risperidone persisted after six months, the authors deemed the long-term use of Risperidone for the treatment of autistic disorders viable in its severe cases. As drug research had generally yielded positive results, Risperidone was FDA-approved for the treatment of ASD with co-occurring instances of irritability, which was the blanket term used for case-specific challenging behavior related to aggression or other disruptive behaviors (Fung et al., 2016).

Importantly, the long-term sample in Troost et al.'s study had only twelve participants in each group. In light of this small sample size, and the fact that Risperidone has been associated with aversive long-term effects such as dyskinesia in treatment for other disorders (Preston et al., 2021), more research into Risperidone and ASD should be conducted.

A third antipsychotic medication that has been used in the treatment of challenging behavior in autism spectrum disorders is Aripiprazole. Like Risperidone, Aripiprazole is a second-generation antipsychotic. compared

to other antipsychotics in its class, Aripiprazole is associated with less weight gain and sedating effects but can often induce nausea and anxiety (Preston et al., 2021). One of the initial studies into Aripiprazole's efficacy was conducted by Owen et al. (2009), who compared outcome rates of problem behavior, discontinuation, and adverse side effects between experimental and placebo groups over eight weeks. The experimental group generally experienced a higher reduction in problem behavior yet also experienced significantly higher discontinuation rates and side effects such as extrapyramidal symptoms and weight gain. Even so, the authors of this study concluded that Aripiprazole was safe and well tolerated for children with autism spectrum disorders, as no severe, aversive experiences were reported during the study's timeline. A more recent study conducted by Ichikawa et al. (2017), using a sample of patients from Japan, corroborate the findings of Owen et al.; they reported that the use of Aripiprazole was well tolerated among their experimental group, and led to no aversive experiences. Importantly, both of these studies only observed the side effects of Aripiprazole treatment in the short term. While Aripiprazole was FDA-approved for severe cases of autism spectrum disorders in 2009, few studies have observed its longitudinal effects. Research by Wink et al. (2014)— who only assessed BMI— observed that Aripiprazole has significant long-term effects on weight gain equal to that of Risperidone. Researchers into pharmacological interventions for ASD will need to conduct additional studies to see what other effects the antipsychotic may bring on with long-term use.

Some researchers have tested the efficacy of drug classes outside those of antipsychotics in the treatment of challenging behavior in ASD. One drug under scrutiny is Naltrexone, an opiate antagonist primarily used to reverse the effects of acute opiate intoxication. It is also used in the maintenance of opiate and alcohol abstinence, as it can block the euphoric effects of drug use, thus decreasing the reward reinforcement of a drug (Preston et al., 2021). Treatments for ASD patients that incorporated Naltrexone, compared to treatments using a placebo-control, resulted in a higher observed reduction of behaviors related to hyperactivity after three weeks; additionally, Naltrexone use had no detrimental effects on co-occurring behavioral treatments (Campbell et al., 1993). More notable to the search for pharmacological interventions for severe topographies in ASD are findings from research into the impact of Naltrexone on SIB.

In his review of the use of opiate antagonism in the treatment of autism spectrum disorders, Deustch (1986) theorizes that SIB results from dysregulations in endogenous opioid systems. Deustch postulates that,

while the use of antipsychotics (here, they are called neuroleptics) could in part normalize these opioid systems, incorporating opioid antagonists into treatment may do so further and, consequently, reduce symptoms of SIB. In 1990, Walters et al. sought to test multiple theories— including Deutch's— regarding the interactions between opiate systems and self-injury by implementing Naltrexone in the treatment of a 14-year-old male. In doing so, they observed significantly decreased rates of self-injury in their client during treatment phases compared to a placebo phase. The authors also observed slight increases in measures of social relatedness, leading them to speculate that, by blocking the binding of endogenous opiates to their receptors, Naltrexone may not only affect the frequency of self-injury, but also the presence of social withdrawal. Finally, reports of the use of Naltrexone in pharmacological treatments for autism spectrum disorders were compiled in a quantitative synthesis conducted by Symons, Thompson, & Rodriguez in 2004. Combining data from a total of 86 subjects across 27 articles, the authors reported that 80% of the sample displayed a significant reduction in rates of SIB, with 47% showing 50% reduction or greater. As self-injury is a dangerous, traumatic, and impairing topography that can have lasting implications on one's developmental trajectory, reducing its occurrence can greatly improve a child's life; Thus, the research presented here is extremely encouraging. However, it should be noted that the sample the authors compiled contained cases of multiple developmental disorders and, thus, was not limited to cases of autism spectrum disorders. Future research that observes Naltrexone's efficacy in populations with ASD specifically will need to be conducted before any inferences can be made on the medication's impact on SIB in the disorder. Treating ASD with Naltrexone is not yet FDA-approved. While no longitudinal studies on the effects of the drug have been conducted, Naltrexone has not been shown to have any aversive effects in patients with ASD in the short-term (ElChaar et al., 2006).

Studies on the use of Divalproex in the treatment of ASD suggest that it is effective in reducing symptoms falling into the DSM-V's "Repetitive patterns of behavior" domain for the condition, and that it even may alleviate aggression in more severe cases. Often considered a first-line agent in the treatment of mania in bipolar disorders, Divalproex is an anticonvulsant thought to increase GABAergic activity and prolong the activation of sodium channels (Preston et al., 2021). In 2005, Hollander et al. conducted an eight-week trial using patients with a diagnosis of any one of the autism spectrum disorders and active displays of repetitive

behavior. Within the sample, nine patients received treatment with Divalproex while four received a placebo. The authors of this study observed a significant difference between the two groups in measures of repetitive behavior, with the group receiving Divalproex showing a greater reduction in these behaviors. The researchers did not report any side effects related to the use of Divalproex; these effects, however, were only monitored in the short term. In light of these findings, Hollander et al. (2009) tested the effect of Divalproex on topographies of irritability and aggression in patients with a diagnosis of one of the autism spectrum disorders. Notably this study had a much larger sample size (N = 55) than that of the previous study. Compared to placebo controls, more patients receiving Divalproex over 12 weeks showed a marked reduction in problem behavior classified as aggression or irritability. The authors reported that patients only experienced mild to moderate side effects as a result of treatment. Notably, the authors found a positive correlation between valproate blood levels and response to treatment within the experimental condition; thus, they speculate that varying levels of the drug's bioavailability across patients in the experimental condition may have been responsible for the differences observed in therapeutic effect. Divalproex is FDA-approved for seizures; however, while sometimes prescribed in cases of seizures with co-occurring ASD, Divalproex is not yet FDA-approved for ASD alone.

Two placebo-controlled studies observing the effects of Clonidine on symptoms in individuals with autism spectrum disorders provide insight into the potential for this medication to reduce problem behaviors that are possibly associated with hyperarousal and irritability.

Clonidine is a presynaptic inhibitor of norepinephrine. It has been used in the treatment of a variety of psychopathological conditions; while commonly used to treat hypertension, it has also been implicated in treatments for anxiety disorders, opiate withdrawal, and even Attention Deficit Hyperactivity Disorder (ADHD) (Preston et al., 2021). Fankhauser et al. (1992) demonstrated that Clonidine treatment could reduce the frequency of hyperactivity and repetitive behaviors in cases of autism spectrum disorders after four weeks of treatment. In the same year, Jaselskis et al. (1992) observed the effects of Clonidine on a population of patients with autism spectrum disorders who displayed topographies of irritability along with hyperactivity. Notably, their sample had experienced no therapeutic response from prior pharmacological interventions that implemented neuroleptics or Methylphenidate. The authors of this study found that Clonidine reduced behaviors related to both irritability

and hyperactivity. While the findings of these two studies suggest that Clonidine may alleviate common symptoms of autism spectrum disorders and, additionally, may alleviate severe behaviors, it should be mentioned that the sizes of the samples used in each were extremely small: nine patients in Fankhauser et al.'s study and eight patients in Jaselskis et al.'s study. Thus, their findings can be deemed only preliminary information for the research into Clonidine and ASD. Because Clonidine is effective in other developmental conditions, it may yield therapeutic benefits to ASD populations. Thus, researchers should conduct further studies into Clonidine and ASD that use larger sample sizes and methods that measure symptoms within the DSM-V's new behavioral criteria. Additionally, as measures of hyperarousal or irritability may only vaguely address severe behavioral topographies, the effect of Clonidine on aggression, SIB, and other challenging behaviors in ASD should be studied specifically.

The literature discussed so far has mainly focused on pharmacological interventions that reduce challenging behaviors related to aggression and SIB. However, some forms of problem behavior may not fall into these categories. For example, some topographies could be related to inappropriate touching, spitting, elopement, disrobing, or other maladaptive, case-specific behaviors. One of these behaviors in particular poses as much of an immediate danger to the client as SIB. Pica, defined as the consumption of non-food items, is thought to be prevalent among a multitude of developmental disorders and is most prevalent in ASD (Fields et al., 2021). While pica may not be extreme in most cases of ASD, some individuals may make frequent attempts to consume toxic items such as magnets or feces. In these life-threatening instances, pharmacological intervention may better ensure a child's safety. Unfortunately, research on the efficacy of medications in reducing pica is scarce and only case-specific; an even smaller fraction have involved a child with a diagnosis of ASD. In their case study, Hergüner & Hergüner (2016) discussed the use of Aripiprazole in a 17-year-old female client with ASD. After four weeks of treatment with Aripiprazole, the client's pica came to a complete halt, which persisted during the total six months of treatment. While the authors speculate that Aripiprazole may be a viable medication for the treatment of pica, this has yet to be empirically tested. In the same year, a case study conducted by Gunes et al. (2016). discussed the efficacy of Methylphenidate in treating pica in a case of ADHD. Their client— a six-year-old girl— displayed a high reduction in pica behaviors after four weeks of treatment on Methylphenidate. Researchers studying the neural mechanisms underlying pica have implicated dysregulations of

the dopaminergic systems in the brain (Schnitzler, 2022). Aripiprazole and Methylphenidate both—albeit in different ways— impact dopamine concentrations; as do other antipsychotics such as Haloperidol and Risperidone (Preston et al., 2021). While more research will be needed to identify proper medications for the treatment of pica— in ASD particularly and in developmental disorders as a whole— the research available provides a case for the use of medications that act on dopamine.

The studies discussed in this literature review present the major findings of researchers seeking the most effective pharmacological interventions for individuals with ASD and

co-occurring challenging behaviors. Many of the medications scrutinized in these studies have had some positive effects on behavioral outcomes. While their results are promising, it must be emphasized that very little of the presented research, if any, is conclusive; findings are confounded by multiple limitations: small sample sizes, over-generalized demographics, and sometimes the lack of causal inference. What is most concerning in these efficacy studies is their tendency to neglect to monitor the long-term effects of medications. Virtually all of the studies discussed only report the short-term side effects of medication, with cut-offs ranging from four to twelve weeks. In regards to cases that may require prolonged use of medications— where problem behavior might be so life-threatening that even one occurrence can pose a great risk to the safety of the individual or others— the literature available offers no insight. Additionally, some of the medications discussed here have been associated with long-term side effects in their use for treatments of other conditions. For example, second-generation antipsychotics such as Risperidone may permanently raise prolactin levels above baseline after prolonged use; the effect that these elevated levels could have on an individual with ASD is currently unclear (McCracken, 2005). Indeed, there are also ethical concerns about delivering pharmacological treatments to individuals with ASD without properly monitoring for all side effects, especially in more severe cases. For individuals who are nonverbal and have not undergone functional communication training, it may be impossible for their concerns or discomfort with medication to be voiced. In a worst-case scenario, a medication could interfere with the child's health, or the child's progress in behavioral therapies. So, while the current research into medications for the challenging topographies of ASD is inspiring, researchers have a long way to go to ensure that these medications are beneficial to and safe for those with these symptoms.

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ANTIPSYCHOTICS AND QT PROLONGATION

Antipsychotic-induced Long QT Syndrome, Torsades De Pointes,and Sudden Cardiac Death: A Review of the Literature

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Abstract

Antipsychotic drugs are essential for patients with various psychiatric disorders, such as psychotic disorders, as well as psychosis and bipolar mania. However, as with any medication, there are unwanted and sometimes dangerous adverse effects. Serious cardiac complications, specifically QT prolongation, could be associated with antipsychotics. This syndrome may potentially lead to a fatal arrhythmia, Torsades De Pointes, which may lead to sudden cardiac death. Special consideration should be taken by clinicians when prescribing antipsychotics to patients. This is a literature review of some of the recent studies discussing antipsychotic- induced long QT syndrome and Torsades De Pointes. Factors to consider when prescribing antipsychotics include, drug dosage and potency. Not only should the drug's potency as an antidopaminergic agent be considered, but more importantly, the potency of blocking the potassium channels, which are responsible for the development of long QT syndrome. The typical antipsychotic, haloperidol, and the atypical antipsychotic, ziprasidone, were found to be the biggest culprits in potentiating the aforementioned complications. Fortunately, drug-induced QT prolongation is curable by withdrawing the causative agent and replacing it with a safer option. It is hoped that this literature review will inform clinicians about effectively prescribing antipsychotics without the risk of developing long QT syndrome in their patients, hereby avoiding sudden cardiac death among patients under antipsychotics.

Introduction

Antipsychotic drugs are the first-line psychotropic medications for the treatment of psychoses (whether in psychotic disorders, major depression, or bipolar disorder) and disorders that fall under the psychotic spectrum in the fifth-edition of the Diagnostic Statistical Manual of Mental Disorders. According to a 2017 Medical News Today online article, it was estimated that about seven million individuals in the United States of America take antipsychotic medications for schizophrenia and other conditions (Sandoiu, 2017). Antipsychotics have increasingly grown in popularity in the US, especially after the development of atypical antipsychotics due to their limited extrapyramidal effects. While these drugs are designed to alleviate psychotic symptoms such as hallucinations, delusions, and disorganized thinking, among others, they also have numerous dangerous adverse effects. Those side effects range from neurological to renal and hepatic. However, the cardiovascular complications that arise from the use of these psychotropic medications are of particular clinical significance. Of these cardiovascular side effects, QT prolongation syndrome, is highly important. The prominence of this specific syndrome lies in the fact that, unlike many other cardiovascular complications, such as Coronary Artery Disease (CAD), this syndrome can result in sudden cardiac death. Therefore, it is vital for clinicians to be encouraged to monitor such a condition, which may, due to the use of certain drugs, lead to sudden cardiac death.

QT prolongation or Long QT Syndrome (LQTS) is an abnormal increase in the QT

interval. The QT is compromised of the QRST waves, which denote the electrical activity of the heart. This interval includes the QRS complex, representing ventricular contraction, and the T wave, which represents the ventricular relaxation. The interval itself is measured from the beginning of the Q wave to the end of the T wave in the electrocardiogram (EKG) paper. The results of the EKG are computerized and provided in the EKG paper as QT value in ms (milliseconds). Generally, a normal QT interval value is below 400 ms to 440 ms. However, women have a longer interval than men and therefore, what constitutes a prolonged QT differs between both genders (from males to females). Typically, males are said to have LQTS if they have a value over 440 ms, while women are diagnosed with the cardiovascular syndrome if they have a value of 460 ms or more (Johnson & Ackerman, 2009, p. 4). If individuals are diagnosed with LQTS, they are at a high risk of developing sudden and dangerous

abnormal rapid heart rhythm (tachyarrhythmia). According to the National Heart, Lung, and Blood Institute in Maryland, U.S.A (n.d.), pictures of LQTs-related arrhythmia often first occur during childhood, if the cause is genetic, and are manifested through unexplained fainting, unexplained drowning, seizures, and unexplained sudden cardiac arrest or sudden death (National Heart, Lung, and Blood institute, n.d.; Ackerman, 1998, p. 250). The rapid beating of the heart is responsible for the fainting, as the heart is not pumping enough blood to the brain. This deprives the brain of nutrients essential for healthy and optimal functioning, such as oxygen and glucose. The National Heart, Lung, and Blood Institute also state that sudden cardiac death is the first sign of LQTS in 1 out of 10 individuals (National Heart, Lung, and Blood Institute, n.d.).

LQTS is an "ion channel disease" of the heart (Ackerman, 1998, p. 250). It occurs as a

result of a disturbance in the ion channels in the cardiac cells (myocytes), which is responsible for coordinating the electrical system or signals through the cardiac cells. When the ion channels are disturbed, the time in which the electrical system of the heart requires to recharge after each beat is delayed (Cleveland Clinic, 2019).

Research suggests that most atypical antipsychotic medications have a better cardiac profile, while typical antipsychotics have been associated with numerous cases of QT prolongation syndrome (Dietle, 2015). Research also shows that psychotic patients on psychotropic drugs are more vulnerable to LQTS and sudden cardiac death than the general population (Vieweg, 2003, p. 205). However, it is hypothesized that certain drug properties and factors, such as dosage, potency, and the therapeutic range play an important role in increasing the liability of the development of LQTS and sudden cardiac death. Other minute factors could include gender and genetic predisposition. In other words, LQTS is not observed in every patient who is on antipsychotics.

This paper will explore the effects of antipsychotics, by class, as it pertains to QT prolongation syndrome (keeping in mind the major factors for consideration; dose and potency). Literature Review

As previously mentioned, antipsychotics pose a significant risk factor for QT prolongation. The clinical significance of LQTS due to antipsychotics lies in the fear of it leading to sudden cardiac death. Interestingly, due to the sometimes-fatal effects of these psychotropic medications on the heart, antipsychotics were frequently described as "quinidine-like" (Glassman & Bigger, 2001, p.1776), a heart medication used to treat abnormal heart rhythms, but paradoxically has been notably

associated with and causes deadly QT prolongation (Ackerman, 1998, p. 253).

One of the notable side effects of antipsychotics is tachycardia, an increase in heart rate. Antipsychotics are also risk factors of tachyarrhythmias (tachycardia and irregular heart rhythm), which may lead to a specific lethal rhythmic disorder of the heart. In other words, LQTS is itself does not cause sudden death, however, the real concern lies in the possible lethal development of Torsades de Pointes (TdP), a specific fatal arrhythmia (Ackerman, 1998, p. 253). TdP causes ventricular tachycardia and fibrillation, a shivering or incomplete contraction of the ventricles (Yap & Camm, 2003, p. 1363).

Multiple studies support the idea that the use of antipsychotics, regardless of the different classes, is associated with risk of QT interval prolongation. For instance, in a 2009 study by Ray, Chung, Hall, and Stein, a Tennessee Medicaid database from January 1990 to the end of December 2005, which included 93,300 individuals between the ages of 30 to 74 years, was utilized to examine and determine the incidences of sudden cardiac deaths among those who use typical and atypical antipsychotics. The study included the name of the antipsychotic prescribed, the dosage, and the duration used. Ray et al. (2009) found that both aforementioned antipsychotic classes were related to an increased (doubling) risk of sudden cardiac death compared to the general population who do not use these medications (pp.6-7; Shulman, Miller, Misher & Tentler, 2014). The negative effect of antipsychotics on the cardiovascular system is attributed to the pharmacokinetic and pharmacodynamic properties of the drugs.

Dose-dependency and Therapeutic Range

QT prolongation is dose-dependent. According to Jones, Campbell, Patel, Brunner, Shatapathy, Thomas, Staa, and Motsko (2013), the risk for cardiac mortality is almost directly proportional to dose levels. It was reported that the risk for cardiac mortality significantly increased when increasing the dosage of typical antipsychotics, although no similar pattern was observed for atypical antipsychotics (p.6). As a result, since a high dosage is associated with an increased risk of cardiac toxicity, LQTS, and TdP, typical antipsychotic drugs with a narrow therapeutic range should be avoided. Conversely, Jones et al. (2013) discovered that the highest increased risk for cardiac mortality with atypical antipsychotics was evident with low doses (p.6). The findings of this extensive study, regarding the indirect proportionality of cardiac mortality risk and

atypical antipsychotic doses, indicate that multiple factors, other than dose levels, must be considered. It is suggested that antipsychotic-induced QT prolongation does not only depend on dosage levels but also relies on the variations in the potency of each drug. This is especially true for atypical antipsychotics (Nachimuthu et al., 2012, p. 247)

Potency and the Therapeutic Range Potency is of higher priority than dose levels. It is important to recognize what is meant by "potency" in this case. An antipsychotic drug can be potent as a D2 (dopamine) receptor antagonist, however, it can have a lower, higher, or equal potency in blocking cardiac potassium channels, hereby affecting the QT interval. According to Shepard, Canavier, and Levitan (2007), numerous typical and atypical antipsychotic medications potently accumulate in the muscular tissue of the heart or the myocardium, aggressively inhibiting the cardiac potassium channels (pp.1263-1265). For this reason, the potency/efficacy of the drug itself is not the main concern. For instance, a particular antipsychotic may need a high dose to be effective (therapeutic dose), but its potency as a potassium channel blocker may be low, making it safer.

Furthermore, another factor to consider is the therapeutic range of the drug. It is possible that there may be a correlation between the therapeutic window/range and the development of LQTS, predisposing TdP. While it seems logical, as previously mentioned, to avoid antipsychotic drugs with a narrow therapeutic range, a drug with a wide therapeutic range can also be problematic, as seen with the atypical antipsychotic drug, ziprasidone.

Typical antipsychotics (First-generation antipsychotics)

Any drug that blocks ion channels, mainly potassium, poses a high risk of contributing to the prolongation of the QT interval.

For example, the first-generation highly neuroleptic antipsychotic, haloperidol, used to treat severe agitations and schizophrenia, is considered a powerful/potent blocker of IKr (cardiac potassium) channel and causes a 15 to 30 ms prolongation in the QT interval (Glassman &Bigger, 2001, p.1777; Nachimuthu, Assar and Schussler, 2012, p.247). Haloperidol, in particular, was implicated in severe and dangerous LQTS and numerous cases of deaths through TdP (Blom, Bardai, Munster, Niewland, Jong, Hoeijen, Spanjaart, Boer, Rooij & Tan, 2011, p. 4). Haloperidol was ranked among the top three drugs with cisapride (used to increase upper gastrointestinal tract motility), and the antihistaminic drug, terfenadine, in potency in blocking cardiac potassium channels (Saxena, Plessl, Linder, Windisch, Hohaus, Timin, Hering & Weinzinger, 2016, p. 5).

Both cisapride and terfenadine were banned due to their strong potassium channels blocking properties.

Another typical antipsychotic drug implicated with LQTS and TdP is chlorpromazine.

However, unlike haloperidol, chlorpromazine is a low-potency typical antipsychotic. This means that the clinician must administer a higher dose to achieve the therapeutic effect. Research shows that the risk of LQTS and TdP is only high when chlorpromazine is given in high doses (Wenzel- Seifer, Wittmann & Haen, 2011, p. 688). In a literature review on LQTS and antipsychotic drugs in psychiatric patients conducted by Zainnuddin and Zaini (2017), the risk of LQTS and TdP were discovered to be dose-related with low potency first generation antipsychotic medications. Those drugs were generally discovered to carry a higher risk than those with a high potency from the same class (p. 5). This aligns with the aforementioned studies discussing the dose- dependency of QT prolongation. Hence, it is advisable to avoid chlorpromazine for patients who need antipsychotics.

Atypical antipsychotics (Second-generation antipsychotics)

Although the atypical/second-generation antipsychotics are generally considered safer, and are therefore more popular, it is important to consider the pharmacokinetic and pharmacodynamic properties of this class of drugs. However, such properties cannot be generalized for an entire class, as each individual drug retains unique properties. The misconception that atypical antipsychotics are safer than typical antipsychotics is linked to their lower extrapyramidal effects and less severe adverse effects. However, a recent 2018 study about the effects of atypical antipsychotic drugs on QT interval in mentally ill patients by Aronow and Shamliyan, revealed a stronger relationship between the use of ziprasidone and the occurrence of LQTS and TdP, than that observed with typical antipsychotics notorious for resulting in sudden cardiac deaths due to TdP, such as haloperidol. Aronow and Shamliyan (2018) compared ziprasidone's effects on QT interval prolongation with placebo and haloperidol and found that the drug in question prolongs the QT interval by more than 30 ms. Not only that, but ziprasidone was also compared to olanzapine and risperidone and discovered that its power in prolonging the QT interval is also stronger than with the aforementioned drugs, despite them belonging to the same class (p.3) This can be attributed to ziprasidone's potency/strength in blocking the cardiac potassium channels

(despite its wide therapeutic range) (Shepard, Canavier & Levitan, 2007, p.1265).

On the other hand, Aripiprazole is considered a safer option for patients with mental disorders who require treatment with antipsychotics (Aronow and Shamliyan, 2018, p.15). A 2007 study comparing the potency of antipsychotics in blocking potassium channels revealed why that might be. Through clinical tests, it was discovered that aripiprazole is one of the less potent drugs, and no clinically concerning or important EKG changes were seen associated with its use (Silvestre & Prous, 2007, p.462).

Antipsychotics with highest LQTS rates

According to a nation-wide 2015 study (in which 17,718 patients participated) published in the Journal of the American Heart Association that explored the risk of ventricular arrhythmia and sudden cardiac death linked to the use of specific antipsychotic drugs, six antipsychotic medications were ranked the highest in causing the aforementioned consequences (Wu, Tsai, & Tsai, 2015, p. 5). Those drugs included, the typical antipsychotics haloperidol, procholorperazine, thioridazine, and the atypical antipsychotics, risperidone, quetiapine, and sulpiride. Furthermore, another study covering the mechanism of drug-induced LQTs and risk factor of TdP by Nachimuthu et al. (2012) revealed that the atypical antipsychotic that produces the highest LQTS was ziprasidone, while the lowest was olanzapine (p. 247). Additionally, The FDA-approved labeling on risperidone, quetiapine, and ziprasidone mentions QT prolongation as a "known action" of the drugs (Vieweg, 2003, p. 213). Finally, the atypical antipsychotic sertindole was pulled from the market after only two years of its creation, due to it being a high affinity antagonist of the cardiac potassium channel and potentiating LQTS, TdP, and sudden cardiac deaths (Rampe, Murawsky, Grau & Lewis, 1998, p. 286).

Conclusion

As previously established, the main concern with antipsychotic medications is that some of them have the tendency to inhibit and block the IKr channel, the potassium channel in the heart (Zolezzi, Cheung, 2019, p. 106). This leads to a syndrome called QT prolongation, which is a predisposing factor of a deadly ventricular arrhythmia called Torsades De Pointe (TdP). Drug properties, most importantly, the drug's potency

in blocking the potassium channel is of an important consideration for clinicians when prescribing antipsychotics to patients who need it.

According to a 2011 study about the risk factors and mechanisms of acquired LQTS, low serum levels of potassium increases the risk of drug-induced LQTS (Kallergis, Goudis, Simantirakis, Kochiadakis & Vardas, 2011, pp. 4-5). Additionally, there are multiple risk factors associated with developing LQTS that also need to be considered, because research shows that apart from drug exposure, most patients diagnosed with LQTS have at least one of the following risk factors; being female, having hypokalemia (low potassium level), congestive heart failure, high drug concentrations, hypomagnesemia (low magnesium level), and ion-channel polymorphisms (Kallergis et al., 2011, p. 4; Nachimuthu et al., 2012, p. 244). Other risk factors include drug-on- drug interactions. For example, clinicians should proceed treating patients who are already taking antiarrhythmic or antibiotic drugs (specifically azithriomycin) with extreme caution. This is because, not only do these drugs contribute to causing LQTS on their own but combining them with antipsychotics may result in TdP and sudden cardiac death (Nachimuthu et al., 2012, p. 245). Patient-education is also very important. Patients should be informed about any food or drinks that may interact with antipsychotics, such as grapefruit juice (Nachimuthu et al., 2012, p. 245). Genetic predisposition should also be accounted for. According to Nachimuthu et al. (2012), TdP tends to occur more than often in 5-20% of patients who already have mutations in certain genes that cause LQTS and are generally borderline LQTS in EKG (p. 245). Those particular patients tend to be poor metabolizers of CYP2D6 dependent drugs (most antipsychotics). Attention should be directed more towards white patients, who are considered poor metabolizers (Nachimuthu et al., 2012, p. 245). Also, any medical conditions known to be associated with hypokalemia should be addressed before prescribing antipsychotics. Such conditions include eating disorders, such anorexia nervosa and bulimia, or any conditions that cause excessive diarrhea or vomiting. Additionally, patients who have had family history of unexplained fainting and other symptoms previously discussed in this paper are more prone to LQTS and TdP as they also have a genetic predisposition. Furthermore, since the risk of LQTS increases with higher drug concentrations (Kallergis, et. al, p. 4), it is recommended to avoid low potency typical drugs, as higher doses are needed to achieve the desired therapeutic effect, which can lead to LQTS and TdP. Finally, genetic LQTS is incurable, but can be managed/treated, whereas acquired LQTS can typically be reversed and cured through discontinuing the causing agent

(the antipsychotic drug used). However, if the patient's condition seriously requires an antipsychotic, a clinician may have to contemplate prescribing a beta-blocker (such as propranolol), so long as it is not contraindicated, to further negate the cardiac effects of the antipsychotic drug.

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The Efficacy of Pharmacological Interventions in Treating Sleep Loss Amongst Elite Athletes: A Literature Review

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Abstract

Sleep deprivation and sleep disorders are responsible for a number of detrimental effects on mental and physical health. Though a large body of research exists on the issue, there is little evidence regarding the role of sleep deprivation in unique populations, such as elite athletes.

Elite athletes have several additional physical and cognitive demands that may be particularly reliant and influential on sleep. However, a large proportion of elite athletes report difficulties with sleep loss due to a host of factors, including practice times, travel, and season length. The increased demand for sleep, alongside accompanying sleep-inhibiting factors amongst elite athletes, suggests a need for interventions targeting sleep loss while limiting next-day adverse effects. This review investigates the efficacy of currently available pharmacological interventions in treating sleep difficulties in elite athletes. The results of this review provide further evidence concerning the need for pharmacological interventions that effectively treat sleep difficulties while reducing the presence and severity of next-day effects, generating better outcomes in performance and well-being among high-performance athletes.

The Efficacy of Pharmacological Interventions in Treating Sleep Loss Amongst Elite Athletes

Sleep is an essential physiological process essential to maintaining physical and emotional well-being and has been shown to moderate other vital processes such as immune functioning, emotion regulation, memory, energy balance, stress recovery, and metabolic functioning (Craven et al., 2022). Additionally, inadequate sleep can result in significant personal and societal burden, affecting interpersonal relationships, well-being, productivity, and safety (Haack et al., 2015; Gingerich et al., 2018). However, despite the known importance of sleep, nearly 45% of the Western adult population fails to obtain the recommended 7-9 hours of sleep per night (Adams et al., 2017). Certain populations, including military members, shift workers, and elite athletes, may be particularly susceptible to sleep loss and its effects (Craven et al., 2022).

Evidence suggests that a large proportion of high-performance athletes experience reductions in sleep quality and/or sleep quantity (Andrade et al., 2021), with 42% of collegiate athletes reporting poor sleep, 38% of athletes reporting fewer than 7 hours of sleep per night, and more than 50% endorsing symptoms of excessive daytime sleepiness (Mah et al., 2018). Several factors, including travel and jet lag, practice times, duration of both season and off-season, anxiety, and competition can affect an athlete's sleep patterns, consequently affecting athletic performance and health (Nedelec et al., 2018). Moreover, athletes often sleep worse during competition periods, particularly the night(s) prior to an important competition (Juliff et al., 2015). Research suggests that even one night of poor sleep in athletes can have several effects on performance, including reduced reaction times, reduced anaerobic performance, reduced muscle strength, and declines in cognitive processes such as visual tracking, focus, determination, and mood (Lee & Galvez, 2012; Juliff et al., 2015; Song & Severini, 2017).

These results point to the deleterious effects that sleep loss can have on performance in elite athletes; however, due to the complexity of sleep function, individual variability in sleep patterns, and the limited availability of athletes to participate in sleep studies, the effects of sleep loss on elite athletes remains poorly understood (Fullagar et al., 2015). This paper examines relevant literature regarding the efficacy of primary pharmacological interventions for treating insomnia in high-performance athletes and provides a critical framework for future research concerning

the assessment and treatment of sleep disorders in elite athletes.

Performance Measures

Performing a sport at an elite level introduces a number of stressors and lifestyle changes that can deliver a significant challenge to adequate sleep, including sport-specific factors (i.e., training, injury, travel, and competition), athlete-specific factors (i.e., individual versus team sport and endurance versus power athletes), and lifestyle/social factors (i.e., caffeine use, technology, and social media use) (Doherty et al., 2023).

The demanding nature of elite training can alter an athlete's circadian rhythm, affecting both sleep and wake states, subsequently increasing the risk of maladaptation and poorer performance (Watson, 2017). For example, Souissi et al. (2020) found that following partial sleep deprivation, exercise performance was reduced, and physical discomfort was significantly greater. Other studies have shown the adverse impacts of sleep restriction on athletes' anaerobic power, tennis serving accuracy, isometric force, perceived exertion, and cortisol levels (Charest et al., 2022). The results of these studies suggest that athletic performance depends on the regulation of sleep and wake states as aerobic, anaerobic, and cognitive performance change throughout the day following the body's circadian rhythms (Kutscher, 2019). However, further complicating the picture, sleep loss and circadian rhythm may have a variable impact on athletes based on the type and demands of the sport and may be altered by training volume and intensity, training timetable, and psychological stress of training. In a study conducted by Azboy & Kaygisiz (2009), the authors found a reduction in maximal exercise capacity resulting from sleep deprivation, with exacerbated effects in volleyball players compared to runners.

On the other hand, research suggests that adequate sleep can have positive effects on next-day performance, with additional research providing evidence for well-regulated circadian rhythms resulting in peak performance. For example, in a study focused on the effects of sleep extension in collegiate basketball players, the researchers found that sleep extension resulted in faster sprint times, greater shooting accuracy, improved vigor, decreased fatigue, and improved overall ratings of physical and mental well-being during practices and games (Mah et al., 2011). These results highlight the complexity of preventing and treating sleep loss in elite athletes as a summation of physiological, psychological, and environmental factors affect individual sleep patterns (Nedelec, 2018) that impact next-day performance outcomes.

Injury and Recovery

In addition to maximizing performance, adequate sleep remains essential to recovery and injury prevention in athletes. In a survey of almost 900 high-level athletes, sleep was consistently named as the single most important recovery tool, regardless of sex, sport, or level of competition (Venter, 2014). Adequate sleep can help induce recovery and repair injury; however, lack of sleep may interrupt natural repair processes making athletes more prone to injury. In one study, researchers evaluated the effects of sleep deprivation on muscle repair in mouse models. The researchers found that sleep deprivation reduced the critical protein synthesis necessary for restoring muscle damage (Yang et al., 2019). Further, lack of sleep has been associated with a range of inflammatory markers, including interleukin-6 and C-reactive proteins (Dzierzewski et al., 2020; Simpson & Dinges, 2007), that hinder muscle repair and injury recovery. Increased inflammation resulting from sleep deprivation may worsen injury severity and extend recovery time, with those sleeping fewer than 8 hours per night 1.7x more likely to sustain an injury than those who sleep more than 8 hours (Milewski et al., 2014). Consequently, sleep quality remains imperative not only for the athlete's success, but for their physical health and well-being as well. Psychological Effects

Previous studies demonstrate a bidirectional relationship between sleep, life stressors, and poor mood states (Lee et al., 2017), with insufficient sleep being associated with worse mood, an increased likelihood of developing a mood or anxiety disorder, and a heightened risk of suicidal ideation. In elite athletes, poor sleep quality resulting from intensive training and increased demand can lead to fatigue and mood changes, including anxiety, depression, and in severe cases, suicidal ideation (Montero et al., 2022). Prevalence of anxiety in adult athletes ranges from 7.1% to 26%, and depression ranges from 15.6-21% (Gouttebarge et al., 2015; Wolanin et al., 2015). In a study conducted on NCAA athletes, sleep disruption was consistently associated with suicidal ideation among college athletes, and 62.6% reported that their mental health symptoms hurt their athletic performance in the previous four weeks (Kern et al., 2017; Khader et al., 2020). Help-seeking behaviors among elite athletes are an additional barrier to treatment as athletes seek mental health treatment at lower rates than nonathletes, with the most significant barrier to seeking mental health treatment being stigma (Castaldelli-Maia et al., 2019). The NCAA has since developed an

initiative to support student-athlete mental health, complete with a "Mental Health Best Practices" consensus document outlining recommendations for addressing some of the core issues affecting student-athlete mental health. Recent revision of this document has added sleep hygiene as a core issue concerning student mental health.

Pharmacological Treatment for Sleep Disorders

Benzodiazepines

Benzodiazepines are a class of psychotropic drugs frequently used to treat anxiety and sleep disorders by dampening neuronal excitability via benzodiazepine receptors present in the central nervous system. Benzodiazepines facilitate inhibitory transmission by enhancing the effects of the chief inhibitory neurotransmitter GABA. As a result, benzodiazepines act as anxiolytic and hypnotic drugs, having proven short-term efficacy in personality disorder (PD), general anxiety disorder (GAD), seasonal affective disorder (SAD), and insomnia (Guina, 2018). However, these drugs can cause a wide range of central nervous system effects, including sedation, slurred speech, incoordination, amnesia, and a lessening of inhibitions (Peng et al., 2022). Research investigating benzodiazepine use in high-performance athletes suggests that benzodiazepines have little to no effect on sleep quality or quantity but can have residual adverse effects on next-day performance outcomes (Reardon & Factor, 2010).

Moreover, several associated side effects may prevent this drug class from acting as a first-line agent in treating insomnia in high-performance athletes, including drowsiness, lethargy, fatigue, and, in extreme cases, impaired motor coordination and addiction, all of which would likely impair athletic performance (Gratwicke et al., 2021). Zandonai et al. (2018) note that they have seen an increase in the number of requests for detoxification from severe benzodiazepine abuse, particularly among athletes. In one case, a 38-year-old professional cyclist was caught using illegal substances at an international race. The cyclist's medical history showed that he had begun using lormetazepam, a short-acting benzodiazepine, during the 2005 competition season to treat insomnia. To counter the drug's sedative effects, the patient, on training days, consumed high doses of caffeine and began using small amounts of cocaine (Zandonai et al., 2022). In another case, a female marathon runner also struggled with lormetazepam addiction after increasing her daily

benzodiazepine dosage to achieve better sleep and enhanced training performance (Zamboni et al., 2022). She was hospitalized for seven days to undergo benzodiazepine detoxification. These case studies highlight the importance of drug monitoring and emphasize the risk of addiction among athletes using benzodiazepines to combat sleep difficulties. Benzodiazepines may be effective for the short-term treatment of insomnia, but evidence remains scarce regarding the efficacy of long-term administration.

Non-Benzodiazepine Sedative Hypnotics

Sedative hypnotics are a newer class of nonbenzodiazepine hypnotics with similar mechanisms to benzodiazepines, but with greater specificity. Sedative hypnotics bind to one of three benzodiazepine receptors, thus enhancing the inhibitory effects of GABA with fewer side effects. Within this class of drugs, Zolpidem, Zaleplon, Eszopiclone, and Ramelteon have been FDA-approved for treating insomnia. Zolpidem, Zaleplon, and Eszopiclone are classified as shorter-acting nonbenzodiazepines and, contrary to benzodiazepines, show little effect on sleep architecture, resulting in less daytime fatigue, fewer cognitive and anxiolytic effects, and fewer risks for dependence and withdrawal (Baldwin et al., 2013).

In athletes, sedative hypnotics may be preferable for short-term insomnia and jet lag treatment. According to Baird and Asif (2018), nonbenzodiazepine sedative-hypnotics are favorable to athletes due to accessibility, effectiveness, and side effect profiles. Lee and Galvez (2012) support this claim, stating that hypnotic sleep aids reliably reduce insomnia secondary to jet lag, with Zolpidem likely being more effective than melatonin and placebo at counteracting jet lag symptoms. Specifically, short-acting agents (Zolpidem, zopiclone) are favored along with 8 hours of sleep prior to competition to avoid “hangover” effects and adverse effects on performance (Baird & Asif, 2018). Studies directly comparing benzodiazepines and nonbenzodiazepine hypnotics suggest that nonbenzodiazepines garner similar efficacy with fewer adverse effects than benzodiazepines and are likely the preferred pharmacological agent of the two for treating athletes with insomnia.

Other Sleep Aids: Antidepressants, Melatonin Receptor Agonists, Antihistamines, Dual Orexin Receptor Antagonists

Several additional pharmacotherapies are utilized to treat sleep disorders, including antidepressants, melatonin, antihistamines, and dual orexin receptor antagonists.

Antidepressants, like Trazadone, Mirtazapine, and Doxepin, improve sleep by obstructing neurotransmitter receptors that cause arousal (i.e., acetylcholine, serotonin, histamine, and norepinephrine) (Porwal et al., 2021), reducing alertness and promoting relaxation. Trazodone has been widely prescribed for off-label use as a sleep aid as it may alter sleep architecture in those suffering from insomnia; however, it should be used with caution due to the adverse events that may occur (Zheng et al., 2022). The inhibitory effects of antidepressants can lead to a range of side effects that may be particularly concerning to elite athletes, including daytime drowsiness, dizziness, headache, and decreased appetite (Cuomo et al., 2021).

The most common supplement athletes consume for sleep concerns is melatonin.

Melatonin use may be particularly warranted and effective in instances involving long-distance travel where multiple time zones will be crossed (Brauer, 2022). Additionally, compared to other prescription and OTC sleep aids, melatonin has demonstrated favorable efficacy and tolerability with few adverse effects. The most frequently reported adverse events are reductions in psychomotor and neurocognitive function or fatigue and excessive sleepiness (Foley & Steel, 2019). Most of these effects occur within a few hours of taking melatonin. However, there are some reports of residual effects on cognitive performance for up to seven hours after daytime ingestions, like impaired proprioception and balance, leading some to caution the use of melatonin in elite athletes until more is known about whether these residual effects are present in the morning after night-time ingestion (Atkinson et al., 2001). Melatonin is not the only medication prescribed with caution, as nearly all currently available agents for treating insomnia have received a "weak" recommendation in the clinical practice (Onge et al., 2022).

Antihistamines are common and readily available medications for those seeking over-the- counter treatments for sleeping problems. Antihistamines bind to histamine receptors, inhibiting the effects of histamine — a key neurotransmitter in wakefulness, thus inducing drowsiness. It is important to note that while antihistamines are marketed and often used as sleep aids, they are not generally recommended by sleep specialists and should never be used long-term as regular use may induce tolerance (Shirley et al., 2020). Additionally, over-the-counter (diphenhydramine) or prescription (doxepin) antihistamines can induce

sleep but may not improve sleep quality. These medications have also been reported to have residual morning grogginess and other effects (Bolin, 2019) and, thereby, may not be the best treatment for sleep problems in elite athletes.

A new class of medication, dual orexin receptor antagonists, are being investigated for efficacy and tolerability in treating insomnia as they have been found to have limited abuse liability, and their discontinuation does not seem associated with significant rebound effects (Mogavero et al., 2023). These drugs act on orexin neuropeptide receptors that stabilize wakefulness, specifically OX1R and OX2R receptors, inhibiting their effects and promoting sleep (Onge et al., 2022). Initial data also suggests that dual orexin receptor antagonists show little to no effect on next-day functioning (Gotter et al., 2013), a common issue found with other agents used to treat sleep disorders.

Limitations

Although there is significant research concerning pharmacological interventions for insomnia, several limitations exist, particularly concerning high-performance athletes. Most medication studies focused on insomnia have been performed with subjects from the general population. The few studies conducted with high-performance athletes generally focus on a small sample or case study, thus limiting the generalizability of the results. Further, it remains difficult to expand the results of these studies across sports as the factors associated with sleep loss vary amongst sport and athlete. The effects of these medications also depend on several factors, including dose, individual differences of the athlete, and the particular demands of the sport.

Another area of constraint concerns the ecological validity of measures. For example, evaluating carry-over effects through reaction time measures may not accurately depict these effects in sports. In other words, a simple reaction time task conducted in a lab may not realistically represent the response execution demanded for high-performance athletes, such as a major league catcher. Finally, there have been debates regarding psychiatric medications and sports.

Though FDA-approved psychiatric medications are not prohibited by the World Anti-Doping Agency (WADA), some argue that certain drugs may give athletes an unfair advantage, further complicating mental-health care among athletes where physical and cognitive demands may differ.

Conclusions and Future Directions

This review investigated the evidence surrounding medication use for treating sleep difficulties in high-performance athletes. High-performance athletes are subject to several potential sleep disruptions, including jet lag, travel times, competition, and practice schedules. These disruptions can affect multiple areas of an athlete's life, including athletic performance, psychological well-being, and injury and recovery. Thus, identifying and treating these disturbances as quickly and effectively as possible is imperative. Current literature surrounding the treatment of insomnia suggests that sedative hypnotics may be preferable to benzodiazepines, particularly among athletes, as hypnotics can reliably treat insomnia with fewer side effects.

Other options are available, including OTC medications; however, all current medications used to treat insomnia have potential next-day effects and varying levels of efficacy. Advances in interventions for insomnia and other sleep difficulties, such as the more recent research regarding dual orexin receptor antagonists, suggest potential treatments that mitigate the adverse effects of sleep deprivation with fewer carry-over effects. Future research concerning pharmacological interventions in high-performance athletes should continue to focus on reducing the presence and severity of these side effects without jeopardizing efficacy, consequently generating better outcomes in performance and well-being among elite athletes.

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Evidence-Based Pharmacological Interventions for Late-Life Depression (LLD): A Literature Review

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Abstract

The escalating prevalence of clinical depression among older adults is a pressing concern, emphasizing the need for effective psychopharmacological interventions. This review aims to evaluate evidence-based pharmacological treatments for late-life depression in elderly patients, synthesizing findings from published studies, systematic reviews, and treatment guidelines.

Despite the profound impact of depression in older adults, research on pharmacological interventions remains scarce. Key findings highlight the efficacy and safety of antidepressants as first-line treatments, and suggest potential benefits of augmentation with second-generation antipsychotics (SGAs). However, comparisons of the effectiveness of antidepressants in older adults remain controversial due to various factors including comorbid mental disorders, physical disorders, polypharmacy, drug interactions and other underlying characteristics unique to the patient. Challenges in diagnosing depression in elderly populations, including symptom presentation and comorbidity with physical disorders, emphasize the need for further research and a comprehensive approach to patient care in elderly populations.

Evidence-Based Pharmacological Interventions for Late-Life Depression (LLD): A Literature Review

Depression is recognized as the primary cause of disability worldwide, playing a significant role in the global burden of disease (Ustün & Kessler, 2002). The purpose of this review is to evaluate current evidence-based pharmacological treatments for late-life depression in elderly patients. This entails synthesizing findings from published studies, systematic reviews, textbooks, and treatment guidelines explicitly tailored for elderly patients experiencing late-life depression. Despite its prevalence and physiological effects, studies investigating the impacts of pharmacological treatment in elderly patients are limited. This review seeks to address this gap in the literature by providing an overview of the current recommendations of treatment as well as challenges in comparing the efficacy of medications for the elderly population, contributing to a more comprehensive understanding of pharmacological treatment options for older adults experiencing late-life depression.

Method

A systematic literature search was conducted using databases such as Google Scholar to identify relevant research articles. The search involved a combination of keywords such as ‘late-life depression,’ ‘elderly depression,’ and ‘geriatric pharmacological treatment.’ Inclusion criteria consisted of peer-reviewed empirical articles investigating evidence-based pharmacological treatments for late-life depression in elderly patients. In addition, systematic reviews, narrative reviews, textbooks, and treatment guidelines were also included to provide a comprehensive overview of the current literature. The publication date range for empirical studies specifically was limited to the last ten years to ensure the accuracy and relevance of the review.

Review of Literature

Burden of Depression

The prevalence of depression has significantly increased in the last decade (Necho et al., 2021), with only one-third of individuals with depression receiving formal mental health care, as reported by the World Health Organization (WHO, 2023). Globally, depression currently affects over 300 million individuals (Holger, 2019), and its economic impact in the U.S. accounted for more than $83 billion in costs in 2000 (Alan, 2010). It is worth noting that the economic burden has since increased and is reflected globally. Moreover, untreated major depression contributes significantly to healthcare costs, elderly patients would subsequently continue using unnecessary medical services and institutionalizations (Raue et al., 2014).

Depression also affects the physical and biological health of individuals throughout their lives, increasing the risk of cardiovascular disease and other debilitating physiological disorders (Marcus et al., 2012). The National Institute of Mental Health claims the the prevalence of major depression was around 8% of the U.S. population (National Institute of Mental Health, 2023).

The prevalence is significantly high among individuals aged 65 and older; a systematic review conducted a meta-analysis of 42 relevant studies and found up to 32% of older adults meet the criteria for clinical depression (Zenebe et al., 2021). Over 60% of suicides are among older adults, with the vast majority, around 85 percent, having an underlying psychiatric or physical ailment (Conwell et al., 2011). Furthermore, nearly 75 percent of older individuals who commit suicide had consulted with their primary care physician within a month, yet their symptoms were unidentified or left untreated (Raue et al., 2014). Factors as to why it can be challenging to identify depression in older adults will be reviewed. Nevertheless, these facts emphasize the need for effective treatment, an accurate diagnosis, and a timely intervention in geriatric treatment.

Evidence-Based Pharmacological Interventions for Late-Life Depression (LLD)

Late-life depression (LLD) is characterized by significant depressive symptoms in adults over the age of 60, who account for 30 percent of all prescription drugs consumed (Preston et al., 2021; Brender, 2021). The current literature summarizes selective serotonin reuptake inhibitors

(SSRIs) and venlafaxine and duloxetine (a selective norepinephrine reuptake inhibitor or SNRIs), along with the antidepressants bupropion and mirtazapine, as the first line of treatment for LLD, reflecting their efficacy in younger populations (Beyer, 2018; Kennedy, 2015; Preston et al., 2021). SSRIs are a class of medications that include: sertraline, fluoxetine, paroxetine, fluvoxamine, citalopram, and escitalopram. They have lower anticholinergic effects compared to older antidepressants like tricyclics and are thus well tolerated by patients with cardiovascular disease (Preston et al., 2021; Kennedy, 2015). It is preferred to use SSRIs due to their favorable side-effects profile, lower risk of overdose, ease of administration, and for their minimal dose adjustments (Beyer & Johnson, 2018; Preston et al., 2021). While fluoxetine is included in the list of recommended SSRIs, it is generally not recommended for elderly patients due to its long half-life and prolonged side effects (Preston et al., 2021; Kennedy, 2015). A meta-analysis investigated how older patients with severe to moderate depression took antidepressants compared with a placebo and revealed significant benefits in using antidepressants (Nelson et al., 2013). This analysis included seven trials with a big sample of 2283 elderly patients; it is essential, however, to consider potential limitations with post hoc exploratory analysis (Nelson et al., 2013). While these analyses may provide insight into the effectiveness of treatment outcomes, they may also overemphasize patient and depression characteristics that are unique to the study sample (Nelson et al., 2013).

Reviewing the literature regarding the comparative efficacy of SSRIs in depression treatment indicated a lack of significant differences among these medications. For instance, a meta-analysis of 15 randomized controlled trials conducted by Thorlund et al. in 2015 revealed no substantial variations in efficacy across different SSRIs. However, it is important to acknowledge that sertraline displayed the lowest risk of inducing dizziness, and that overall variations were associated with differences in side effects rather than efficacy (Thorlund et al., 2015). Adverse events reported in the study include raised blood pressure and prolonged QT interval using venlafaxine (Thorlund et al., 2015). Both duloxetine and venlafaxine have been associated with an increased risk of dizziness, which may increase the chances of falling, a concern that is detrimental for elderly patients to be aware of (Thorlund et al., 2015). Adverse effects need to be considered when customizing a treatment plan, particularly in older patients, to ensure the safety and efficacy of the intervention.

There is extensive research that suggests the potential benefits of

augmentation with second-generation antipsychotics (SGAs) in optimizing antidepressant response; however, the research is limited and unexplored in the elderly population. Investigating the potential effects of augmentation is imperative, considering that only half of elderly patients respond to initial treatment (Bruce & Sirey, 2018). A study was conducted to investigate the benefits and risks of augmenting or switching antidepressants in older adults with treatment-resistant depression (Lenze, 2023). Patients were randomly assigned to either augment their antidepressant with bupropion, switch to bupropion, or augment with aripiprazole (Lenze, 2023). The findings suggest that augmentation of antidepressants with aripiprazole significantly improved patients' well-being over ten weeks compared to switching to bupropion, and there was an overall higher incidence of remission observed (Lenze, 2023). However, notable limitations exist in this study.

Since there was no placebo group and patients were aware of their medications, patients may have potentially responded positively due to receiving two drugs rather than one (Lenze, 2023). Moreover, the dropout rate was high in their study, possibly due to adverse effects common with SGAs, which include sedation, dizziness, headaches, and constipation (Preston et al., 2021; Kennedy, 2015). These findings emphasize the need for further research in geriatric psychiatry to examine the suitability and effectiveness of augmentation with SGAs for late-life depression.

Challenges in Diagnosing Depression in the Elderly

Diagnosing depression in older adults can be challenging due to several factors, primarily due to the presentation of symptoms and comorbidity with physical disorders. Firstly, elderly patients may report psychiatric symptoms as somatic illness, potentially overlooking depression (Kennedy, 2015; Preston et al., 2021). For instance, older adults may describe complaints such as persistent pain, fatigue, gastrointestinal symptoms, and weight loss rather than expressing feeling lonely or sad (Kennedy, 2015). Furthermore, polypharmacy and potential drug interactions pose additional challenges in elderly patients as they are often prescribed multiple medications for various comorbidities (Kennedy, 2015). In addition, studies excluding patients with comorbid physical disorders significantly limit the generalizability of the results, considering the high prevalence of comorbidities among the elderly population (Kennedy, 2015). For instance, a study conducted by Rabin et al. in 2022 revealed a notable gap in the literature. An extensive systematic review

found no studies investigating pharmacologic antidepressant treatment effects in older adult cancer patients (Rabin et al., 2022). This discovery emphasizes the need for further research in geriatric psychiatry regarding physical disorders.

Moreover, comorbidities can substantially affect treatment outcomes that are often overlooked. A study investigating the association between obstructive sleep apnea (OSA) and the response to venlafaxine in older adults with major depressive disorders revealed significant differences in treatment outcomes (Waterman et al., 2016). Older adults with OSA exhibited higher rates of impairment in health measures and a lower likelihood of responding to venlafaxine compared to those without OSA (Waterman et al., 2016). Specifically, patients without OSA were almost twice as likely to respond to treatment as those with OSA (Waterman et al., 2016). These results are reflected in another study that claims OSA may be associated with a poorer response to treatment with SSRIs in a sample with a diverse range of ages (Roest et al., 2011; Waterman et al., 2016). Overall, potential solution to mitigate these challenges is by adopting a comprehensive approach when evaluating elderly patients. This approach involves considering their medical history, potential adverse effects of medications, awareness of physical disorders and comorbidities, and their potential influence in pharmacological treatment outcomes. Regardless of the chosen medication, safety and consideration of comorbidities precede differences in efficacy across age groups.

Conclusion

In conclusion, this review reveals the importance of comprehensive evidence-based pharmacological interventions for late-life depression in elderly patients. While antidepressants and augmentation strategies show promise, challenges in diagnosis and treatment continue due to a lack of studies. Future research should prioritize geriatric pharmacological interventions and how factors like physiological disorders and polypharmacy can influence the effectiveness of these interventions. Regardless of the chosen medication, prioritizing safety and consideration of comorbidities outweigh variations in effectiveness across all age groups.

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Practices and Efficacy of Self-Medication of Psychopathology with Psychedelic Substances

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Abstract

Psychedelics as novel treatment in psychiatry are receiving more attention, as popularity and awareness of psychedelic use, both recreational and therapeutic, is rising. However, current applicability of the potential held in controlled research and psychedelic assisted therapy is limited, due to the slow nature of research and the diminished accessibility of relatively uncommon treatment facilities or practitioners. Classic psychedelics, despite their controlled status, as well as Novel Psychoactive Substances can be relatively easy to obtain in comparison to authorized psychedelic therapy, facilitating widespread naturalistic use. Many people experiment with using psychedelics to self-medicate certain psychopathologies and seek spiritual growth. Because naturalistic use of psychedelics is already (and increasingly) common, it is important to understand the ways in which people are choosing to engage with these substances, especially when doing so as a form of therapeutic care.

The purpose of this literature review was to investigate the behaviors and efficacy of self-medication of psychopathology with psychedelic substances. The review focused on current literature reporting data of naturalistic use. A search was conducted using Google Scholar and PubMed with the key terms "self-medication," "psychedelics," and "microdosing," and the seven most relevant papers were selected. Reviews were excluded, as were studies on self-medication with psychedelics for pain or headaches. The review revealed that depression and anxiety were the disorders most commonly targeted by self-medicators, and LSD and psilocybin were the most commonly reported self- medication substances. Though self-medication commonly appeared as one of the top motivations for psychedelic use, its prevalence was inconsistent across studies. Efficacy in self-medication appeared greater than in traditional treatments via self-report, with some evidence that full psychedelic doses were better than microdoses. The review also revealed significant limitations across current literature, owing partly to study design and partly to naturalistic use behaviors, wherein composition, dosage, and frequency of substances employed were not reported. There was also a significant gap in evaluating which disorders respond best to psychedelic self-medication, and whether efficacy may be related to optimal pairings between given disorders and the selected psychedelic substance.

Practices and Efficacy of Self-Medication of Psychopathology with Psychedelic Substances

Novel use of psychedelic substances as treatment for various forms of psychopathology represents a relatively new frontier in psychopharmacology and mental health care, with significant increases in clinical trials and the advent of some dedicated treatment centers. At the same time, naturalistic psychedelic use rises. Increased interest in psychedelics is paralleled by a similar cultural awareness and shift towards spiritual development and self-actualization. While some psychedelic use has always been and remains recreational—and while normalization of psychedelics brings this use further into the mainstream—interest in healing or self-enhancement is also common motivation for psychedelic use. Increased awareness and conversation around these substances and potential effects, both in naturalistic and therapeutic contexts, has also led to appropriation for self-medication practices. The internet allows widespread access to anecdotal information about applications, acute effects, subsequent benefits, and dosing, via many fora such as Reddit, Bluelight.org, Shroomery.org, and Erowid.org, among others. Turning to online fora and self-medication is common in cases of treatment resistance under traditional medication or therapeutic modalities, and in circumstances of lack of healthcare access or with otherwise ineffective treatment conditions. As psychedelics grow within complementary and alternative medicine, it is important to understand the demographics, substances, settings, targeted conditions, and motivations of psychedelic self-medication. The purpose of this review is to identify trends in naturalistic use for self-medication of psychopathology and evaluate the efficacy of self-medication with psychedelics, including the balance of potential risks and health benefits, based on current literature. While chronic pain, migraines, and cluster headaches are also common targets for self-medication, in this review focus will remain on commonly targeted psychopathologies, such as depression, anxiety, and ADHD.

Motives

A study by Rolando & Beccaria (2019) reported on attitudes and motivations of Italian "psychonauts" (dedicated users of psychedelic and related substances, e.g., LSD, psilocybin, mescaline, DMT, LSA, MDMA, PCP, and ketamine) via online forum with respect to Novel Psycho- active Substances (NPS). Fora can be valuable to investigate emerging trends

in drug use, especially concerning self-medication and self-enhancement, as many members are engaged in intentional rather than recreational use. The authors found main forum topics to be NPS recipes and formulas, experience reports, and questions about effects of certain substances. Main motives were spiritual needs and learning, self-development, and self-treatment. Half the questions posted regarded solving physical or psychological health problems, with depression as the most common target. Previous studies were cited reporting correlation of psychedelic use with coping and spirituality and association with low levels of addiction potential. Traditional psychedelics generally are not habit forming and do not exhibit withdrawal symptoms; some forum members find prescription drugs more harmful due to unwanted effects and addictive potential, and often report them to be less effective, inadequacy of traditional treatment having spurred psychedelic use. This qualitative study was not specific at the sample level about which conditions and treatments were relevant in these views, though it does quote individuals—for example, one member reported prior treatment with three SSRIs, olanzapine, and valproate to no effect. Another common theme was the comparison of natural vs. synthetic substances, with natural substances said to have better profiles of health-related risks and outcomes as well as an inherent spiritual intelligence. Potential for relief by natural compound rather than synthetic prescription, on top of the connection to nature and a spiritual intelligence, may be attractive to many who self-medicate with psychedelics as antidepressant and anxiolytic agents. The authors note that forum members frequently report "bad trips" and lessons to be learned through them; however, skewed towards support for psychedelic use, they seem to overlook potential for exacerbation of existing psychopathology, particularly dissociative disorders. (Roland & Beccaria, 2019). It should also be mentioned that potential for psychosis and mania is present with psychedelics, especially in known schizophrenic and manic patients, and dissociative effects of some psychedelic substances can be unfavorable with unstable ego development. The authors warn against generalizing attitudes and practices across communities, whose modes of use (recreational, self-exploratory, self-medicating, self-enhancing) often reflect very different values and goals when it comes to psychedelics. The study is limited by lack of demographic information or generalizability of attitudes, and lack of statistics on prevalence of disorders and self-medication.

Self-Medication

Mason & Kuypers (2018) conducted a survey study to determine how commonly psychedelic users self-medicated and how effective they found it compared to traditional treatment. Prevalence of mental disorders in the sample of psychedelic users was higher than the general population (46%), but it unclear whether that was motivation for psychedelic use or whether psychedelic use was a contributing factor. Depression and anxiety were the most prevalent conditions in the sample, and 22.2% of the sample (N = 436) had used/were using psychedelics to treat a diagnosed mental disorder. Self-rated effectiveness (whether treatment worked, whether symptoms disappeared, and whether quality of life improved) was significantly higher for self-medication compared to traditional treatment offered by a professional (Mason & Kuypers, 2018). This study did not evaluate which mental disorders were most prevalent amongst self-medicators, nor whether any disorders were more or less likely to show greater improvements. It also did not distinguish between substances when determining efficacy compared to traditional treatments. It does, however, provide general evidence that psychedelic self-medication is experienced as more effective.

Kopra et al. (2023) similarly investigated self-treatment with the psychedelics LSD and psilocybin, looking at patterns of use, self-reported outcomes, and outcome predictors via data from the Global Drug Survey 2020. Of 113,284 responders, 10,268 self-treated with psychedelics in the past year (valid % = 13.8), with 3,328 using at least LSD and 2,494 using at least psilocybin. A final sample of 3,364 responders reported finding either substance most useful for self-treatment, 56.5% of whom were diagnosed with one or more mental health disorders, the most common being depression (40.2%) and anxiety (20%). Self-medicators reported positive outcomes across a 17-item scale measuring well-being, psychiatric symptoms, social-emotional skills, and health behaviors. One or more negative outcomes, reported at 22.5%, were more common than in clinical settings, but for most lasted 7 days or fewer. In general, high intensity of experience was related to higher outcome scores and longer duration of positive outcomes, with some difference between LSD and psilocybin: LSD was associated with lower outcome scores and a higher number of negative outcomes than psilocybin, the latter of which was related to the intensity of the experience. The study acknowledges limitations which are common in this area: expectancy effects and volunteer biases, unknown purity/accuracy of reported substances, and

unknown dosage/schedule of self-medication. They also note lack of information about co-administered substances or medications, lack of validated symptom scales, and potential recall bias in retrospective self-report (Kopra et al., 2023).

Microdosing

Motivations for microdosing are slightly different than those for general psychedelic use.

Andersson & Kjellgren (2019) conducted a qualitative study of microdosing discussions on YouTube, finding that self-treatment and self-optimization were the main motivations—certain lifestyle trends (e.g., biohacking, personalized medicine, and transhumanism) were prevalent. Given the absence in microdosing of alterations in consciousness, it is unsurprising that spiritual development is not an emphasis or the path to wellness. The most common disorder reported as a target for self-treatment was depression, though anxiety, PTSD, bipolar disorder, and substance-use disorders were all reported. Notably, this was the only study mentioning successful use of psychedelics for ASD, though in a limited anecdotal capacity. Regarding dosage, a common structure was the Fadiman protocol, wherein 1/10 of a recreational dose is taken every four days over a few weeks, though a recreational dose is not standardized. One account of self-medication reported discovering that a "loading phase" of sub-microdose levels until tolerance is developed prevented side-effect anxiety, similar to gradual titration strategies in traditional treatment (Andersson & Kjellgren 2019). This study was subject to the same limitations as the first: lack of specific demographic information or descriptive statistics on prevalence of disorders and self-medication (type, dose, and schedule).

Hutten et al. (2019) conducted an online questionnaire on self-rated effectiveness (SRE) of microdosing psychedelics, using the same effectiveness questions mentioned above. Similar to Roland & Beccaria (2019) and Mason & Kuypers (2018), Hutten et al. found that SRE of micro- dosed psychedelics was higher than conventional treatment options, across all three questions for ADHD and anxiety disorders and on one or two questions for depression, bipolar, substance-related, and personality disorders. However, they found efficacy of microdosing for depression and anxiety lower than with regular doses of the same substances. Still, they state that a controlled, clinicalexperience of full psychedelic doses is costly and impractical for many, especially if ongoing treatment is required, necessitating a better understanding of microdose

efficacy. They also suggest that daily or multiple times daily dosing of conventional medications can increase both costs and side effects, which along with unwanted effects (e.g., evening crashes with stimulant use) makes micro- dosing more attractive (Hutten et al., 2019). This study does not report on schedules or durations of the microdosing practices of the sample, it does not consider symptom or disorder severity and how that affects efficacy, nor does it compare efficacy based on psychedelic substance used, which may differ based on the substances themselves as well as congruence of the substance's mechanisms of action with the targeted condition.

While previous studies discussed have been observational or retrospective, Haijen et al. (2022) conducted a prospective naturalistic study on self-medicating with microdosed psychedelics to treat adult ADHD. Participants reported improvement in ADHD symptoms and an increase in general well-being after four weeks of microdosing. Notably, 20% of participants did not see improvements in ADHD symptoms, which may be attributable to inaccuracies in dosing, reasonable given the lack of control or monitoring of dosage and substance composition in naturalistic studies (Haijen et al., 2022) This was a short study, which did not provide information about total length of participants' microdosing, whether there is attenuation with long-term self-medication, or how long positive effects might persist after discontinuation. Like many studies, it did not report dosage or schedule of participants' microdosing, nor did it report any differences between substances utilized, which is especially relevant in a study of ADHD, as certain psychedelics (e.g., LSD) have more of a stimulating effect and may be potentially better suited for such a disorder.

Petranker et al. (2022) used the Global Drug Survey 2019, an earlier collection of the survey analyzed by Kopra et al. (2023), to evaluate benefits and challenges to microdosing LSD and psilocybin and to determine prevalence of testing when using psychedelic substances. The most common "approach-intention" (positive outcome sought by participant) was to improve mood and life satisfaction, while the most common "avoid-attention" (negative circumstance to prevent) was to escape negative feelings such as depression and anxiety. The most commonly reported benefit was improved mood and reduced depression symptoms. A further finding from this study was that illegality of substances was not perceived as a challenge within the sample (Petranker et al., 2022). Other studies indicate that illegality of traditional psychedelics causes people to turn to NPS (Soussan & Kjellgren, 2016), but this large worldwide study indicates that that is not the case as far as

microdosing populations are concerned. This result likely reflects selection bias, given that those using psychedelics are unlikely to hold illegality as a deterrent, while those using NPS in place of traditional psychedelics may well be deterred by illegality. The most concerning finding of this study was that only 37.88% of LSD users and 46.31% of psilocybin users tested their substances before consumption, and a small percentage of participants used a substance despite it being different than expected, while others "tested" by taking a full dose of the substance to observe effects (Petranker et al., 2022). This has obvious implications for safety of self-medication practices, and it limits results of self-report studies on naturalistic psychedelic use—because testing is uncommon, effects may be from substances other than those reported, simply because the participant is unaware of what they are actually consuming. This is not necessarily true of all communities. The psychonauts discussed earlier are more likely to have certainty about substances they are consuming—in fact, a motivation for seeking out NPS instead of established psychedelics is a sense of safety and confidence in the product you receive (Soussan & Kjellgren, 2016)—but those interested in NPS expect something other than the traditional substances; meanwhile, the NPS and illicit drug markets overlap, meaning many expecting traditional psychedelics may receive substances they did not intend to consume.

Discussion

Review of current literature shows depression and anxiety to be most commonly self-medicated with psychedelics, though wide ranging conditions and desires for spiritual-/self-enhancement are reportedly addressed successfully. LSD and psilocybin self-medication is reported most often. While proportions of users self-medicating are inconsistent, multiple studies report greater SRE in full and microdoses than in traditional treatment. Lack of data on microdosing dosage or schedule prevents suggestion of common practice, though 1/10 a "regular" dose every few days was mentioned.

Regardless of anecdotal reports and promising clinical research, most psychedelics are Schedule I substances, raising ethical issues regarding online fora sharing of trip reports, formulas and dosing strategies, and self-medication experiences. Most fora state interests in harm reduction, and users report senses of responsibility to share experiences to help others. Still, vulnerable individuals may be enticed to pursue illegal

action in the name of health, taking on physical risk in addition to legal, via dealer interactions, substance impurities or misrepresentation, and potential adverse effects, including exacerbation of psychopathology. Community fora may aid more informed decision making, but given the unregulated nature of illegal substances, one can only mitigate so much risk. Further, legal status may inhibit disclosure if acute medical treatment becomes necessary. That being said, these practices are not simply a passing fad, nor are they necessarily new as much as they are newly recognized. Many social factors—including many forms of lack of access to healthcare, distrust or lack of faith in the medical system, a sense of overmedicalization of psychological and spiritual issues, and insurance and cost difficulties—will continue to turn people towards alternative coping methods and wellness management practices. Self-medication and exploration with psychedelics are not going anywhere, leaving an ethical obligation towards research on effects, mechanisms, and best practices and communication of that research to those affected.

Much information is lacking from current studies, some of which is due to naturalistic context: Specific dosage information in naturalistic use, especially in microdosing, is unreported, and in many cases unknown even by users themselves. Frequency in both regular psychedelic doses and microdosing is also understudied or else underreported. As noted, few users test substances to confirm composition, further affecting validity of reported effects. Studies in which substance/dose could be confirmed and more information is collected on dosing frequency would greatly improve understanding of both practices and effects of self-medicating psychedelic use, as would investigating efficacy between specific substances for specific diagnoses. Another question future studies might include in surveys is how subjects arrived at self-medication and their particular practice (substance, dose, schedule)—not simply their motivation to engage but how they first identified the option. There is also a realm of study which may consider the spiritual healing element as self-medication in pursuit of general wholeness and the effects this may have on psychopathology.

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Psychotropic Medication Patterns and the COVID-19 Pandemic

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Abstract

The COVID-19 pandemic impacted several areas related to rates of mental illness and access to mental healthcare, including patterns in prescription and uptake of psychotropic medication. This literature review discusses eight peer-reviewed articles located through the PubMed database that analyze psychotropic medication patterns in relation to the timeline of the pandemic. Each of these is a large-sample, population-based cohort study, mostly accessing public health records, ranging from the whole country, to specific age ranges (youth and pediatric), and a university cohort. Five of the studies employed methodology that compared trends before and during the pandemic, while the remaining three looked at trends after the onset of the pandemic. Overall, data indicated patterns of increased prescription of psychotropic medications following the pandemic. Some contradictory findings and variations in the specific time following the onset of the pandemic may be indicative of low generalizability between global regions, due to factors like variable impact of the pandemic and differing access to healthcare.

Keywords: psychotropic medication, COVID-19, pandemic, mental health

The COVID-19 pandemic, beginning in March 2020, affected many aspects of healthcare and medication usage (Vindegaard & Benros, 2020). This includes an impact on patterns of psychotropic medication use, such as rates of prescription and uptake in various populations across different age brackets and countries. This paper reviews eight peer-reviewed scientific articles, found by a literature search conducted through PubMed, that each investigate the patterns of use of psychotropic medication related to the timeline of the pandemic. The literature mainly includes descriptive studies using large population-based samples that explore increases and decreases in psychotropic medication and prescription. Three of the included studies explore patterns following the pandemic onset, either in the immediate weeks and months during lockdowns, or in the years since. The remaining five articles include a comparative analysis of the change in these patterns in contrast to trends prior to the pandemic. It is important to understand how a global event like the COVID-19 pandemic may have brought changes such as increased prescription due to increased mental illness during lockdown, or decreased use due to reduced access. This paper begins with studies that compare psychotropic medication use before and during the pandemic, moving into those that look more in depth at patterns in the weeks immediately following lockdowns, and then looking specifically at youth, including college and pediatric populations. The setting of each study is different, including the United States (California and Wisconsin), Canada, South Korea, Northern Ireland, Finland, Denmark, and France.

Based in Northern Ireland, Maguire et al. (2022) made use of individual-level medication data from a population-wide prescribing database including information from 2012 to 2021 (n = 1,801,860) to explore the impact of the pandemic on uptake of psychotropic medication (including all medications classified as hypnotic, anxiolytic, antipsychotic and antidepressant medications). Using a time-series analysis, the researchers found that receipt of these medications followed a consistent upward trend since 2012, with uptake in March 2020 surpassing expected values. These trends returned to expected patterns by May 2020 for all categories except hypnotics, which remained higher than expected, particularly for those above 18 years, males, and those in rural areas. The researchers suggest that stockpiling of medications at the beginning of the lockdown is a likely explanation for the initial spike, but also conjecture that any increase in mental health morbidity was counterbalanced by lower access to medication, leading to the return to usual trends. The study had an overall robust methodology, with the sample including the

whole population of Northern Ireland, and additional stratified analyses of gender, age, household composition, area-level deprivation, and rurality (Maguire et al., 2022).

These results vary in different regions of the world. Leong et al. (2022) made use of administrative health data from Manitoba, a province in Canada, to longitudinally describe the incidence (new use) and prevalence (total use) of psychotropic medication use before and during COVID-19, from 2015 to 2020. In the first three months following in-person restrictions, they found a decrease in new prescriptions of anxiolytic and antidepressant psychotropic medications (n = 1,394,885). However, at the end of 2020, this was followed by an overall increased new use of antidepressants and antipsychotics, especially for females and those 40 years and older, with highest use in those 80 years or older (Leong et al., 2022). A major limitation of the data used both in this study and others included in this literature review is the potential gap between prescriptions provided and actual consumption of the medication by patients.

With somewhat contradictory findings, a cross-sectional investigation by Hirschtritt et al. (2021) analyzed patterns using data from the Kaiser Permanente Northern California electronic health records (n = 2,405,824). Over a period of 13 weeks following March 4, 2020, some shifts were observed: increased prescription fills for trazodone, decreased fills for benzodiazepines and hypnotics, and consistent fills for antidepressants. Ongoing prescriptions either remained stable or exhibited minor reductions lacking clinical significance, but relative rates of new prescriptions declined across various medication categories (Hirschtritt et al., 2021). However, the study lacked any examination of the pandemic's long-term impacts on these trends, and historical trends before 2019 were not considered. Another limitation to the generalizability of the study was the reliance on prescription data from only one insurer.

Looking at a narrower part of the population in a different part of the United States, Marconi et al. (2023) focused on college students at the University of Wisconsin-Madison, delving into mental healthcare prescriptions spanning from 2015 to 2021. Employing both cross-sectional and time-series analyses, the study found a surge in psychiatric medication prescriptions during 2020 and 2021, compared to the historical baseline average for the entire cohort. This study also found different patterns across different months in the year, with heightened prescription trends during April to May and September to December, suggesting an association between these increases and the academic calendar. Overall, a

consistent escalation in psychiatric medication prescriptions was observed over the years, with a significant spike during the pandemic era (Marconi et al., 2023). Potential impacts of university-associated factors, such as student relocation away from campus facilities to their homes, are a limitation in considering the direct impact of the pandemic on actual rates of prescription in this population, as students may have accessed medication prescriptions at other locations.

Other studies have also placed a focus on youth, ranging from children to young adults. Bliddal et al. (2023) conducted a register-based descriptive cohort study of all individuals in Denmark aged 5 to 24 years (n = 108,840). They found an increase in psychotropic medication use (antipsychotics, anxiolytics, hypnotics and sedatives, antidepressants, and psychostimulants) and both incidence and prevalence of some psychiatric disorders between March 2020 to June 2022. The most notable increase was among individuals aged 12 to 17 years, seen in both those with and without a psychiatric history in the previous five years. Though the Danish health registers provide a comprehensive data source, the researchers note that one of the limitations of the study is delays in updates to the register during the pandemic (Bliddal et al., 2023).

Focusing on a narrower age range in another Nordic country, Kuitunen (2022) examined the pediatric population of Finland. A quarterly analysis of psychotropic medication (psycholeptics, antidepressants, and psychostimulants) purchases for children aged 6 to 12 was conducted using data sourced from the Pharmacy Register (n = 402,091). A comparative assessment was made between the first (April 2020 to March 2021) and second (April 2021 to March 2022) years of the pandemic to a previous reference year (April 2019 to March 2020). The study revealed an uptick in psychotropic medication use during the pandemic, particularly in the second year. Notable increases were observed in antidepressant and psychostimulant purchases, with no significant change noted for psycholeptics (Kuitunen, 2022). A limitation of the study is that due to the unavailability of individual-level data, distinguishing between incident and prevalent cases was not feasible.

In another European region, Valtuille et al. (2024) conducted a cross-sectional study analyzing all psychotropic medication prescriptions (antipsychotics, anxiolytics, hypnotics and sedatives, antidepressants, and psychostimulants) dispensed to individuals aged 6 to 17 years in France from 2016 to 2022 (n = 8,839,143). The study employed an interrupted time-series analysis, revealing steady and persistent increases in prescription rates for all psychotropic medication categories following the

onset of the pandemic. Apart from psychostimulants, the prescription rates for all other psychotropic medications exceeded expected rates. This was more significant with adolescents than younger children. The researchers suggest this is in line with the escalating prevalence of mood and anxiety disorders within the pediatric population, exacerbated by the pandemic increasing rates of these disorders (Valtuille et al., 2024).

Looking at the association between an aspect of the virus itself and psychiatric care, Kim et al. (2022) conducted a population-based cohort study using National Health Insurance claims data to examine the trends of psychiatric visits and medication prescriptions (antianxiety, antidepressants, sedative-hypnotics, and antipsychotics) specifically among individuals tested for COVID-19 in South Korea (n = 212,678). The study observed a peak in psychiatric visits for this population in March, with a statistically significant increase in psychiatric outpatients among patients without pre-existing mental illness during the pandemic. Moreover, psychiatric medication prescriptions also peaked between March and April 2020. The researchers highlighted the heightened need for psychiatric care among those who tested positive, and suggested this may be due to factors such as increased isolation, stigma, fears, and uncertainty prevailing during the early stages of the pandemic. Notably, South Korea, the second most infected country at one stage of the pandemic, implemented rigorous public health measures, the timeline of which aligns with the trends found related to the psychiatric visits. The focus solely on individuals tested for COVID-19 could indicate a potential correlation with the extended quarantine periods and isolation they may have experienced. A limitation of the study is that it captures only the early phases of the pandemic (Kim et al., 2022).

Overall, most of these studies indicate an upward trend in the prescription and uptake of psychotropic medication during and following the pandemic, but it is evident that these trends vary based on a number of factors. It is notable that though these studies had huge samples, each of them was limited to a specific population – either a country, a region, university, or healthcare-related group. Some of the differences and contradictory findings between these studies could be related to factors such as whether the healthcare was publicly funded or not, the significance of the impact of COVID-19 on the region (including factors such as the total number of cases, number of waves, or length of lockdowns), the gap between the number of prescriptions and the actual use of the medication, and so on. The variations in these psychotropic medication related rates remain vast across different regions of the world due to disparities in

access and care, and governmental responses to the pandemic also varied, indicating that these trends cannot be generalized between groups. However, the overall trend in all of these studies, to varying levels and with slightly different patterns, indicates increases in psychiatric medication prescriptions beyond expected values. This highlights an area of research with great future scope and implications for future global events that are similar to the COVID-19 pandemic, to begin more closely examining how specific factors influence these trends, how these further influence mental health outcomes, and to use this information to be better prepared and able to respond in the future.

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Exploring Non-FDA-Approved Administration Routes of Ketamine for Treatment- Resistant Depression

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Abstract

The psychedelic drug esketamine has been FDA-approved for treatment-resistant depression, but only via intranasal administration. This method is effective, but it presents a high cost to patients. The purpose of this review is to examine the efficacy and utility of non-FDA-approved routes of administration of ketamine for treatment-resistant depression. A literature search was conducted, and recent investigations of intravenous, intramuscular, oral, and subcutaneous administrations of ketamine were included. Notable advantages of each respective administration route were flexibility of dosing, lower cost, convenience, and high drug bioavailability. Studies across the administration routes utilized different administration schedules, doses, and depression severity measures, making it difficult to claim one method as superior. These non-FDA-approved methods may be suitable in some cases of treatment-resistant depression and should continue to be scientifically evaluated.

Keywords: ketamine, treatment-resistant depression, administration routes, FDA approval

Ketamine is a psychedelic drug that acts as a glutamatergic n-methyl-D-aspartate (NMDA) receptor antagonist in the brain (Ahuja et al., 2022). In addition to its anesthetic and analgesic properties, it has the potential to produce dissociative sensations and hallucinations. Moreover, it has begun to show promise as a rapid adjunctive treatment in treatment-resistant depression in the form of esketamine, or Spravato. Spravato, an intranasal (IN) spray, has been FDA-approved to treat treatment-resistant depression when combined with an oral antidepressant. This method is effective at reducing depressive symptoms and suicide risk, but it is costly, with a price tag of $5,664-$8,142 in the first month alone (Bahr et al., 2019). Thus, there have been ongoing studies of the safety and efficacy of alternative administration routes of ketamine. The aim of this brief review is to explore non-FDA-approved routes of administration of ketamine in treatment-resistant depression and to evaluate the advantages and considerations of these administration forms.

The most front-running administration route of ketamine is intravenous (IV) (Ahuja et al., 2022). The administration schedule is 0.5 mg/kg, given slowly over a 40-minute interval (Phillips et al., 2019; Marcantoni et al., 2020). This flexibility of pacing is useful because delivery can be adjusted mid-administration based on a patient's unique experience of side effects. Clinical response, defined as a 50% reduction in depression scores relative to baseline, has been achieved in 36.45-41.48% of patients within 24 hours and 47.55% of patients within 2- 7 days (Marcantoni et al., 2020). It remains as effective when given thrice weekly for two weeks. There is a risk of transient side effects such as hypertension, dizziness, and dissociation, although these effects rarely lead to adverse events and are comparable to those experienced in IN ketamine (Phillips et al., 2019; Cavenaghi et al., 2021). Further, it is still very expensive; the patient is expected to pay $500-$1000 per infusion (Bahr et al., 2019).

Intramuscular (IM) injection of ketamine has been examined as an alternative to IV ketamine because of its comparable efficacy with time and cost advantages. IM ketamine is typically injected in the upper arm at 0.5 mg/kg, but it is effective for some at only 0.1 mg/kg and can be increased above 0.5 mg/kg if a patient does not demonstrate improvement (Thase & Connolloy, 2023). IM administration affords a stable absorption rate and high bioavailability due to the drug's direct entry through muscle, bypassing first-pass metabolism (Tham et al., 2022).

IM ketamine has demonstrated a 47-55% reduction in Patient Health Questionnaire-9 (PHQ-9) depression scores after 6 injections within 1

month (Ahuja et al., 2022; Bonnett et al., 2021).

From a technical aspect, IM administration is faster-acting and less expensive compared to IV administration because it does not require extensive medical tools, such as an IV pump (Ahuja et al., 2022). The estimated wholesale cost of ketamine solution for injection is $2.30, a much lower administrative cost than both IN and IV ketamine (Bahr et al., 2019). The lower cost makes treatment more accessible to groups with lower average income. However, like IV ketamine, IM ketamine must be administered in a medical facility (Thase & Connolloy, 2023).

Oral ketamine is perhaps the most convenient method of administration; however, it is far less studied than IV and IM ketamine. It can be administered as a one-off treatment, intermittently for 3-6 weeks, 3 times per week, or even 2-3 times per day at 2.0-2.5 mg/kg (Andrade, 2019). It is somewhat effective, demonstrating a 38% score reduction on the Montgomery-Asberg Depression Rating Scale (MADRS) when administered three times per week in liquid form (Domany et al., 2019). While the first dose must be administered in a medical setting to evaluate individual reactions to the drug, once safety has been established, it can be self-administered at home, something no other administration route can offer. Oral ketamine is far less expensive than IN and IV ketamine, although its exact cost to patients is unclear. One of the biggest challenges of oral ketamine is its diminished ability to reach systemic circulation. Because orally administered drugs must be metabolized before reaching the bloodstream and NMDA receptors, there is a potential for degradation of the drug's therapeutic agent. To compensate, the oral ketamine dose is higher, which can lead to an increased risk for negative side effects caused by excess amounts of a residual ketamine metabolite, norketamine (Andrade, 2019).

Subcutaneous (SC) ketamine is rarely studied compared to the other methods, but preliminary studies demonstrate high success and low side effects. It is administered in the abdomen or upper arm starting at 0.1 mg/kg, but it can be increased depending upon patient response. Like IM, SC administration optimizes absorption rate and drug bioavailability (Tham et al., 2022). It is generally effective, with 43.75-80% of individuals achieving clinical response on the MADRS within 4 doses (Cavenaghi et al., 2021; Tham et al., 2022). SC ketamine offers a very low cost to patients, with two doses costing $2.70. Furthermore, the side effects are transient like in IN and IV ketamine (Cavenaghi et al., 2021). There are few negative considerations of SC that have not already been mentioned.

Overall, it appears that alternative routes of administration of

ketamine may be appropriate for treatment-resistant depression. Among these routes, the highest reduction in acute depression has been demonstrated in SC ketamine (Tham et al., 2022), while IV ketamine may be best for maintenance treatment (Phillips et al., 2019). IM and SC ketamine optimize ketamine's bioavailability at the lowest cost to patients (Tham et al., 2022; Ahuja et al., 2022; Andade 2019; Cavenaghi et al., 2021). While oral ketamine offers the most convenience because it can be administered at home, it is associated with the highest risk of side effects because of its higher dose (Andrade, 2019). The selected studies utilized variable measures to track depression improvement, such as the MADRS and the PHQ-9, which may undermine the reliability of a conclusion about the suitability of one administration route over another. These non-FDA-approved administration routes of ketamine should continue to be explored as viable options for treatment-resistant depression.

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Melatonin for Elite Athletes

Efficacy of Melatonin as a Sleep Aid for High Performance Athletes: Effects on Mental and Physical Performance

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Abstract

The importance of sleep in maintaining optimal health is often not stressed enough. Sleep regulates many physiological functions of the body, and a disruption in sleep may cause a wide range of problems from metabolism dysfunctions to adverse cognitive effects or disturbance in cognitive functions, and in extreme cases, death, due to an increased risk of cardiovascular disease. High-performance athletes are specifically susceptible to suffer from sleep problems due to both physiological and environmental factors. Certain metabolic differences in athletes may be responsible for depleting certain elements such as phospholipids from the blood, which negatively affects sleep. Moreover, athletes are more prone to Gastroesophageal Reflux Disease (GERD), which has been implicated with sleep disturbances and deprivation. On the other hand, environmental factors include their overall lifestyle, which makes them also more susceptible to pain, and therefore, more restless. High-performance athletes are also more likely to be exposed to nocturnal light, which depletes melatonin, the sleep hormone; and in a vicious cycle, sleep deprivation causes further depletion in the production of this hormone. Special attention should be given to studying this population, not only due to their increased risk factors, but also due to the effect of the depletion of melatonin on their performance. Melatonin helps with muscle and brain growth and is a naturally occurring hormone but is easily depleted by the aforementioned factors. Melatonin dietary supplements have success with athletes as a sleep aid. This is mainly due to its low toxicity, and no exhibited risks of abuse, tolerance, or dependence. Melatonin, like sedative-hypnotics, are best ingested 8 hours before an event to ensure strong physical and mental/cognitive performance. However, research still lacks in this area with this particular population and the long-term use of melatonin has never been addressed. It is hoped that this paper will shed light on what little literature there is about the efficacy of melatonin as a sleep aid for athletes and its physical and cognitive effects. Perhaps this paper may give ideas or suggestions for the need of more research in this topic.

Introduction

While it may be tempting for individuals to skip a few hours of sleep to catch up on work, it is important to realize that sleep deprivation, disruption, or problems can negatively affect health on multiple levels. Sleep problems can arise from a disturbance in either quantity or quality of sleep. Sleep plays a pivotal role in maintaining optimal brain or cognitive and physiological functions. In a 2017 nonsystematic literature review examining the short and long- term health consequences of sleep disruption conducted by Medic, Wille, and Hemels, it was revealed that a general and health-related reduction or diminishment in the quality of life, attributed to deficits in memory, behavior, performance, and cognition, is a short-term health consequence of sleep disruption (p.151). On the other hand, long-term consequences ranged from health problems (increased risk of hypertension, decrease immune function, cardiovascular disease, metabolic syndrome, diabetes, and cancer, among others) somatic problems (pain, headache, and abdominal pain), psychosocial problems (mood disorders and emotional distress, and diminished performance specifically in a study of 135 otherwise healthy children) (Medic, Wille & Hemels, 2017, pp.151-156). In addition, Alhola and Polo-Kantola (2007) found that sleep deprivation affects a wide range of cognitive domains, such as attention (specifically vigilance but also auditory and visuo-spatial attention, and reaction speed and lapses), working memory (long and short-term), decision-making and critical-reasoning, and response-inhibition (pp.553-556).

High-Performance Athletes: Significance

Keeping this in mind, high-performance or elite athletes are an important population to consider. Sleep deprivation, disruption, and/or problems can induce devastating consequences and adverse effects for this group of athletes in particular. Other than the aforementioned effects, sleep for athletes is of additional and particular importance. This is because, sleep helps, not only with cognition, but in tissue repair and recovery, which ultimately affects performance (Dohery, Madigan, Warrington, and Ellis, 2019, p.4). Furthermore, according to doctor Halson (2019), with athletes, not only does sleep deprivation cause a reduction in performance, learning and cognition, but also in susceptibility to weight gain (due to appetite regulation disturbances) and reductions in immune function, as well as an increased risk of injury, which is further aggravated

by the inability to adequately recover in a timely manner. In an article published in the health, nutrition, and fitness sciences website Isagenix Health, Colgan (2014) found that sleep deprivation was responsible for a devastation in performance with athletes, significantly reducing peak power in cycling, causing marked declines and reduction in knee extension, leg press, bench press, and dead lift strengths, as well as a significant reduction in sprinting speed and endurance performance

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Risk Factors: Physiological and Environmental

As previously mentioned, almost every individual is at risk for developing sleep problems. However, high-performance athletes commonly face this problem. This is mainly due to physiological factors that characterize them. Furthermore, environmental and lifestyle factors also play a role in attributing to athletes' sleep problems. A recent 2018 study comparing metabolic profiles of high-performance athletes from different sporting backgrounds conducted by Al-Khelaifi and colleagues shed light on some of these physiological factors that differentiate this group of athletes from other groups and non-athletes. The comparison was done through a metabolic profiling of serum samples from 191 athletes, in which a total of 743 metabolites were analyzed. Of these metabolites, high-performance athletes displayed a marked decrease in diacylglycerols, and a marked increase in the levels of phospholipid metabolites (Al-Khelaifi et al., 2018, pp.1-7). These findings are noteworthy because an increase in phospholipid metabolites suggests an overall reduction in the level of phospholipids in the blood. Phospholipids play a vital role and is a main element in the induction of sleep. As exhibited by the findings, not only is sleep deprivation secondary to high metabolism of phospholipids, another important metabolite, diacylglycerol, is implicated. Diacylglycerol metabolite is considered by numerous professionals to be a cross-species marker of sleep debt (Weljie et al., 2015, p.2569). In this similar study to Al-Khelaifi, Welijie et al. (2015) measured the levels of diacylglycerol in rats and humans following chronic sleep restriction. According to the findings, a significant depletion in the quantity of the metabolite diacylglycerol was witnessed in both subjects (rats and humans) (p.2569). Moreover, athletes have another risk factor that contributes to sleep deprivation. High-performance athletes are reported to have a higher incidence of Gastroesophageal Reflux Disease (GERD) than their non-athletic counterparts (Peters and Moeller, 2004, p.107). A link has been found with the intensity of exercise in an athlete and gastroesophageal

reflux, which can be said to be a directly proportionate link. In other words, as the intensity of an exercise increases, so does GER (Peters and Moeller, 2004, p.107).

Interestingly, GERD has also been found to be associated with sleep disturbances. Jung, Choung,

and Talley (2010) discovered that there is a causal link between the disease and sleep disturbances and that this may also be "bidirectional" (p.22). In the literature review, it was also reported that at least 50% of those suffering from sleep problems have comorbid conditions, with GERD being specifically high in those who suffer from chronic insomnia (Jung et al., 2010, p.23).

Finally, environmental and lifestyle risk factors in athletes include their demanding schedules and increased stress, both physical and mental. To further clarify, high-performance athletes experience restrictions and stressors on personal life, in which their lifestyle poses a challenge to sleep due to the, as previously mentioned, physiological and psychological demands, as well as the heavy competition and training schedules (Nedelec et al., 2018, p.1). Furthermore, disturbed sleep has long been associated with chronic pain. Due to the busy schedule of athletes, with training, competition, and injury, pain may be experienced. Although evidence is scarce at this point, Dijk (2010) suggests that due to this, athletes may have lower sleep quantity and quality than the general population (p.24). Also, in a 1981 study in which Shapiro, Bortz, Mitchell, Bartel, and Jooste recorded sleep on six athletes (for four consecutive nights) after completing a 92-kilometer marathon, results showed that sleep was prominently affected and decreased throughout these nights. However, the greatest wakefulness was on the night of the marathon, in which the culprit was suggested to be muscle pain (pp.1253-1254).

Moreover, Nedelec et al. (2018) also identified "social jet lag," due to the specificity of the aforementioned schedules, to be the most influential factor resulting in lack of or inconsistency of sleep. This, in addition to the extensive and increased exposure of electric light and media devices in this particular population compared to others, undoubtly contributes to lack of sleep and sleep disturbances (pp.1-2). An increased exposure to light is one of the factors that affect melatonin, which leads us to the next point; melatonin and its importance and implication in sleep and functioning.

Melatonin, Suppression of Secretion, and Melatonin Supplements

Melatonin is a naturally occurring endogenous hormone in the body. This hormone is stored and secreted by the pineal gland and demonstrates sedative effects, making it an influencer of sleep facilitation and core temperature changes, which also affect and improve sleep (Halson, 2014, p.19; Baird and Asif, 2018, p.36; Doherty, Madigan, Warrington, and Ellis, 2019, p.6). It also promotes sleep through vasodilation (Baird and Asif, 2018, p.36). To further explain, melatonin acts as a regulator for sleep and wake cycles, energy, muscle growth, brain growth, and body fat (Colgan, 2014), all of which are essential for top athletic recovery and performance. According to Colgan (2014), these roles of melatonin make it the "largest control system" in human physiology. Intriguingly, the secretion of melatonin is known to be suppressed by night-time exposure of lights (even if it is dim), and prolonged use of electronic devices (you and your hormones, 2018), a major risk factor with athletes, mentioned in the above paragraph. Furthermore, lack of sleep (restricting to six hours a night) also contributes to the decreased secretion of melatonin (Colgan, 2014), which may result in a non-ending and dangerous cycle.

Melatonin supplements exist and can therefore be used as a sleep aid for athletes. The purpose of this paper is to discuss the efficacy of melatonin supplements as sleep aids with high- performance athletes. Melatonin's mechanism of action, including its pharmacodynamics and pharmacokinetics will be very briefly discussed, as well as its advantages, disadvantages and side effects, and its effects on mental and physical performance, as it pertains to athletes. Also, what is missing in research and information about melatonin will be considered. Finally, and as a conclusion, recommendations and suggestions will be made to aid in finding a possibly more efficient sleep aid for high-performance athletes.

Melatonin Reduction Dangers in High-Performance Athletes

The significance of sleep and the implications of lack of sleep, specifically with those at a higher risk of sleep problems, high-performance athletes, has been established. In addition, the role of the hormone melatonin in healthy and adequate sleep, and its importance in major aspects of human physiology, including energy, and muscle and brain growth, among others, has also been recognized. It is now important to understand the dangers posed by the reduction or depletion of melatonin. Colgan (2014) explains that inflammation and C-reactive

proteins significantly rise with low melatonin levels and poor sleep, while hormonal rhythms decline causing impaired immunity. This further supports the fact that athletic performance can and will be severely hindered due to impaired recovery. Furthermore, cortisol (the stress hormone) rises and testosterone, as well as other growth hormones declines, with the decrease of melatonin levels, causing muscle loss and fat gain in athletes, which cannot be corrected or controlled by diet or training (Dattilo, 2011, p.221), making it counterproductive to overall athletic performance.

Melatonin as a Sleep Aid for High-Performance Athletes

In a 2018 clinical review by Baird and Asif regarding medications for sleep in athletes, it was stated that melatonin and nonbenzodiazepine sedative-hypnotics have long come into favor for athletes (due to accessibility, side effect profiles, and effectiveness), with the former described as the most common sleep aids recommended by physicians (p.36).

However, it is important to mention that literature about the efficacy of melatonin in managing sleep problems for athletes specifically is somehow scarce. Yet melatonin has been shown to be effective with elite or high-performance athletes in combating jet lag, as melatonin has been found to be beneficial in "resetting" sleep cycles (fatiguescience, 2017; Lee and Galvez, 2012, pp.213-214). However, articles published in the medical website Mayo Clinic suggest that melatonin supplements may also be helpful in the treatment of sleep disorders, specifically delayed sleep phase, as well as providing relief from, not only jet lag, but also insomnia (Bauer, 2017). Moreover, Atkinson. Drust, Reilly, and Waterhouse (2003), propose that the administration of exogenous melatonin (in the form of supplement pills, for example) leads to "hypnotic and hypothermic responses" (p.809), which may lead one to further believe that it does somehow affect and help with sleep deprivation. On the other hand, it is important to understand that melatonin generally changes or alters timing of sleep (tricks your brain into thinking it is night time), therefore helping in regulating sleep, while hypnotic medications rapidly prompt and prolong sleep (Bartle & Wheeler, 2015, pp.19-21).Mechanism of Action

Electrophysiological experiments with animals have shown that melatonin displays "GABA-like" effects (Zhang et al., 2017, p.2232). Through treating rats with melatonin, Zhang et al. (2017) also found that melatonin reversed the down-regulation of GABA alpha-2 receptor

expression in the rats' amygdala (p.2236). GABA is an inhibitory neurotransmitter in the central nervous system (Gottesman, 2002, p.231) and therefore, an increased level of GABA will counteract glutamate, causing sleepiness. An earlier study by Cheng, Sun, Ye, and Zhou's (2012) on the effects of melatonin on rats also supports this, as it was discovered that melatonin enhances the natural inhibitory function of the GABAergic system, which also may provide clues for some neuroprotective properties of melatonin (p.177). Per Zhang et al.'s (2017) findings support melatonin's role in weakening the up-regulation of glutamate. Therefore, it was postulated and proven through the study of melatonin's mechanism of action in rats that melatonin maintains the "balance" between glutamatergic and GABAergic transmission (Zhang et al., 2017, p.2232), consequently effectively aiding in sleep.

Advantages of Melatonin

It has been established throughout various studies and literature that the ingestion of melatonin induces sleepiness (Tordjman et al., 2017, p.436), therefore, if it is being taken as a sleep aid, it achieves its desired therapeutic effect. Several studies, including the meta-analysis by Brzezinski, Vangel, Wurtman, Norrie, Zhdanova, Ben-Shushan, and Ford (2005) on the effects of exogenous melatonin on sleep indicate that melatonin effects numerous measures of sleep (p.43). Brzezinski et al. (2005) also conducted a systematic analysis of placebo-controlled studies that proved the efficacy of melatonin in significantly reducing sleep onset latency, increasing sleep efficiency, and increasing total duration of sleep (p.48).

However, the biggest advantages of melatonin lie in its good safety profile (non-toxic) (Biran et al., 2014, p.718), and very minimal and non-life-threatening side effects. For example, in a 2016 study about the safety of melatonin in humans, exogenous melatonin was shown to be safe, even in extreme or high doses (Andersen, Gögenur, Rosenber & Reiter, 2016, p.169; Doherty et al., 2019, p.6). This suggests that melatonin has a very wide therapeutic window/range, rendering it safer than benzodiazepines or nonbenzodiazepine sedative-hypnotics for example. Furthermore, there is no risk for tolerance, dependence or addiction, withdrawal or rebound insomnia with melatonin as a sleep aid. Also, adverse effects, although minimal (Trodjman et al., 2017, p.438), do not include excessive daytime sleepiness, negative cognitive effects, muscle weakness, and/or dizziness or vertigo (Khullar, 2012, p.2; Bartle & Wheeler, 2015, p.21).

Furthermore, the efficacy of melatonin can also be attributed to its optimal size, which facilitates its ability to easily cross physiological barriers. It is also characterized by its high lipid solubility and partial water solubility (Doherty et al., 2019, p.6).

Additionally, professional American football players are more liable to brain and head injuries due to their involvement in the high contact sport. Trodjman et al. (2017) found that melatonin is quite effective as a neuroprotective agent in animals' gray and white matter. The neuroprotective properties of melatonin ranged from reducing inflammatory response, cerebral oedema formation (which is a major concern in some high-impact sports), and blood-brain permeability, as well as influencing neurogenesis and neuronal survival, motor recovery and locomotor activity after strokes (p.438).

Disadvantages and Side Effects of Melatonin

The side or adverse effects of melatonin ingestion can be considered as mild and minimal. They range from hypotension, gastrointestinal distress, and insulin insensitivity (Baird & Asif, 2018, p.36). Other, perhaps, a little uncomfortable, but still mild side effects may include headaches, vivid dreams (due to an increase in REM cycle), nightmares, and nausea (Halson, 2014, p.20). However, those adverse effects are usually short-lasting (Bauer, 2017). According to Andersen et al. (2016), no serious adverse effects have been reported or indicated in studies as implicated with the use of melatonin (p.169). However, extra caution should be taken with female athletes using melatonin dietary supplements. This is because, although individuals were reported to use melatonin for up to two years with no side effects, it is suggested that large doses of melatonin over-time can affect how ovaries work, though it is not clear how or in what way (Women, Wisdom, Wellness, 2018). However, the most significant disadvantage in the administration of exogenous melatonin is that, as a dietary supplement, it is not approved by the Food and Drug Administration (FDA). Therefore, it is not subject to the strict quality control standards seen with prescription medications or drugs (Herman, 2011, p.108). This poses a great risk because some over-the-counter melatonin formulations offered in drug stores may be contaminated, and therefore, produce or induce more serious side effects (due to additives) (Baird & Asif, 2017, p.36) not typically seen with melatonin, or worse, dangerous and unexpected drug-drug interactions. However, generally speaking, clinical trials have shown that adverse

effects of exogenous melatonin are rare (Peuhkuri, Sihvola & Korpela, 2012, p.2).

Finally, although it has been established that melatonin is generally considered nontoxic,

doses of 10 mg or higher may raise blood plasma levels or concentrations up to 60 times higher than their normal ranges/values, which may lead to tolerable but uncomfortable side effects of hypothermia, fatigue, and daytime sleepiness, which will not benefit athletes when performing (Dollins, Zhdanova, Wurtman, Lynch & Deng, 1994, p.1826).

Effects on Mental and Physical Performances

A recent 2018 study about the effects of melatonin ingestion in teenage athletes showed promising results regarding the effects of the hormone on cognitive/mental performance. The study by Cheikh, Hammouda, Gaamouri, Driss, Chamarki, Cheikh, Dogui, and Souissi (2018), examined the effects of a single melatonin dose of 10mg on ten male elite judokas after high intensity evening training. The subjects went through two test sessions, with a week between each, and were given either a single 10-mg tablet of melatonin or a placebo in a double-blind randomized order administration. Cheikh et al. (2018) found that not only was sleep quality increased and improved, but there was also a strong positive effect on cognitive performance sport/physical performance, as well as reduced perceived exertion (p.1284). Another study by Ghattasi, Hammouda, Graja, Boudhina, Chtourou, Hadhri, Driss, and Souissi (2016) in which the morning ingestion of melatonin (dose was administered at 7:30 am) after short-term maximal athletic performances was explored and examined showed similar results. Similarly, twelve Tunisian soccer players from the soccer squad were administered 5 mg of melatonin or placebo in a randomized order and tested at eight in the morning, 12 noon, and 4 in the afternoon, all of which were after the ingestion. The cognitive and physical tests results were accumulated and recorded from 10 trials (p.96). The results indicated significantly high cognitive performances (especially in the domain of vigilance), specifically at 4 in the afternoon, whereas 8 am results showed lower physical performances. Finally, melatonin ingestion showed no effects on physical or cognitive performances at 12 noon (Ghattasi et al., 2016, pp.97-98; Flores et. al, 2018, p.126). Furthermore, Smits, Nagtegaal, van der Heijden, Coenen, and Kerkhof studied melatonin effects on chronic sleep onset insomnia in 40 elementary

school children who played sports and suffered for over a year from chronic insomnia (p.86). The participants were given 5 mg of melatonin once a day for a period of four weeks, and this yielded positive results on performance (Smits et al., 2001, p.87).

2.6 What is missing?

As previously mentioned, research and literature on melatonin use in athletes as a particular population is scarce. Therefore, there seems to be a need for not only more clinical trials and research, but also on factors such as dose-dependency, and long-term efficacy and effects of melatonin ingestions, and whether or not it can be problematic. Although the suggested/recommended dose range is usually 0.3 mg to 5 mg, there is still no clear-cut answer as to why a lower dose may work for some but not for others. This usually results in a number of trials before a sufficient or effective therapeutic dose can be determined for each individual. It may be because every individual's circadian physiology is different and unique, making it hard to predict the required dose.

Conclusion: Suggestions/Recommendations

While melatonin is considered the safest option, mainly due to its impressive safety profile (wide therapeutic window; low toxicity), lack of tolerance, and withdrawal, there has been problems with administering the effective therapeutic dose required for each individual. As previously mentioned, this leads to trial and error, and if the insomnia is severe, it may not be ideal. Furthermore, as previously mentioned, melatonin does not directly induce sleep but works on changing sleep timing, while sedative-hypnotics may help with directly inducing sleep in a faster way. Generally, benzodiazepines are discouraged due to their high abuse potential or risk and dependence, nonbenzodiazepine sedative-hypnotics are preferred (Baird & Asif, 2018, p.37). Augmenting the treatment with either another drug or nutritional supplement such as valerian or tryptophan would help facilitate sleep even more (Halston, 2014). Also, since decrease in physical performance has been seen following immediate melatonin ingestion, it is advised to allow for eight hours of sleep prior to athletic performance, which is similar to sedative- hypnotics. According to Baird and Asif (2018), numerous experts believe that sedative-hypnotic sleep aids are the second-line agents to melatonin (p.38). Many athletes are attracted to sedative-hypnotics during travel and nights prior to

big competitions (provided that they ingest it, like melatonin, at least 8 hours before the event), due to its efficacy and capability to greatly improve sleep quality. One suggestion would be to use short-acting agents, such as zolpidem, in a very low dose, with melatonin, allowing for an 8-hour rest prior to the event to successfully avoid "hangover" or adverse cognitive effects and negative physical effects on performance. However, as previously mentioned, more study addressing the effects of the aforementioned substances on athletes' performance parameters and their circadian rhythms is needed before one is to make definite recommendations.

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Using Antipsychotics to Treat Irritability
in Children & Adolescents with ASD

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Abstract

Children and adolescents with Autism Spectrum Disorder (ASD) often exhibit a wide array of symptoms, including difficulties with social communication and restricted, repetitive patterns of behaviors. There are currently no medications to treat the core symptoms of ASD. However, two antipsychotic medications have been approved by the FDA to treat irritability – another common symptom observed in this population. The purpose of this review is to provide a critical analysis on the efficacy of antipsychotics to treat irritability, associated adverse events, and novel therapies to improve effectiveness and/or mitigate potential risks. The Cochrane Library and PubMed databases were used to identify relevant studies published between 2019 and 2024. Compared to non-treatment and other types of treatment, patients receiving risperidone or aripiprazole showed the greatest improvements in measures of irritability. These findings provide support for the use of FDA-approved medications to treat irritability in children and adolescents with ASD. However, significant adverse events were associated with the use of atypical antipsychotics, including metabolic effects. Due to the short-term nature of most studies, updated information on clinical guidelines and recommendations were limited. Although recent developments revealed promising results to address issues of risk while maintaining effectiveness, there is much to be discovered regarding the long-term outcomes for individuals with ASD. These factors must be considered when prescribing antipsychotic medications within a pediatric population.

Keywords: antipsychotic, autism, ASD, developmental disability, child, adolescent, pediatric psychiatry, irritability, treatment, efficacy, safety

Using Antipsychotics to Treat Irritability in Children & Adolescents with ASD

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by deficits in social interaction and communication, as well as restricted and repetitive behaviors (American Psychiatric Association, 2013). Irritability is also common in ASD, which manifests as a persistent, agitated state and intense expressions of anger (Breaux et al., 2023). According to the World Health Organization (WHO, 2023), approximately 1 in 100 children worldwide are affected by ASD and prevalence rates have increased in recent years (Gitimoghaddam et al., 2022). However, there are currently no medications to treat the core symptoms of ASD (National Institute of Child Health and Human Development [NICHD], 2021). Non-pharmacological interventions are the first line of treatment to target the core symptoms of ASD (Gitimoghaddam et al., 2022). Atypical antipsychotics, specifically risperidone (ages 5-16) and aripiprazole (ages 6-17), are the only medications approved by the U.S Food and Drug Administration (FDA, 2019) to treat symptoms of irritability in ASD. Atypical antipsychotics alter neurotransmission by blocking dopamine and serotonin receptors, which are likely implicated in ASD (Meza et al., 2022). Although these medications are commonly prescribed in clinical practice, there may be significant risks (Caplan et al., 2022). Using the Cochrane Library and PubMed databases, this review examined several studies published between 2019 and 2024 to determine the efficacy and tolerability of antipsychotics to treat irritability in children and adolescents with ASD. Analysis of available guidelines for the use of antipsychotics is provided, as well as for novel therapies that address issues of safety and effectiveness in a pediatric population.

Efficacy of Antipsychotic Medications to Treat Irritability

In order to determine the efficacy of a drug, evidence must show that patients' conditions improve when taking the drug rather than a placebo. Iffland et al. (2023) evaluated 131 randomized controlled trials (RCTs) conducted over a 30-year period to determine the efficacy of existing psychotropic medications to treat behavioral symptoms of ASD, including irritability. Of these studies, the majority focused on a pediatric population with only 23 studies involving adults. Atypical antipsychotics were more likely to reduce irritability when compared to placebo, as indicated by a minimum 25% decrease in Irritability scores on the Aberrant Behavior Checklist (ABC-I). Within this medication class, studies primarily used

either risperidone or aripiprazole. In another review, Salazar de Pablo et al. (2023) found that treatment with atypical antipsychotics led to significantly better outcomes in measures of emotion dysregulation and irritability in children and adolescents with ASD. These results are consistent with previous studies that found atypical antipsychotics to be more effective than placebo in reducing irritability in ASD.

Amongst the class of antipsychotic medications, aripiprazole and risperidone had the strongest evidence to support usage within this population. When compared to placebo, only aripiprazole and risperidone significantly reduced irritability, whereas other antipsychotics (i.e., haloperidol, lurasidone) did not (Salazar de Pablo et al., 2023). Studies also compared efficacy between the two FDA-approved drugs. Using a randomized, double-blinded parallel-groups design, DeVane et al. (2019) found that groups receiving risperidone showed more improvement in ABC-I scores compared to aripiprazole, although these differences were only significant at weeks 3 and 6 in a 22-week study. Overall, both treatment groups showed highly significant reductions in ABC-I scores compared to baseline. Similarly, Salazar de Pablo et al. (2023) found that effect size differences between aripiprazole and risperidone were small, suggesting that the two medications are comparable in terms of efficacy. Interestingly, analysis of time-dependent and dosage effects showed that the minimum dosage recommended by the FDA for both drugs (2mg/day for aripiprazole; 0.5-1.0 mg/day for risperidone depending on weight) led to significant decreases in irritability within one week of treatment (DeVane et al., 2019). Continued improvements in irritability scores were observed past the dose titration endpoint, which suggests that early intervention, rather than increased dosage over time, might be a better indicator for clinical improvement in this population. Furthermore, some individuals may experience significant relief with the minimum dosage, which may reduce the likelihood of undesirable outcomes and ease both physician and parental concerns about antipsychotic use.

Other classes of psychotropic medications were examined to compare effectiveness for treating irritability in ASD. Salazar de Pablo et al. (2023) found that following antipsychotics, medications indicated for Attention-Deficit/Hyperactivity Disorder (ADHD) also significantly reduced irritability, although these differences were not significant when stimulants and non-stimulants were considered separately. Iffland et al. (2023) also suggested that ADHD medications may slightly reduce irritability. However, Breaux et al. (2023) found that amongst medication classes examined (i.e., antipsychotics, antidepressants, ADHD medications, mood

stabilizers, and others), ADHD medications had the smallest effect size for treating irritability in various childhood disorders, including ASD. This was compared to antipsychotics, which had the largest effect size. Taken together, these results suggest that ADHD medications may affect symptoms of irritability, but the evidence is insufficient to support usage as a first-line treatment. Despite the lack of consistent evidence, Caplan et al. (2022) found that stimulants had higher reported usage (58%) than antipsychotics (33%) in children with ASD. Although the researchers did not investigate medications to treat irritability specifically, these results suggest that the consensus on prescribing medications in clinical settings may be mixed due to the complexity of ASD and lack of FDA-approved interventions to treat core symptoms. It should also be noted that ADHD symptoms often co-occur with ASD (WHO, 2023), which might explain the higher usage of stimulants in this population. Antidepressants, mood stabilizers, glutamatergic blockers, opioid antagonists, diuretics, neuropeptides, and fatty acids were also examined, however, none significantly affected irritability in ASD (Breaux et al., 2023; Iffland et al., 2023; Salazar et al., 2023). In general, clinicians should recognize that there is currently not enough evidence of efficacy for treatments other than atypical antipsychotics to reduce irritability in children and adolescents with ASD.

Adverse Events Associated with Antipsychotic Usage

Although substantial support exists for the efficacy of antipsychotics to treat irritability in children and adolescents with ASD, potential adverse effects (AE) – particularly metabolic and neurological problems – associated with this drug class must be considered. Of 61 patients in the DeVane et al. (2019) study, 77% receiving risperidone and 61% receiving aripiprazole experienced one or more AE. AE that prompted discontinuation of either medication included increased aggression, stomachaches, enuresis, tremors, tachycardia, and weight gain. 70% of patients taking risperidone experienced significant weight gain compared to 26% of those taking aripiprazole. Other studies also found that risperidone may have a particularly elevated risk for weight gain (Alfageh et al., 2019; Salazar de Pablo et al., 2023). Sleep-related AE (i.e., sedation, somnolence, and difficulty sleeping) were more prominent in patients receiving aripiprazole (DeVane et al., 2019). Additional AE included dizziness, fatigue, abdominal pain, constipation, hypersalivation, nausea, and vomiting (Iffland et al., 2023). Although extrapyramidal

symptoms (EPS) are associated with antipsychotics, studies did not find significant differences in measures of EPS for children and adolescents taking antipsychotics (DeVane et al., 2019; Iffland et al., 2023). Of these symptoms alone, however, akathisia was more common in patients taking aripiprazole (Salazar de Pablo et al., 2023). It is important to note that many studies did not report findings on long-term AE. For those that did, more weight gain was observed with longer treatment (Alfageh et al., 2019; DeVane et al., 2019). Risk of neuroleptic malignant syndrome (NMS) may also raise concerns in prescribing physicians, however, only one study addressed this potentially fatal AE. In their review, Alfageh et al. (2019) did not find any cases of NMS, although this finding may be limited by the lack of RCTs on antipsychotic use in children with ASD and associated risk of NMS. More research is needed to adequately determine the long-term AE, given that many individuals with ASD are exposed to antipsychotics at a young age. Further considerations should be made for those with comorbid health conditions.

Approximately 33% of patients with ASD experience seizures (NICHD, 2021). Salazar de Pablo et al. (2023) found that autistic individuals with epilepsy experienced significantly lower efficacy when treated with antipsychotics. This is likely due to the combined use of antipsychotics and antiepileptic drugs, which act to reduce the serum concentration of drug needed to relieve symptoms of irritability. Ultimately, physicians must evaluate the known benefits and risks of using antipsychotics to treat irritability in children and adolescents with ASD. Frequent monitoring and individualization of treatment should always be at the forefront of psychiatric care, especially when multiple diagnoses are involved.

Novel Therapies and Potential Targets of Research

Recent studies have focused on enhancing the effect of antipsychotics to treat irritability. Behmanesh et al. (2019) conducted a clinical trial with propentofylline adjunct to risperidone in children with ASD. Propentofylline has been shown to exert anti-inflammatory and neuroprotective effects by inhibiting adenosine reuptake, which appears to be a promising drug target for ASD. Significant time-treatment effects were observed in the combination-therapy group compared to those receiving risperidone alone, as indicated by the ABC-I and Childhood Autism Rating Scale (CARS). No significant differences in AE were reported in either group. Additionally, Momtazmanesh et

al. (2020) examined the effects of sulforaphane when combined with risperidone. Sulforaphane has certain antioxidant properties that may be lacking or dysfunctional in ASD. Compared to patients receiving risperidone only, those also receiving sulforaphane showed significantly greater improvements in ABC scores for Irritability and Hyperactivity/ Noncompliance. Significant time-treatment effects were observed for both measures in the combination-therapy group. Notable differences in AE included increased appetite (13.3%) and headaches (13.3%) in the sulforaphane group and diarrhea (20%) for those taking risperidone alone. These results suggest that emerging therapies targeting potential biological underpinnings might be more effective in treating irritability and other symptoms of ASD when used in conjunction with existing medications. However, further investigations are warranted to determine long-term effects.

Other studies examined factors involved in minimizing AE associated with antipsychotics, such as weight gain. Garfunkel et al. (2019) found that certain DNA single nucleotide polymorphisms associated with diabetes may affect the efficacy of metformin, which was previously shown to reduce weight gain due to antipsychotic usage in children with ASD. Variable responses to treatment could be implicated by factors, such as genetic influences, and more studies are needed to clarify these nuances to guide treatment decisions to address weight gain. Future studies should examine the impact of personalized care within this patient population. Hermans et al. (2022) reported on initial findings that predicted higher overall BMI z-scores due to antipsychotic-induced weight gain observed in the first 15 weeks of treatment. In a follow-up study, the researchers planned to use therapeutic drug monitoring (TDM) to quantify serum drug concentrations, which will allow physicians to determine optimal doses to maximize efficacy and reduce risk for AE. Comparison between TDM and "care as usual" groups should elucidate differences in efficacy and long-term outcomes following this 52-week treatment study. More studies should explore the impact of individualized care and differential responses to antipsychotics using a longitudinal design as these findings will help to address the current knowledge gap in long-term treatment outcomes for a complex diagnosis, such as ASD. Conclusion

This overview synthesized the most recent evidence regarding the use of antipsychotics to treat irritability in children and adolescents with ASD. Currently, risperidone and aripiprazole are the only FDA-approved interventions to treat irritability within the target population.

Evidence has shown that these medications are effective in

reducing irritability when compared to placebo or other pharmacological agents. However, there are significant adverse events associated with antipsychotics, such as weight gain. These risks, as well as patient beliefs and values, must be considered in the development of a treatment plan. Newer studies have focused on targeting possible underlying mechanisms in the pathophysiology of ASD. Future studies may seek to identify methods to individualize treatment and monitor the long-term outcomes associated with antipsychotic use in this population. Additionally, more guidelines for practitioners should be established as there may be a lack of consensus on treatment protocols for psychotropic medications in ASD. Furthermore, a thorough evaluation of non-pharmacological approaches must be conducted to address specific symptoms of ASD. Clinicians should ultimately consider the use of non-pharmacological strategies to treat core symptoms first and then determine the appropriateness of combining pharmacological agents, such as antipsychotics, when symptoms of irritability are also present in a pediatric population.

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Efficacy of Sertraline Monotherapy in Pediatric OCD: A Review of Clinical Trials

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Abstract

Obsessive-compulsive disorder (OCD) is a prevalent mental health concern affecting many individuals all across the lifespan. Childhood and adolescent OCD is not uncommon and, without treatment, will likely continue into adulthood. The Food and Drug Administration (FDA) has approved four medications for use in pediatric OCD, one of them being sertraline. Sertraline has shown promising results in conjunction with psychotherapy, but its efficacy as a monotherapeutic invention needs further examination. This literature review aimed to compare monotherapeutic use of sertraline to combined psychotherapeutic and pharmacological interventions in symptom improvement for children and adolescents with obsessive compulsive disorder. A literature search through PubMed was conducted where a few older baseline studies were included while relevant studies from 2020 onward were the focus. The review revealed that the combination of sertraline with psychotherapy is widely accepted as the most effective treatment of pediatric OCD while support does exist for significant improvement as a monotherapy. The studies reviewed include evidence for success in both short-term and long-term studies and showed efficacy and safety in all time frames.

Efficacy of Sertraline Monotherapy in Pediatric OCD: A Review of Clinical Trials

Obsessive-Compulsive Disorder (OCD) is a psychiatric disorder characterized by the presence of obsessions and/or compulsions. Obsessions are defined as "recurrent and persistent thoughts, urges, or images" that cause significant distress and that the individual tries to ignore or neutralize with an action, or, compulsion (American Psychiatric Association [APA], 2022). Compulsions are repetitive physical or mental acts performed with the intention of reducing distress or preventing a situation. Compulsions typically fall into themes of contamination, harm, or symmetry. Some common examples of compulsions are hang washing, praying, checking locks, and counting. In order to be diagnosable OCD, the obsessions or compulsions must cause significant distress and/or take up a significant amount of time every day. OCD can be diagnosed all throughout the lifespan and typically occurs in children between ages 8-12 years old or between the late teen years and early adulthood. It is currently estimated that around 500,000 youth in the United States (around 1 in 200) have OCD but it is theorized that these percentages may be conservative considering the stigmatized nature of the disorder (POTS Team, 2004).

Common treatments for OCD include both psychotherapy and psychopharmacology. Typically, cognitive-behavioral therapy (CBT) is the psychotherapy of choice, specifically exposure and response prevention (ERP) therapy. The United States Food and Drug Administration (FDA) has approved four medications for the treatment of pediatric OCD including clomipramine, fluoxetine, fluvoxamine, and sertraline (POTS Team, 2004). Research has been conducted in recent years to test the efficacy of different treatments. In this paper, the efficacy of sertraline for the treatment of pediatric OCD will be reviewed. Specifically, the use of sertraline as the sole intervention for pediatric OCD will be analyzed.

The first major study that tested the efficacy of sertraline use in pediatric populations was performed in 2004 called the Pediatric OCD Treatment Study (POTS). The objective of this study was to evaluate CBT, sertraline, and a combined treatment plan for treatment of childhood and adolescent OCD. This study included 112 volunteer participants that had a diagnosis of OCD (based on DSM IV criteria) and were aged 7-17 years old. This study was a random control study where the participants were placed into three groups to determine their treatment method for 12 weeks. To test for symptom improvement, participants were given the Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) before and after

treatment. Clinical remission as defined by the study was a starting score of at least 16 reducing to 10 or less. All three treatment groups showed a statistically significant increase compared to placebo. CBT treatment alone and sertraline alone had similar results but were both less successful than combined treatment. The rate of clinical remission for sertraline alone was 21.4% compared to 53.6% for combined treatment and 39.3% for CBT alone and 3.6% for placebo. Remission rate for combined treatment and CBT alone were the same but sertraline alone had a much lower remission rate.

Additionally, placebo and sertraline did not significantly differ in remission rate. All treatments were proved to be acceptable and safe treatment options while combination of CBT with a selective serotonin reuptake inhibitor (SSRI) or CBT alone would be the recommended initial treatments based on efficacy (POTS Team, 2004).

A meta-analysis performed in 2022 used similar measures to compare methods of treatment by comparing CBT and different pharmacological intervention based on CY-BOCS score change. The research team found that combined CBT and pharmacological treatment was most effective. When using pharmacological interventions, escitalopram was the most effective followed by fluvoxamine, sertraline, clomipramine, and paroxetine which were all more effective than placebo. The average score change for sertraline was 3.49 points on the CY-BOCS scale. So again, while sertraline on its own is more effective than placebo, it pales in comparison to combined pharmacological and psychotherapeutic interventions (Tao et al., 2022).

Another earlier study also used the CY-BOS scale in addition to other outcome measures to examine safety and efficacy of sertraline hydrochloride in children and adolescents with OCD. In this 1998 study, 187 patients including 107 children and 80 adolescents either received only sertraline or placebo. The sertraline dose was titrated up to a maximum 200 mg/d dose and was given for 12 weeks. In addition to the CY-BOS scale, the National Institute of Mental Health Global Obsessive Compulsive Scale (NIMH GOCS), the NIMH Clinical Global Impressions of Severity of Illness (CGI-S) and Improvement (CGI-I) rating scales were used. Patients treated with sertraline showed significantly greater improvements than those who did not receive medication on the CY-BOCS, NIMH GOCS, and CGI-I. The efficacy difference was present at week 3 and persisted throughout the study. This study noted that age and sex did not affect treatment response. Uniquely, this study also tracked patient side effects and found that presence of insomnia, nausea, agitation,

and tremor were significantly greater in those receiving sertraline. Overall, this study confirmed that sertraline is a safe and significantly effective mono-therapeutic intervention for pediatric OCD in the short-term (March et al., 1998).

While March et al. proved the short-term effect of sertraline, Cook et al. in 2001 focused on the long-term treatment of pediatric OCD. In this study, 72 children and 65 adolescents with OCD were treated with 50 to 200 mg of sertraline daily in a 52-week extension study. To test improvement, the CY-BOCS, CGI-S and CGI-I were used. Significant improvements were demonstrated with 72% of children and 61% of adolescents meeting response criteria (defined in this study as a 25% or greater decrease in CY-BOCS). Long-term sertraline treatment was well tolerated with no notable discontinuations due to medical issues. Improvements were seen with continued treatment through the 52 week treatment, further defending the use of a monotherapeutic sertraline approach as an effective form of pediatric OCD intervention (Cook et al., 2001).

Melin et al. also were interested in long-term treatment of pediatric OCD interventions and focused on treatment gains at the three-year follow up point (2020). This study used

CY-BOCS scores to test treatment outcomes in pediatric patients with CBT or combined CBT and sertraline treatment. While this study does not look at sertraline monotherapy, it is important to consider as it provides insight into long-term efficacy. At the follow-up point, there was a significant decrease in CY-BOCS scores with an average decrease of 5.9 points from when treatment began to the three-year point. 90% of participants were responders of treatment and 73% were in clinical remission. Overall, this study supported positive long-term effects of evidence-based treatments whether it was only psychotherapy or a combined approach (Melin et al., 2020).

Another long-term study performed in 2020 looked at 35 participants who were treated with combination psychotherapy (CBT) and sertraline at a 7-9 year follow-up point. This study was unique to the other long-term follow-up studies as it utilized psychiatric assessments to test for present OCD diagnosis and for any other mental disorder diagnosis. At this follow-up, 39.4% of participants maintained their OCD diagnosis while 30.3% had a different mental disorder and 30.3% did not have any diagnoses. Interestingly though, the history of CBT or sertraline treatment did not predict OCD at the follow-up. From these findings, this research team concluded that new dynamic treatment strategies should be developed to

enhance long-term prognosis (Fatori et al., 2020).

A study performed in 2021 by Kim et al. looked into factors that may affect treatment outcomes- specifically age. This study pool had 56 children aged 7-17 involved who were exposed to three different treatments: CBT with standard sertraline, CBT with slow dosing of sertraline, and CBT with placebo. Age of participants was factored with symptom outcomes of "improved", "unchanged" and "deteriorated". After analysis, age was found to be a moderator of the mediation effect for physical anxiety symptoms in OCD in all treatment conditions. Age suppressed correlations with OCD outcomes- most evidently in the 8-10 year old age range. Kim et al. bring forth an interesting factor that other discussed studies did not mention. Similarly, Boaden et al. considered a unique factor in sertraline use for pediatric OCD when considering risk of suicidal behavior or ideation. This study looked at the use of antidepressants for many pediatric psychiatric disorders. Specifically for sertraline and OCD, the meta-analysis noted that sertraline and fluoxetine were the most efficacious antidepressants in the treatment of OCD. Additionally, compared to the other antidepressants, sertraline was the only medication that ws associated with a reduced risk of suicidal behavior/ideation (Boaden et al.). Both of these studies bring in unique things to consider when considering sertraline as a treatment for pediatric OCD.

In summary, the use of sertraline as a treatment for pediatric OCD has been examined through many studies in the past 25 years. Its use as an effective treatment option is agreed upon throughout all studies but its use as a monotherapeutic agent differs. When combined with cognitive behavioral therapy, sertraline seems to have the greatest therapeutic effect but some studies show a significant efficacy on its own. However, only a few studies have analyzed this monotherapeutic effect so more research must be done to conclusively claim that pediatric OCD can be reasonably treated by sertraline monotherapy.

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To Intervene with Medication:
An Overview of the Existing Pharmacological Treatment Options
in Pediatric Obsessive-Compulsive Disorder

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Abstract

It has been demonstrated that the best treatment for pediatric OCD may be a combination of medications and exposure response prevention therapy, although medications might only be considered when symptoms are moderate to severe. The FDA approved medications for the treatment of pediatric OCD are Fluoxetine, Fluvoxamine, Sertraline, and Clomipramine, of which Clomipramine is a tricyclic while the remainder are SSRIs. However, the first line of treatment in children is usually exposure response prevention therapy, which may subsequently be coupled with one of the aforementioned medications when it alone has not worked to treat symptoms of OCD. Among the FDA approved drugs for pediatric OCD, none of the SSRIs have emerged as being the clear contender for best agent of choice with the greatest degree of efficacy. Rather, clinicians should prescribe on a case by case basis with regards to factors such as patient response to medication, preferred half-life, and tolerability for each agent. A meta- analysis conducted by De Nadai and colleagues demonstrated that treatment response rates ranged from 49-57% for Fluoxetine, 42% for Fluvoxamine, and 42-53% for Sertraline.

Contrastingly, Clomipramine yielded a greater 58-75% treatment response rate at the expense of leading to an increased side effect profile. Regardless, exposure response therapy remains the gold standard intervention for the treatment of OCD in children. Pharmacotherapy has positive treatment effects when utilized, but no medication has been shown to demonstrate true remission of symptoms for OCD. This analysis will aim to explore the mild differences in treatment efficacy for the use of the FDA-approved SSRIs in pediatric OCD, while discussing their benefited use in tandem with exposure response prevention therapy.

Obsessive-Compulsive Disorder is a destructive mental illness characterized by unwanted thoughts and fears that lead to repetitive behaviors (Obsessive-Compulsive Disorder, Mayo Clinic, 2020). The first component of the disorder involves obsessions, which are the aforementioned intrusive thoughts. Subsequently, compulsions are the various ritualistic behaviors individuals perform in order to alleviate their resulting distress. Onset of the disease usually begins before the age of 25, and is "most often seen in childhood or adolescence" (OCD Program, Stanford, 2023). An NIH report from a group of children and adolescents in 1989 exclaimed that "the mean age of onset was 9.6 years for boys and 11.0 years for girls" (Swedo et al., 1989). As such, methodology of treatment for this group has become a great concern and steps have been taken to find therapies and medications that are most effective for remission of symptoms.

According to the International OCD Foundation, the best treatment for pediatric OCD "includes both medication and a type of cognitive behavioral therapy called exposure and response prevention therapy (ERP)" (Medications for Pediatric OCD, 2023). Indeed, their use is "supported by the treatment guidelines of the American Psychiatric Association (APA) and the American Academy of Child and Adolescent Psychiatry (AACAP)" (Medications for Pediatric OCD, 2023). However, psychiatrists may choose to begin medication only when the child does not respond well to ERP (Medications for Pediatric OCD, 2023). Furthermore, it should only be fully considered as a plausible intervention when symptoms of OCD are severe and when ERP has not successfully treated any of the symptoms (Medications for OCD, 2023). By this mechanism, the introduction of medications in pediatric OCD is more of a supplement to help manage symptoms and lower overall anxiety so that the child may potentially be able to try ERP therapy again with more success (Medications for Pediatric OCD, 2023).

When the introduction of psychiatric medications becomes a necessity, it is important to consider a wide variety of options when prescribing the best option for an individual case. Once it is clear that medications are a valid choice to proceed with, the doctor should recommend one of the FDA-approved selective serotonin reuptake inhibitors (SSRIs), a class of antidepressants, that have been shown to treat OCD. There are only four psychiatric medications that have been FDA-approved for the treatment of OCD in children, of which three are in the class of SSRIs (Medications for Pediatric OCD, 2023). These three are fluoxetine (Prozac), fluvoxamine (Luvox), and sertraline

(Zoloft) (Medications for Pediatric OCD, 2023). The final approved medication is clomipramine (Anafranil), which is in the class of tricyclic antidepressants.

The supplementation of the aforementioned medications with ERP is critical. A meta- analysis of 21 studies featuring 1113 patients showed that "ERP combined with medication therapy was significantly better than medication therapy alone" (Mao et al., 2022). Interestingly it was actually found that roughly 40-60% of patients who were solely treated with SSRIs experienced.reductions in their obsessive-compulsive symptoms (Mao et al., 2022).

Subsequently, ERP for OCD seemed to have a very comparable level of efficacy (Mao et al., 2022). However, the analysis goes on to exclaim that the most effective treatment outcomes will be obtained upon combining psychotherapy and medication treatments (Mao et al., 2022).

A meta-analysis of several randomized controlled trials revealed that the SSRIs had a significant effect on treatment outcomes with respect to a placebo group, indicating an effect size of 0.46-0.48 (De Nadai et al., 2011). Interestingly enough, the tricyclic antidepressant, clomipramine, "showed a significant advantage over SSRIs in efficacy relative to a placebo" (De Nadai et al., 2011). Indeed, effect sizes for the treatment efficacies of clomipramine, sertraline, fluoxetine, and fluvoxamine were 0.85, 0.47, 0.51, and 0.31, respectively (De Nadai et al., 2011).

The SSRIs may be started as young as 6 years old in the case of sertraline, while clomipramine should not be considered until the child is at least age 10 (De Nadai et al., 2011). In the case of every one of these medications, administration should begin "at the lowest recommended dose, with incremental increases every 2-4 weeks based on efficacy and tolerability" (De Nadai et al., 2011).

Among the drugs that have been FDA-approved for treatment of pediatric OCD, none of the SSRIs have emerged as a clear contender for the best individual choice of medication.

Rather, clinicians select any given drug based off of "preferred half-life, observed patient response, and idiographic tolerability of an individual agent" (De Nadai et al., 2011). This is due to the fact that the SSRIs differ from one another in distinct ways with regards to their pharmacodynamics and drug interactions (De Nadai et al., 2011). The SSRIs are the first line of pharmacological treatment for pediatric OCD, as they appear to have a more mild profile of adverse side effects (Kotapati et al., 2019). If the initial choice of SSRI proves to be ineffective, patients may be advised to either switch to a different SSRI or to have

the medication augmented with CBT or with the tricyclic antidepressant, clomipramine (Rosenberg, 2022).

Due to the fact that the SSRIs appear to be rather effective in the treatment of OCD, it has been hypothesized that "deficient serotonin function is a key element in the pathophysiology of OCD" (Pharmacological Treatments, Stanford Medicine, 2023). Even though the mechanism of action is similar, it is difficult to predict how a patient may respond to each individual drug. As such, trial periods of about 10-12 weeks at tolerable dosage levels are recommended to determine whether the drug of choice is producing a clinically significant response (Pharmacological Treatments, Stanford Medicine, 2023). Disappearance of all symptoms rarely occurs for individuals with OCD, but any potential benefits may become noticeable by about 6-8 weeks of continued use (Pharmacological Treatments, Stanford Medicine, 2023). Individuals who do not respond well to a particular SSRI may, in fact, end up responding better to a different SSRI or behavior therapy (Pharmacological Treatments, Stanford Medicine, 2023). As such, it is important to consider all options among the FDA-approved drugs for the treatment of OCD.

A placebo-controlled trial was conducted by Liebowitz & colleagues to determine the safety and efficacy of the use of fluoxetine in children and adolescents with OCD. This research, conducted between 1991 and 1998, randomly assigned 43 patients to a placebo group and a fluoxetine group for 8 weeks (Liebowitz et al., 2002). Dosages ranged from 60mg/day to 80mg/day based off of adjustments to each individual's treatment plan, and results showed that fluoxetine patients showed significantly lower scores on a measure known as the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) following an additional maintenance phase of another 8 weeks (Liebowitz et al., 2002). This aforementioned scale is especially designed to rate the severity of obsessions and compulsions in children and adolescents aged 6- 17 years (CY-BOCS, 2007). Interestingly enough, results from the placebo-controlled trial indicated that fluoxetine patients appeared to only exhibit improvements after the extended 16 weeks of intervention, but not 8 weeks (Liebowitz et al., 2002). Indeed, another study appeared to demonstrate similar results, indicating that fluoxetine was associated with significantly greater improvement on the CY-BOCS than a placebo control (Geller et al., 2001). The potential effectiveness of fluoxetine was thus demonstrated in this sample of children and adolescents, but its full effect took over 8 weeks to develop (Liebowitz et al., 2002). Additionally, fluoxetine has a long half-life of up to 72 hours, meaning that a single missed dose is not enough to cause an issue (Brasic,

2022). However, this may also be a potential drawback, as if side effects do occur, "eliminating all active metabolites can take a long time" (Brasic, 2022). The starting dose for fluoxetine in children is anywhere from 2.5mg to 10mg per day, while the starting dose for adolescents is between 10-20mg/day (Rosenberg, 2022).

A more recent analysis on fluoxetine use for remission of obsessive and compulsive symptoms in autistic children has also shown significant improvements at the 16-week mark, with respect to a placebo control group (Reddihough et al., 2019). Another study by Coskun & Zoroglu (2009) indicated significant improvements in OCD symptoms following fluoxetine administration for several weeks, but also revealed the presence of symptoms of behavioral disinhibition in a portion of the sample. Administration of fluoxetine is best to start at lower doses, and as individuals improve in their ability to manage any side effects, dosage may slowly be increased over time (Estevez, 2022). This medical review has also stated that fluoxetine is the most popular prescription among psychiatrists, but that it is best supplemented with exposure and response prevention (ERP) therapy (Estevez, 2022).

Fluvoxamine is the second FDA-approved SSRI for the treatment of OCD in children. A double-blind, placebo-controlled research study was conducted to determine the safety and efficacy of this medication in the aforementioned population (Riddle et al., 2001). In this study, subjects had been assigned to either a placebo group or a fluvoxamine group, where they took 50-200mg of the medication per day. Following the 10 week intervention period, significant differences were found between the experimental and control groups (Riddle et al., 2001).

Specifically, "42% of subjects taking fluvoxamine responded to treatment as opposed to 26% taking the placebo" (Riddle et al., 2001). An additional benefit of fluvoxamine appeared to be its relatively rapid onset of action and strong efficacy in dealing with short-term treatment of pediatric OCD (Riddle et al., 2001).

Indeed, fluvoxamine has been indicated for use in children ages 8-17 (Brasic, 2022).

Fluvoxamine has shown to cause "reduction in repetitive thoughts, maladaptive behaviors, and aggression, while increasing social relatedness and language use" (Brasic, 2022). Therapeutic benefits may take anywhere from 2-8 weeks to materialize, and it is necessary to continue taking the medication so that it may realize its full potential (Cambridge University Press, 2021). The elimination half-life of fluvoxamine ranges from roughly 15-20 hours, meaning that adherence to daily dosage is much more

important than for those individuals taking another medication, such as fluoxetine (Perucca et al., 1994). Recommended dosage levels for children range from 50- 200mg/day, and it has shown to be rather well-tolerated by most pediatric patients (Cheer & Figgitt, 2002). The most common side effects of fluvoxamine in children appear to be dizziness, dry mouth, feeling nervous or anxious, and general gastrointestinal ailments like constipation or diarrhea (Memorial Sloan Kettering Cancer Center, 2021). If a dose of fluvoxamine is missed, it should be taken as soon as possible, although if the next dose is rapidly approaching, one should not double dose (Mayo Clinic, 2023). Ultimately, fluvoxamine is a rather effective SSRI, as "reductions in symptoms of anxiety with its use have been observed for up to one year in children and adolescents with OCD" (Cheer & Figgitt, 2002).

The final FDA-approved drug for the treatment of OCD is sertraline. Recommended dosages for sertraline administration in children is anywhere between 50-200mg/day (Medications for Pediatric OCD, 2023). The average elimination half-life of sertraline is roughly 26 hours (ZOLOFT, FDA, 2014). A past randomized, double-blind, placebo-controlled research study involving 187 children and adolescents demonstrated greater levels of improvements for the patients treated with sertraline as opposed to those who received the placebo (March et al., 1998). As with the previous studies on fluoxetine and fluvoxamine, this research utilized the CY-BOCS to show improvements in obsessive and compulsive symptoms. To be specific, about 42% of patients who received sertraline appeared to have symptom reduction, as opposed to only 26% in the placebo group (March et al., 1998). Any improvements in symptom severity appeared to emerge within the third week of treatment, and then proceeded to persist until the study had concluded (March et al., 1998). Interestingly enough, the side effect profile of those in the sertraline group appeared to also be significantly greater than those in the placebo group.

Primary side effects were insomnia, agitation, nausea, and tremors.

Another study on long-term sertraline treatment of OCD in children and adolescents supported past results, indicating that 72% of children (ages 6-12) and 61% of adolescents (ages 13-18) demonstrated improvements on the CY-BOCS (Cook et al., 2001). As opposed to the previous research study by March and colleagues, this analysis showed few side effects, and instead showed that sertraline treatment was rather well received (Cook et al., 2001). The long- term treatment plan in this

analysis extended as far as 52 weeks, and up until this point, sertraline was “effective and generally well tolerated in the treatment of childhood and adolescent OCD”, and that more improvement was demonstrated as treatment continued on for longer (Cook et al., 2001). If any side effects do emerge, they most often materialize as nausea, diarrhea, dry mouth, trouble sleeping, and fatigue (Le, 2021).

Overall results from studies on sertraline, fluvoxamine, and fluoxetine indicate that there are not very many significant differences between efficacy and treatment outcomes for each medication. They all share similar side effect profiles and exhibit comparable treatment improvement rates. They are all additionally considered as first line medications for the treatment of OCD in children and adolescents whenever exposure response prevention proves to be insufficient on its own. Clinicians may choose to prescribe a specific SSRI and wait to see how the client tolerates the medication before either raising dosage or switching to another of the FDA-approved SSRIs. Paroxetine, Citalopram, and Escitalopram are three additional SSRIs that are occasionally recommended for treatment of pediatric OCD, although these are not FDA- approved (Medication for Pediatric OCD, 2023).

An additional consideration prescribers may make when considering medication for pediatric OCD is the potential administration of clomipramine, a tricyclic antidepressant.

Clomipramine is considered the second-line of treatment, but it has actually had “greater efficacy in reducing obsessive-compulsive symptoms in comparison to SSRIs” (Brasic, 2022). Despite this, clomipramine has a much higher side effect profile and severity rate amongst children, which is why it has been relegated to second-line status (Brasic, 2022). Indeed, the meta-analysis conducted by Mao & colleagues (2022) supported the claim that clomipramine has a higher efficacy than the SSRIs, although its side effects are “far more pronounced and less endurable”. Furthermore, clomipramine was also the first antidepressant to demonstrate any kind of treatment efficacy for children with OCD, although the FDA recommends that only children ages 10 and over should be taking it (De Nadai et al., 2011). Its effect size on symptom reduction is 0.85, which is rather high relative to a placebo, and higher even than the efficacy of the SSRIs when compared with placebo (De Nadai et al., 2011). In addition to many of the side effects associated with the antidepressant SSRIs such as fatigue, tremor, and constipation, clomipramine notably has a strong association with cardiac arrhythmia, which is why it is often not considered as a first-line of treatment (De Nadai et al., 2011).

Regardless of the various benefits and side effects of SSRIs and clomipramine on pediatric OCD symptom treatment, ERP is always considered as the first-line of treatment in this population (Treating OCD in Children & Teens, 2023). Children and adolescents who display mild symptoms should always be started on ERP. Subsequently, pharmacological treatment should be considered when improvements have not been seen after several exposure sessions. Evidence from clinical research studies has shown that "there is greater improvement for OCD symptoms from combined SSRIs and ERP when compared with ERP alone" (Core Interventions in the Treatment of OCD and BDD, NIH, 2023).

On occasion, CBT may also be recommended as a treatment pathway for pediatric OCD. With this being the case, one research study found that there had been greater improvement in symptoms of OCD via a combination of sertraline and CBT versus just sertraline alone (Core Interventions in the Treatment of OCD and BDD, NIH, 2023). A similar research study later found that the combination of CBT and fluvoxamine also demonstrated superior outcomes as opposed to fluvoxamine alone (Core Interventions in the Treatment of OCD and BDD, NIH, 2023). Indeed, one of the major reasons as to one might try the combination approach would be due to the increased suicidality rate involved with SSRIs. Due to OCD's high comorbidity rate with depression, prescribers should "take care to monitor for increases in suicidal thinking or behaviors when considering pediatric OCD SSRI trials" (De Nadai et al., 2011). In fact, the best method to proceed with pediatric OCD appears to simply be to begin with ERP or CBT in mild or moderate cases, and together with an SSRI only in severe cases (De Nadai et al., 2011).

Although side effects are mild in most cases, the use of SSRIs in the treatment of this unique disorder is most often limited to situations where therapy and exposure have already failed to yield the desired results. There is additionally the debate of whether to try clomipramine as an agent that is supposedly more efficacious in symptom resolution, at the expense of risking a greater side effect profile. However, before this decision is made, one must consider the unique aspects of every FDA-approved SSRI for pediatric OCD treatment, and choose to prescribe one drug over another by seemingly miniscule differences. Even then, the FDA-approved drugs are only the medications that have had "large studies completed using pediatric patients" (Medications for Pediatric OCD, 2023). Other existing SSRIs may not have been granted FDA- approval on the grounds that they have not yet had these expensive and extensive clinical trials conducted

on a sufficiently large sample of pediatric patients. As such, the choice of what to prescribe is seemingly dependent on an individual's ability to tolerate the medication, their particular response to both its positive and adverse effects, and patient preference. No significant efficacy differences have been observed amongst the FDA-approved SSRIs for pediatric OCD, and no direct comparisons have been made within a single trial (De Nadai et al., 2011). An important step moving forward would possibly be to construct a large-scale study involving a placebo control group as well as three different experimental groups, each consisting of individuals receiving fluoxetine, fluvoxamine, and sertraline. Indeed, existing literature on preferred SSRI of choice appears to be rather limited to a few randomized control trials that all yielded similar levels of efficacy. A future study should absolutely strive to expand upon these analyses to truly determine if there is an ideal route to pharmacological treatment.

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Degree of discontinuing olanzapine intramuscular injection, and the adherence of treating schizophrenia under long-acting injection of olanzapine: a literature review

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Abstract

Although psychotic medication has already gained a huge success in treating schizophrenia, the way of injecting medication still affects effectiveness and adherence of treatment. The problem caused by medication discontinuation cannot be ignored since it may destroy achievements from previous medical treatment. There are uncontrolled factors causing patients to quit the medication, such as side effects of current medication, environmental factors, lack of improvement, poor doctor-patient relationship and lack of self-awareness. Creating intramuscular injection is to decrease the degree of discontinuing the medication and improve the adherence of treatment. In this literature review article, there are reliable sources and evidence supporting that, intramuscular injection of olanzapine decreases the degree of patients discontinuing the olanzapine, which further increases the adherence of treating schizophrenia.

Methods

Different types of studies would be selected to draw a conclusion, which can be categorized as cohort study, RCT, systematic review, open-labeled study, meta-analysis and cross-sectional survey. All studies will be selected from PubMed and related to intramuscular injection of olanzapine and the adherence of treating schizophrenia under medication discontinuation. Applying JBI Critical Appraisal tools to assess the quality of selected studies, based on answering questions and assigning scores.

Conclusions

Based on selected studies in this literature review, concluding that intramuscular/long- acting injection can decrease the degree of patients discontinuing olanzapine, and this long-acting injection can contribute to a high adherence of schizophrenia treatment. However, whether intramuscular injection can be used in other psychotic medication is still explored by psychopharmacologists, and the future development of medication injection determines if long-acting injection can cause an effect on treating other psychotic disorders.

Introduction

Antipsychotic medications contribute to the modern progress of treating schizophrenia and other severe psychiatric disorders. The choice of medication under psychiatrists' advice plays an essential role in eliminating clinical symptoms related to delusion, hallucination, mania, and other dramatic mental expressions. Pharmacological medication could be diverse, and patients must be extremely cautious when receiving the prescribed medication. The major medications used in treating schizophrenia can be categorized as typical antipsychotics (first-generation) and atypical antipsychotics (second-generation), and olanzapine is an atypical antipsychotic medication possessing fewer side effects than typical antipsychotic medications. The mechanism of action of olanzapine blocks the activity of dopamine and serotonin neurotransmitters in the brain, which is highly effective in eliminating psychotic symptoms such as hallucinations, delusions, and distorted behaviors (David et al. 2022). Although this kind of second- generation antipsychotic is highly recommended, it is still common for schizophrenia patients to quit or discontinue the medication due to some factors. Research has shown that most patients who orally take olanzapine have a history of quitting medication without psychiatrists' formal indication, which severely affects patients' treatment progression. Patients relapsing with their disorder is quite common in the psychotic area, and one research has shown that among the 11,856 individuals diagnosed with schizophrenia, 5506 (46.4%) were re-hospitalized with schizophrenia during the first five years of follow-up (Köhler et al. 2019). Almost all schizophrenia patients will experience discontinuation and further improve the risk of relapse, even for olanzapine, which has fewer side effects than other antipsychotics. There are numerous possible causes of nonadherence in patients with schizophrenia; these include disease-related factors (e.g., symptom severity; substance use co-morbidity), patient related factors (e.g., perceptions of treatment acceptability and benefit) and treatment-related factors (e.g. regimen complexity, adverse events and lack of efficacy) (San et al, 2018).

Oral injection is a conventional way of taking prescribed medication, and although it is the injection way that most patients choose to take the medication, the degree of orally discontinuing psychotic medication is high. The invention of intramuscular injection is to decrease patients' discontinuation of medication, which is achieved by administering medication directly into the arm muscle. This kind of long-acting injection can be effectively used in schizophrenia patients who need to take olanzapine, because intramuscular injection can consistently adjust

medication levels and improve treatment adherence, and intramuscular injection can also be absorbed more effectively than conventional injection. Intramuscular injection requires to be administered at typically 2- 4 weeks intervals, but oral injection of olanzapine requires daily taking, which is not as convenient as intermuscular injection. In this literature review, we specifically discussed the advantages of taking olanzapine by long-acting injection and deficits of keeping the conventional way to take olanzapine, and how intramuscular injection influences adherence.

Adherence is particularly important in treating schizophrenia because the conditions of schizophrenia are chronic, which means ongoing treatment is crucial in preventing the relapse of disorder. Adherence to medications can be defined as "the process by which patients take their medication as prescribed, described by three quantifiable phases: initiation, implementation, and discontinuation" (Vrejins et al, 2012). Discontinuation of medication would be the most unexpected situation that draws the previous systematic treatment down. Interventions used in improving adherence to treatment can avoid patients' active discontinuation and further develop more clinical strategies to prevent relapse and the vicious cycle caused by discontinuation of medication. In this literature review, we specifically discussed the advantages of taking olanzapine by long-acting injection and deficits of keeping the conventional way to take olanzapine, to confirm whether the Intramuscular injection of olanzapine, as an effective long-acting injection, can improve the adherence of schizophrenia treatment. Therefore, stable and followed adherence can contribute to a promising treatment outcome, and non-adherence to treatment may lead to a poor outcome and increase the risk of relapsing symptoms. This impediment can even exacerbate some conditions if patients do not follow doctors' clinical recommendation and medical instructions.

The problem caused by medication discontinuation cannot be ignored since it may destroy achievements from previous medical treatment. There are uncontrolled factors causing patients to quit the medication, such as side effects of current medication, environmental factors, lack of improvement, poor doctor-patient relationship and lack of self-awareness. Creating intramuscular injection is to decrease the degree of discontinuing the medication and improve the adherence of treatment. In this literature review article, there are reliable sources and evidence supporting that, intramuscular injection of olanzapine decreases the degree of patients discontinuing the olanzapine, which further increases the adherence of

treating schizophrenia.

Search strategy and selection criteria

This study only collects studies searched from PubMed. Including keywords in discontinuation of olanzapine, intramuscular injection of olanzapine and adherence of treating schizophrenia, and most studies should be published within five years. But excluding contents related to short-acting injection, other long-acting injection beside intramuscular and oral injection, treatment resistance and studies focusing on other psychiatric disorders rather than schizophrenia. The content of articles has to be related with practice of olanzapine or other familiar antipsychotics but only limited in second- generation antipsychotics, and all articles should focus on participants with schizophrenia rather than other psychotic disorders. This literature review doesn't focus on discussing symptoms of schizophrenia but will discuss some specific side effects-based injection ways.

Design and analysis

This literature review concludes 20 studies related to intramuscular injection of olanzapine and adherence of treatment. Including cohort study, RCT, systematic review, open-labeled study, meta-analysis and cross-sectional survey are study types we choose to make our conclusion in this literature review. These studies will be assessed under JBI Critical Appraisal: Revised JBI checklist for RCT, checklist for systematic review, checklist for open-labeled study, checklist for meta-analysis, etc. Due to existence of multiple research types involved in this study, applying JBI checklist to different studies' evaluation will be an essential action, since can further ensure articles cited in this literature review are qualified and organized. "JBI offers a suite of critical appraisal instruments that are freely available to systematic reviewers and researchers investigating the methodological limitations of primary research studies. The JBI instruments are designed to be study-specific and are presented as questions in a checklist" (Barker et al, 2023). Although the types of selected studies are multiple, each study is evaluated under same standard: sample size, way of injecting medication, diagnosis of patients, number of studies included, effectiveness of long-acting injection, types of antipsychotics and adherence of treatment. Eventually, we can summarize their findings to conclude that intramuscular injection of olanzapine can

increase adherence of schizophrenia treatment and decrease the degree of discontinuing olanzapine.

For open-labeled study, the content must be related with safety and efficiency of antipsychotics under oral injection and long-acting injection, the study should conclude more than 50 patients and show the separate effectiveness when schizophrenia patients take the medication. Evaluating whether symptoms of schizophrenia are mitigated or recovered depends on positive and negative syndrome tests. Also, the open-labeled study should mention side effects under both injections.

For cross-sectional study, JBI appraisal tools will assess it based on project plan, meeting agenda, daily schedule and reading log. The selected cross-sectional study should relate to preferences from clinical professional care and patients, which means this survey needs to investigate the major impression of intramuscular injection in most patients and professionals. This medication impression can help us realize whether patients prefer long-acting injections over oral injection, and what advantages the long- acting injection may has during the treatment.

For the selected meta-analysis study, the study should involve more than 50 RCTs and overall participants should above 10000 patients. The topic of meta-analysis will perform a comparison between oral injection and long-acting injection in preventing relapse of schizophrenia, which should provide this literature review with abundant information and valuable references, to have a comprehensive understanding how injection affect prevention of relapse, and performing a quantitative method to indicate which injection can decrease the probability of relapse.

For the selected literature review, it mainly discussed pharmacological properties of using olanzapine and physical absorption of olanzapine, also needs to mention about patient population and groups which prefer the long-acting injection over oral injection.

For the cohort study, this selected study will discuss all second-generation antipsychotics, since olanzapine is one of the second-generation of antipsychotics. Also, this study should involve the consequences of treatment failure, such as relapse, treatment discontinuation, rehospitalization and suicides.

After concluding these types of studies, we can make a conclusion whether long- acting injection of olanzapine is a expected way to decrease discontinuation and improve treatment adherence.

Results

Treatment of psychotic disorder is long-term and time-consuming. Olanzapine is an atypical second-generation antipsychotic usually seen from treating schizophrenia, especially to the patients who don't show a successful achievement in other antipsychotics or have a severe side effect by trying other antipsychotics. Olanzapine as a first-line treatment of schizophrenia, it can significantly decrease hallucinations, delusions and deviant behaviors. Recurrence of psychotic symptoms sometimes is unpredictable, even with antipsychotics treatment and functional improvement in a short- term. Schizophrenia patients orally taking olanzapine have a high medication discontinuation, which leads to poor adherence. Nonadherence is a crucial component predicting whether patients' episodes will relapse and exacerbate in the future. "Significant predictors of medication nonadherence include substance misuse, depressive symptoms, poor disease insight, and lower occupational status" (Coldham et al, 2002). Indeed, relapse and rehospitalization is abnormally high in schizophrenia cases, 60-80% patients relapse their symptoms within five years. Based on 10 years' experience at a UK high-secure hospital, poor adherence to antipsychotic treatment can be as high as 50% and is associated with risk of relapse and hospitalization, and long-acting antipsychotics injections are defined as assisting healthcare professionals in controlling poor adherence (Attar et al, 2022).

Discontinuing antipsychotics is a common clinical phenomenon in treating schizophrenia, and factors that may lead to reduction or discontinuation of antipsychotics are diverse and situational. Based on a study that mainly discusses family member's perspective on reducing and discontinuing antipsychotics, the persistence of schizophrenia patients are very unstable and fragile, it's usual for them to witness their relative has a relapse due to medication reduction or discontinuation, and majority family members notice that patients frequently altered their dosage without a supervised clinical professionals, indeed, the stability of taking medication is such difficult to schizophrenia patients. " Parents of people with psychosis have often experienced difficult and frightening episodes in their caring role that can generate high levels of anxiety and feelings of responsibility in maintaining their loved ones' stability"(Lewis et al, 2022).

However, incidence of adverse effects of olanzapine didn't mitigate under an alternative way of injection, weight gain, anticholinergic and sedation are the common side effects schizophrenia patients will have after intramuscular injection of olanzapine. But frequency of patients injecting olanzapine dramatically decreases because LAI only requires patients to take the medication for 2 to 4 weeks interval, which is more convenient, and patient will have clinical supervision for each time's injection. According to a cross-sectional survey that collected 336 participants from 60 sites, to indicates whether patients' satisfaction is related to flexible adjustments of injection sites and dosing characteristics. This survey highlights that long-acting injection can afford patient some adjustments that oral injection cannot have, and importance of providing patients with options can contribute their treatment, therefore, finding a right therapeutic regimen for schizophrenia patients can be highly individualized and obtaining a shared decision making between patients and professionals healthcare are positive to keep treatment adherence (Robinson et al, 2023). Compared with oral injection, intramuscular injection has more flexible characteristics in respecting patients' preference and personal- convenience, and these adjustments decrease the possibility of discontinuing the medication and further increase the treatment adherence. A claim-based study related to antipsychotic adherence between schizophrenia patients receiving oral and long-acting injection, provides that a smaller percentage of patients receiving LAI were non-adherent, and had longer continuous period than oral injection (Marcus et al, 2015). Under the circumstances of discharging from hospital, patients received from LAI perform a stronger stability and adherence in injecting the medication, and olanzapine is just one of intramuscular injectable antipsychotics in treating schizophrenia. The long-acting injection of olanzapine doesn't only affect improve the adherence of schizophrenia treatment, but also decreases the mortality in patients who is drug-naïve.

Intramuscular injection is not exclusive, or only can be used in olanzapine, one study provides that ziprasidone is intramuscular injectable as well. A long-acting injection of ziprasidone can be conducted under specific circumstances, such as acute episode of schizophrenia. "Ziprasidone IM demonstrated significant and rapid reduction in agitation, and sequential oral formulation keep stability and continuation of the treatment can further ensure efficacy" (Wu et al, 2023). Indeed, the practical application of long-acting injection doesn't limit on olanzapine, but can be used in several antipsychotics, such as haloperidol, fluphenazine, risperidone, aripiprazole and paliperidone.

These medications are available in a long-acting injectable form that can be administered intramuscularly every few weeks, under supervision from professional healthcare. A meta-analysis of 92 randomized trails including 22645 participants exhibits enough information and data in exploring whether oral and long-acting injection of antipsychotics can effectively prevent relapse and recurrence. This article applies Cochrane Risk of Bias tool and CINeMA to conduct a comparison between placebo and several types of antipsychotics, both oral injection and long-acting injection are performed in this meta-analysis, which results to a best-performing treatment in schizophrenia, especially for long-acting injections of olanzapine, having the highest confidence level for relapse prevention. "In terms of relapse prevention, all antipsychotics – with the exception of clopenthixol-oral (OS), haloperidol-LAI and (zu) clopenthixol-LAI – were significantly more effective than placebo. "High" confidence was found for the following antipsychotics (ordered from the largest to the smallest point estimate): amisulpride-OS, olanzapine-OS, aripiprazole-LAI, olanzapine-LAI, aripiprazole-OS, paliperidone-OS, and ziprasidone-OS" (Ostuzzi et al, 2022). After the comprehensive analysis, intramuscular injection provides patients with a flexible way that can decrease the degree of discontinuing olanzapine, and patients can sustain a long-term adherence of treatment under using long-acting injection, which supports the thesis of this literature.

Side effects between oral injection and intramuscular injection

For an open labeled study, the tested medication is ziprasidone rather than olanzapine, but still can be used to introduce whether there are differences of side effects between oral injection or long-acting injection, because severity of side effects can influence patients' impression to each injection. If intramuscular injection can cause less side effects than oral injection, then receiving side effects from long-acting injection should be the biggest factor improving treatment adherence of patients. But the study didn't exhibit a major difference in adverse effects between different injections.

Time interval in intramuscular injections

Memory loss and malfunctional ability in managing habits are common in schizophrenia patients. These aging characteristics can cause psychotic patients not to strictly follow the doctor's recommendation and

order, which can be reflected on forgetting to take the medication, the relative behavior of discontinuing the medication. Time interval of orally taking olanzapine is a daily activity that schizophrenia patients must seriously follow. The daily dosage of taking olanzapine is usually between 5mg to 10mg per day, which means patients must raise a habit of taking medication every day. But the time interval of long-acting injection is comparatively longer, patients only need to come to specific site to finish their intramuscular injection. For older people, lower starting dose (150 mg/4 weeks) to be considered for people 65 and over. Possible serious risks of weight gain and increases in cholesterol and triglycerides are more common in teenagers than in adults. No dosage adjustment required based on renal and hepatic function (Riboldi et al, 2022). Shorter involvement spending on taking medication can be a expected phenomenon to patients who are difficult for them to take the medication per day, a longer interval of taking medication can be preferred by patients who feel annoyed of taking medication. Comprehensively speaking, a longer interval can be a advantage to intramuscular injection, and it can decrease the degree of discontinuing the medication and improve the treatment adherence.

The JBI appraisal tool is a research approach used in evidence synthesis, which includes a rigorous process of assessing and synthesizing research evidence. After applying to JBI appraisal tools, out selected articles related to treatment adherence and long-acting injection of olanzapine have a strong statistical method and thesis question, although still with the exitance of publication bias, our selected articles can provide us enough evidence-based information.

Discussion: Limitations of literature

The biggest limitation of this literature review is collecting a few RCTs used to conclude our finding. RCT is the gold standard of testing a hypothesis or a theory, due to the limited RCTs related to intramuscular injection of olanzapine and adherence of schizophrenia treatment, our findings are not purely based on RCTs. Excluding a lack of citing RCT, we still have the limitation of publication bias, which means significant findings are more likely to be published than studies with null or negative results. This can overestimate the effectiveness of literature review, and there is not any statistical comparison made under RCTs. Another limitation is that the author obtains a strong subjective perspective when searching the keywords through PubMed, such as deliberately search or seek research related to disadvantage of oral injection and positive effects

under long-acting injection. The number of selected articles is less, and should involve more related studies in the future, which can increase the effect size of schizophrenia patients.

Pharmacological implications

The mechanism of olanzapine is to block several neurotransmitters from the brain, such as dopamine, serotonin, norepinephrine and histamine, which can affect patients 'dopaminergic and serotonergic levels. Beside affecting dopamine and serotonin, olanzapine exhibits an affinity to alpha-1 adrenergic, histamine H 1 and muscarinic receptors (Sun,2022). These components influenced by olanzapine can contribute to some side effects, such as sedation and weigh gain, which explains why 60% schizophrenia patients have experience of discontinuing olanzapine because of side effects of olanzapine. Although long-term of using olanzapine can induce hypertriglyceridemia, causing a higher risk of cardiovascular disease, the underlying mechanism remains unclear (Huang et al, 2022). There are other studies indicating that olanzapine toxicity can trigger rapid fluctuation between somnolence and agitation, and this mental fluctuation still needs more exploration and research.

Intramuscular injection and allergic reaction

Although patients receiving intramuscular injection of olanzapine can improve the treatment adherence and decrease the risk of discontinuing medication, it's common for psychotic patients to have some allergic reaction, which means intramuscular injection may triggers some allergic reaction or severe cutaneous reactions. Paliperidone is another second-generation antipsychotic used to treat schizophrenia, and long-acting injection of paliperidone can cause adverse reaction of skin to patients who experienced allergic diseases before. The updated research shows that this side effect is exclusively for patients who have allergic disease, which negatively affects patients' attitude toward the whole treatment. "With regards to paliperidone, adverse reactions were found to occur in under 2% of treated subjects. The skin and subcutaneous tissue disorders that occurred included acne, dry skin, eczema, erythema, hyperkeratosis, pruritis, rash and urticaria" (Borojevic et al, 2022). Approximately 2% of schizophrenia patients receiving from long- acting injection can appear skin-related adverse effects, which may decrease patients' active participation in selecting intramuscular injection as main

way of taking medication. Patients with allergic reaction may insists on using oral injection because of avoiding exclusive subcutaneous tissue side effects caused by intramuscular injection, although patients rejecting intramuscular injection can avoid unnecessary side effects from skin, they still have a potentially high risk in discontinuing medication in the future.

Gastrointestinal effects in long-acting injection

There is limited research indicating that long-acting injection can cause certain side effects to psychotic patients, on the contrary, it's possible to reduce certain risk of side effects with oral injection. Because intramuscular injection mainly relies on digestive system, it's common for patients to have gastrointestinal effects. But in the case of intramuscular injection of olanzapine, gastrointestinal effects is less than oral injection of olanzapine since directly injecting through muscle doesn't require digestive system to process olanzapine, which means gastrointestinal effect can be restrained under long- acting injection of olanzapine, but still need further studies to explore.

Long-acting injection and treating attitudes

Most articles have indicated that intramuscular injection can prevent disorder relapse and recurrence, but controlling a third factor is very important in future studies. Naturalistic studies of psychiatric medication should play a major role in exploring whether ways of injection can affect patients' treatment adherence. Long-acting injection is different with other conventional way of taking the drugs, it combines with flexible choices and adjustment, it can make patients feel causal and relaxed because its long- interval, which means a naturalistic study can provide us information does patients choosing long-acting injection have a more optimistic attitude than patients choosing oral injection. Briefly speaking, whether improving treating attitude of patients can contribute to a more expected treating outcome, because being optimistic or holding a good mood to take the medication can improve patients' self-awareness, therefore, to actively continue the medication. Future studies related to treatment adherence can expend to patients' mood and optimistic attitude, whether the change of injection way can improve their mood, self-awareness, positive attitude.

Psychosocial interventions in schizophrenia

Psychological assistance and relative therapy can are highly recommended in psychotic patients, since CBT can help to mitigate patients' anxiety, depression and other negative attitudes toward treatment. Indeed, the theory of psychosocial assistance is the same as allowing patients to randomly select their own preferred location site to take the long-acting injection, which potentially increases their activeness and willingness. Orally taking medication is more likely a kind of behavior forced by clinical professionals, but long-acting injection can allow patients to make their own decision, if long-acting injection combines with psychological assistance, we can reasonably believe it's possible to consolidate a more health and confident attitude when taking the treatment.

Conclusion

Based on the literature review and discussion, it can be concluded that intramuscular injection of olanzapine can potentially improve treatment adherence and reduce the risk of discontinuing medication in patients with schizophrenia. However, there are limitations to the literature review, including a lack of RCTs and potential publication bias. Pharmacological implications of olanzapine include potential side effects, such as sedation and weight gain, and the mechanism behind these effects remains unclear. Patients receiving intramuscular injection of olanzapine may experience allergic reactions or adverse skin reactions, which may negatively impact treatment adherence.

While long-acting injections can potentially reduce gastrointestinal effects, further studies are needed to explore this effect. It is also important to consider the impact of injection methods on patients' treatment attitudes and adherence. Future studies should aim to expand the types of antipsychotics that are eligible for intramuscular injection and explore the impact of injection methods on patients' treatment adherence and overall well-being. The article discusses the importance of medication adherence in treating schizophrenia and other severe psychiatric disorders. Antipsychotic medications such as olanzapine are commonly used to treat these conditions and can be administered orally or via intramuscular injection.

Although olanzapine has fewer side effects than typical antipsychotics, patients still commonly discontinue the medication,

which can lead to relapse and poor treatment outcomes. Various factors contribute to non-adherence, including disease-related factors, patient-related factors, and treatment-related factors. The article specifically focuses on the advantages of taking olanzapine via intramuscular injection and how it can improve treatment adherence compared to the conventional oral medication route. Improving medication adherence is crucial in preventing relapse and achieving promising treatment outcomes, and interventions to improve adherence should be considered to avoid discontinuation and further develop clinical strategies. Applying to different types of articles to this literature review article can have some advantages that information related to specific function of injection can be comprehensive, although RCT is the gold standard of experiments, other studies such as open-labeled study and cross-sectional study still provide us a clear picture how long-acting injection can have an effect in preventing relapse and recurrence.

Comprehensively speaking, based on selected studies in this literature review, concluding that intramuscular/long-acting injection can decrease the degree of patients discontinuing olanzapine, and this long-acting injection can contribute to a high adherence of schizophrenia treatment. However, whether intramuscular injection can be used in other psychotic medication is still explored by psychopharmacologists, and the future development of medication injection determines if long-acting injection can cause an effect on treating other psychotic disorders.

long-acting injection of olanzapine could be a good option for patients who want to improve their treatment adherence and avoid the risk of actively discontinuing or reducing the olanzapine. But to the patients who may have skin and subcutaneous tissue disorder, intramuscular injection may not be the suitable injection for them. Anyway, long-acting injection of olanzapine should be advocated during the treatment of schizophrenia.

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The Neurobiology of Anxiety Disorder: Changes in the Brain, Genetics, and Treatment
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Anxiety is a response that all people encompass when in situations where they feel fearful or uncertainty. While this may be perceived as a healthy response in one instance, as it begins to consume one's day to day life, where there is constant worry and nervousness this may be a sign of generalized anxiety disorder (Harvard Health Publishing, 2011). Stress is good in moderation, in which it is a motivating factor that helps complete tasks or keeps one out of engaging in any reckless behavior. But stress can very much be reckless, where you are so overwhelmed and cannot focus on subjects in front of you. An example of this is studying for an exam but putting so much pressure on yourself to do well that once you get to the test you are so overwhelmed and your performance declines. Anxiety disorder is one of the most common psychiatric disorders effecting about 10% of individuals at some point during their lives. Although anxiety disorders tend to be less visible than other disorders such as Schizophrenia or Alzheimer's disease, they can be just as disabling to the brain and how it functions (Bystritsky et al., 2013). Since the diagnoses of anxiety disorder are hard to pinpoint, they are continuously being studied, but the focus for diagnosis is based on the DSM-5 or the Diagnostic Criteria, in which a person has excessive anxiety for at least six months, disturbing one's behavior. Treatments often used for anxiety disorder are antidepressants or psychotherapy, dependent on the persons condition (Harvard Health Publishing, 2011). In this paper I will focus on the development of generalized anxiety disorder, how it arises and effects brain function, and the best treatment to reduce symptoms of anxiety.

Generalized anxiety disorder (GAD) is an excessive form of anxiety in which a person feels constant worry or uncertainty that is unprovoked and uncontrollable, but also interferes with their day to day lives (Harvard Health Publishing, 2011). According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), an individual with generalized anxiety disorder finds it difficult to control their own worries and their anxiety and worry are associated with three or more of the following six symptoms, with at least one of these symptoms present more days than absent. These symptoms include restlessness or feeling on edge, being easily fatigued, difficulty concentrating or having a blank mind, easily irritated, tense muscles, and difficulty sleeping (Gale and Davidson, 2007). Think of that little panic you may get when you oversleep for work. You get overwhelmed as you rush to get dressed and out the door, but also thoughts of uncertainty flow through your mind as you wonder what your boss may say or what the consequences may be for this. Now imagine feeling like this every day for long periods of time, without a specific

reason and not being able to manage this feeling. You feel trapped and out of control of your own life and this can lead to other health risks. As a person begins to age from mid-teens to early 30s, one starts to face more stress factors such as school, bills, jobs, and the future itself, which is where GAD diagnosis is more prevalent. Generalized anxiety disorder arises from a variety of biological and environmental factors such as brain chemistry, genetics, experiences, and development and personality. Some risk factors for this disorder, tend to be low socioeconomic status and exposure to childhood adversity. Therefore, children who experienced physical or sexual abuse during their childhood, are at an increased risk. It affects about 6.8 million adults in the United States and is more prevalent in females than males but the reasoning for this is still speculative and not well understood, but women experience a series of reproductive changes associated with hormonal changes throughout their lifetime causing this stress response (Bahfami and Yousefi, 2011). A person who has a negative or timid temperament and avoids any form of danger, because they are scared of the outcome or see the worst aspect of things to occur, may be more prone to having GAD then a person who is optimistic and puts themselves in the position to experience danger and therefore adapts to this "fight-or-flight" response at the appropriate time (Mayo Clinic, 2017). Along with personality, comes one's life experiences. According to Mayo Clinic, a person who has experienced significant life changes such as moving every so often, the change of schools frequently, getting bullied, or other traumatic or negative experiences causes a person to be more susceptible to developing this disorder.

As constant worries become an everyday matter, over a course of six months, that cannot be shaken, this is classified as generalized anxiety disorder and some symptoms include a racing heart, dry mouth, tense muscles, difficulty concentrating, sleep problems, sweating, and restlessness, all which may occur at the same time (Harvard Health Publishing, 2011). As these have an integral effect on each other this can lead to an increased risk towards one's health, such as a greater risk for heart failure, digestive complications, headaches, and migraines, sleeping impairments or even worse alcohol dependence. It can also be disabling to everyday activities, in which a person has an impaired ability to perform tasks efficiently because of not being able to concentrate, they lose their energy, and often have an increased risk of depression and lack the motivation to want to do anything. Addiction to alcohol and drugs is a common problem in those that struggle with anxiety. It is seen as a coping mechanism, in which after a hard day at work you may come

home and have one or two drinks, but someone with GAD can easily have three or more drinks to silence their minds, causing them to "self-medicate" and become dependent, which can lead to addiction. Alcohol is a GABA agonist working on the brain, in other words, it mimics the brains response to GABA, the inhibitory neurotransmitter of the brain. So, while alcohol is reducing this over activity of stress working on the brain, it leads to dependence for coping. Generalized anxiety disorder can be very disabling and impair a person's ability to perform tasks quickly or efficiently because of the constant thought or worry that it will not be completed on time or correctly. It begins to drain all of your energy to the point that you lack the will to want to complete your tasks. While this may begin to have detrimental effects on one's health, it also leads to effects on a person's cognition, far beyond depression. Depression and anxiety often coexistent within one another since they have very common symptoms. Depression deals with the difficulty to make a mental effort to complete a task in which a depressed person just feels hopeless in simpler terms, whereas cognition deficit, commonly found in those with anxiety would be the constant worry of completing a task, but simply not being able to focus to get it done, due to being so worried and helpless (Harvard Health Publishing 2011). Anxiety arises from differences in brain chemistry and chemical imbalances such as norepinephrine or serotonin, but after a long period anxiety begins to prey away at the central nervous system, and this results in an activation of brain circuits and neurotransmitters located in the limbic system, brain stem, and higher cortical areas to begin firing out of control (Martin et al., 2009).

Harvard Health Studies (2011) indicates that two brain circuits are activated when a person is confronted with a dangerous situation, and once activated this sensory response, such as noise or smell, is relayed to different regions of the brain, which is better known as the flight-or-fight response. The first circuit is the cortical areas that deal with thinking and decision making, for an example, asking yourself what will I eat for breakfast this morning and deciding to eat eggs and toast. Areas of the brain that deal with these decisions include the prefrontal cortex, which is responsible for executive function- planning, predicting consequences based on one's actions, and understanding one's own behaviors. Next you have the orbitofrontal cortex that is responsible for coding the information taken in and controlling one's impulses and mood. Lastly, the ventromedial frontal area controls reward processing and how our body responds to emotion. In a healthy individual, these cortical areas regulate impulses, emotions, and behavior through the inhibitory control

of emotional-processing structures (Martin et al., 2009). In an individual with GAD, evidence has been found that there is a deficit in the functional connectivity of these higher cortical areas, which is why impulses and reactions to stimuli are not managed properly (Stein and Sareen, 2015). This is where the second circuit comes into play. The second circuit deals with the emotional aspect of a situation or the limbic system, such as looking at a stove and thinking of a time in which you may have burned your hand while cooking, so you are extra cautious. The limbic system allows for the sensory, affective, and cognitive integration of pain and how the body is to sense this pain. The hippocampus is a structure apart of the limbic system that plays a role in stress-response and the amygdala allows the body to respond to fearful stimuli. Stress works through the hypothalamus, activating the Locus Coeruleus- Norepinephrine, ventral hippocampus circuit. This activation causes an anxiety response from the amygdala due to evoking a memory that is tied to a bad experience, which is more often linked to PTSD or Post-traumatic stress disorder. While it affects the memory response circuit, it also affects many other circuits such as the learning circuitry, which again is why it may be hard for an individual to focus on or learn a task. After considering some imaging studies, it has been identified that individuals with GAD have undergone structural, chemical, and functional changes within their brain reflecting their illness/symptoms, but specifically linked to disruption of activity in the emotional centers rather than higher cortical areas (Madonna et al., 2019). Although these imaging studies are beneficial, whether these differences in brain chemistry are causing GAD or are caused by GAD itself are still unclear. While the amygdala is responsible for the response to fear, in GAD patients this response is abnormal. The amygdala becomes oversensitive and reacts to situations that are not truly threatening, provoking an emergency stress response, causing the brain to create its own fears (Harvard Health Publishing, 2011). A study on amygdala volumes was done in pediatrics with generalized anxiety disorder (De Bellis et al., 2000). The comparison of brain regions between GAD individuals versus control subjects were taken into account based on age, sex, height, weight, socioeconomic status, and IQ. It was found that right and total amygdala volume, was much larger in the GAD individuals than the normal subjects, indicating that those with anxiety disorder may be predisposed to this hyperactive stress response, but again further studies still need to be done as these findings are still somewhat unclear. Through the use of neuroimaging studies, scientists are able to better understand how anxiety disorders, such as GAD, demonstrate an enhanced activation

in the fear networks of the brain enabling a patient to undergo the symptoms of anxiety.

For treatment measures to be taken into account, an assessment must be done to evaluate any behavioral or somatic symptoms, including psychosocial stressors, developmental issues, genetics, and past medical history including trauma and substance abuse (Munir & Takov, 2021). This is known as the Hamilton Anxiety Scale. It is a scale that consists of 14 items that are defined by a series of symptoms that measures both psychic anxiety and somatic anxiety. Psychic anxiety often affects the mind and thought process or the mental capacity, while somatic anxiety is associated with the autonomic symptoms such as tense muscles, sweating, or shortness of breath. Patients are then rated by the level to which he or she has that condition (Hamilton, 1959). Based on the severity of one's symptoms determines whether they should be treated or not, but if they are showing signs of depression or suicide, hospitalization and treatment are highly recommended. Following this, there are two main treatments which are cognitive behavioral therapy (CBT) or psychotherapy and a series of medications to suppress the symptoms such as antidepressants. Since GAD patients are more likely to have heightened interpretations of external stimuli causing one to often be tense, psychotherapy is thought to help develop cognitive or behavior strategies to manage cognitive and somatic symptoms that are exceeding the norm. Specifically, exposure therapy, is known to be highly effective for treatment because patients are systematically and repeatedly exposed to stimuli that are provoking their anxiety until their fear subsides (Holzschneider & Mulert, 2011). Through this method, patients are thought to regain their brain structure and function. Another method is the use of relaxation practices such as yoga or deep breathing, in which a person can decrease any physical tension within their body. Cognitive behavioral therapy is treatment that includes psychoeducation, changing ones thought patterns and adjusting to a healthier lifestyle, and a gradual exposure to anxiety driven situations and learning how to manage one's response to this.

In terms of pharmacological treatment, some first line drugs include selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), antidepressants, and Benzodiazepines. SSRIs and SNRIs increase neurotransmitter activity in the brain which is essential to amygdala and hippocampal function. SSRIs are thought to correct the chemical imbalance taking place in the brain, more specifically working on the neurotransmitter serotonin that plays an important role in feelings of happiness, concentrating, memory, and sleep. They reduce

cognitive symptoms such as constant worry and help with feelings of depression. Some side effects of SSRIs and SNRIs are anxiolytic effects for a period of 2 to 6 weeks but are thought to build up tolerance which is essential to treating someone with anxiety (Bandelow et al., 2017). SSRIs are currently considered to be the first line medication for many forms of anxiety, including GAD and are safe for long term use and are non-addictive (Anxiety and Depression Association of America, ADAA, 2020). It is important to speak with a physician if one is considering stopping or reducing this medication because stopping abruptly, could cause an imbalance in the brain leading to much worse symptoms then before. Antidepressants are used to treat those with GAD at times, but this is dependent on their severity and are strongly advised to be used with caution in patients who are considered to be at risk for suicide, along with starting usage at a low dose and slowly increasing the dosage as needed (Bandelow et al., 2017). Benzodiazepines are used by a relatively small percentage of patients but is associated with central nervous system (CNS) depression and cognitive impairment. Benzodiazepines are GABAergic, meaning they inhibit neuron activity in the brain and therefore decrease locus coerulus response to stress, which is very beneficial for someone experiencing anxiety. They reduce physiological symptoms one may be experiencing such as tense muscles or frequent panic. While it can be beneficial in some instances and are fast acting, those that are treated long term with benzodiazepines often become dependent and because of this, the use of this drug must be carefully considered. Benzodiazepines are now considered unsafe for continuous use due to its addictive property and is not recommended for individuals with addiction problems or suicidal thoughts (Harvard Health, 2014). The FDA has now required that all benzodiazepine prescriptions have warning labels, regarding the risks of addiction and withdrawal symptoms (Harvard Health, 2014). Of the treatment measures mentioned, a combination of psychotherapy and medication has shown to be the most effective because balancing between the two is thought to enhance the effectiveness of medication without having to increase the dose and have someone become dependent on a drug (Bandelow et al., 2017). Therapy is thought to be advantageous to the point that an individual can be removed from any type of medication, but this must be carefully considered as a relapse can occur years later. At the end of the day, GAD patients should be aware of their options in terms of treatment and find something that works best for them but also a treatment that they feel most comfortable with.

Current research, on general anxiety disorder has provided a greater

understanding of the processes the brain undergoes when under constant stress and how this effects activity of one's daily living. Our current understanding is that constant worries that are unprovoked and lasting for six months are classified as generalized anxiety disorder and the symptoms that accompany it can lead to increased health risks that play a critical role on brain function. The understanding is that individuals that have been predisposed to traumatic or negative events during their childhood are likely to develop GAD. The relationship here is that factors of stress, lead to deficits of two brain circuits, both the cortical areas and the limbic areas, that fire out of control causing that constant feeling of panic, with a focus mainly on the emotional centers. Because each individuals' symptoms for GAD differs, treatment measures vary based on how severe it affects one's ability to function every day.

More complete studies on generalized anxiety disorder can analyze the factors that are linked to the onset of this disease, including sex, genetics, and the environment of upbringing. Through this knowledge, researchers can develop and provide prevention strategies along with better treatment measures. Once we have a clearer understanding of the relationship between onset of the disease, how it effects the brain, and the most effective way to prevent one from undergoing an anxiety disorder, research can help assist physicians in providing treatment and knowledge of the disorder to their patients, to help them live a normal and healthy live to the best of their capability.

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Thank you for being an integral part of the Mind, Mood & Medications community. Your engagement fuels our passion and propels our field forward.

We look forward to the insights we will gain and share in the issues to come.

With gratitude and enthusiasm for our collective future,

Derek H. Suite, MD, MS
Editor-in-Chief
Student Journal of Mind, Mood & Medications

Derek H. Suite, MD, MS, is a board-certified psychiatrist and an academic leader in the field of neuro-psychopharmacology. As an Assistant Clinical Adjunct Professor with Columbia University's Teachers College since 2015, Dr. Suite has been instrumental in shaping the understanding of psychopharmacology of tomorrow's leaders in mental health, bringing over 25 years of clinical experience to his role as an educator and mentor.

Dr. Suite's academic journey began with obtaining his undergraduate and Master of Science degrees from Columbia University, and medical degree from Drexel University College of Medicine, followed by a residency in psychiatry at Montefiore Medical Center/Albert Einstein College of Medicine, where he selected as a Chief Resident.

Throughout his career, Dr. Suite has demonstrated exceptional leadership in multidisciplinary settings, spearheading initiatives that bridge the gap between clinical practice and academic research. His scholarly work, published in peer-reviewed journals, has significantly contributed to the understanding of critical issues in psychiatry, including, trauma, racial health disparities, and the psychological dimensions of urban mental health.

Dr. Suite's dedication to advancing the field is further exemplified by his pioneering the Student Journal of Mind, Mood, and Medications. This academic, student-driven publication serves as a platform for emerging scholars to engage with cutting-edge research and clinical perspectives in psychopharmacology and mental health.

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