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Excuse me! Whose mother are you?

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You've probably seen it: a vacuum cleaner commercial filmed for Mother's Day a while back was censored. Two women who've never met before run into each other at one of the company's stores; as they're looking at vacuum cleaners together, one senses something they have in common and asks, "You're a mom, aren't you?" She has sensed and recognized something in the other woman. Both are on a quest related to their children. In that sweet moment where motherhood brings them together—a place that encompasses a child's mischief and fears—they share their feelings about finding solutions. It's a matter of "maternal" female solidarity. Later, we see one of the women calling out as she enters her home: "My little boy!" And a dog enters the scene, running excitedly toward his mother with a toy in his mouth. An investigation into the commercial was quickly launched on the grounds that it "did not align with society's family values," and as a result, the ad was pulled by the company. The attempt at censorship sparked a level of debate that might not have occurred if no action had been taken at all. Although there were quite a few attacks alleging that it undermined the "sacred status of motherhood" and insulted "family values," perhaps even more—let's hope so—posts emerged expressing support and criticizing the censorship.

In light of the debates sparked by this advertisement, might we say a few words from a psychoanalytic perspective—on the one hand, regarding motherhood, bonding, and the relationship between humans, animals, and nature; and on the other, regarding the maternal and the feminine, which are deeply rooted in the depths of the psyche?

The dependence experienced by a human infant—due to its very early entry into the world and its inability to survive without a caregiver—has been defined by Freud as "fundamental helplessness" (Hilflosigkeit) (1,2,3). This situation not only places the infant in a state of need but also provides an experience of omnipotence because the things it needs simply materialize. The person caring for the infant is usually the mother, but at times it can be anyone of any gender who occupies a "maternal" role. The "mother" who cares for the infant holds, feeds, cleans, comforts, and puts the infant to sleep. Through physical touch, her voice, and her scent, she keeps the infant alive not only physically but also emotionally. To the child, who has not yet developed a sense of self during this period, she offers her own self as a kind of emotional vessel. She feels, experiences, and internalizes on the child's behalf; she absorbs what she receives from the baby, processes and transforms it within herself, and then returns it to the child. This is the time-as Erikson describes in the first stage of his "eight stages of human development"-when "basic trust" or "mistrust" develops, as the infant feels, "I am what I have been given" (4). An infant who experiences a sense of oneness with the mother in the early stages gradually begins to distinguish between "self" and "other"-as the mother comes and goes, is absent, or directs her gaze elsewhere-toward her spouse, partner, or father-and thus

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takes the first steps toward becoming a subject. This process never unfolds entirely ideally, and various disruptions and disappointments are common. However, when there are significant disturbances or traumatic experiences, they can have profound effects on the child's psychological development.

So, in terms of the mother-baby unit (5) which Winnicott described with the words "there is no such thing as a baby?", there is a state of being "One" in the early period. Following the period of experiencing "sameness" and similarities, the Oedipal phase begins, during which gender differences are recognized and it is realized that the mother's object of desire is someone else, thus reaching the threshold of socialization. When this threshold is not properly crossed—either due to being the object of the mother's desire or denying its impossibility—the door opens to psychosis or perversions. According to Elda Abrevaya, the ability to invest libidinally in the "mother" once she can be recognized as the first object is a fundamental element in enabling an individual to make room for the "other" in their life (6,7).

As you know, Freud's theory focuses primarily on the Oedipal stage and the period that follows it. The pre-oedipal stage is not a phase on which he concentrates. He first spoke of "psychic bisexuality" in 1905 (8) and continued to develop his arguments regarding this concept in his later works. While defining this concept and writing on femininity, he struggles to address the feminine element in the psyche (9). This leads him to describe "the rejection of the feminine" in his late-period essay "Analysis Terminable and Interminable" as the foundational bedrock of psychoanalysis (10). Despite his intuitions regarding femininity and the mystery of female sexuality, what Abrevaya describes as "had come up against his own foundational bedrock" (6) may have led him to this point. However, the criticisms and contributions of his followers, especially female psychoanalysts, to Freud's theory have brought the issue to a point where there are very rich discussions today (11).

Let us, then, explore the pre-oedipal stage a bit further. During this period, the fact that the mother—the first love object—is a woman leads to the first psychological template being feminine for children of all genders (7). Julia Kristeva describes this process as "endogenous homosexuality" (12), while Evelyne Kestemberg characterizes it using the concepts of "primary homosexuality" and "primary identification" (13), both of which refer to the "feminine" element inscribed at the very foundation of every person's psyche. Here, identifications are based on "sameness." The mother's desire for the father as her partner is also present from the very beginning. Abrevaya emphasizes that "the father's possession of the phallus is significant not in terms of the power and authority it might represent," but rather "in that it signifies sexual difference" and "the father's masculine, libidinal body is the object of the mother's desire" (6). The severing and rejection of the maternal bond defines the transition to the symbo-lic order and socialization. However, the question of how this symbolic order functions and what its structure is also merits consideration.

Let's move on to the social sphere for a moment. The formation of societies and the construction of the symbolic order are based on exclusion. The process that Freud discusses in Totem and Taboo begins with the killing and eating of the flesh of the primitive tribal chief, who owns everything and everyone, by his rebellious sons (14). Following this first murder, the sons establish "a patriarchal social contract" centered on the taboos of incest, murder, and cannibalism. Although it has undergone transformations through various revolutions throughout history, this patriarchal social contract continues to exclude women and the feminine. In ancient Greece, during the transition from tyranny to democracy, citizens were invited to participate in politics, speak in the public sphere, and build a self-governing society. If you ask who the citizens are, they are free, adult men. Women, children, slaves, the mentally ill, and foreigners cannot be citizens. According to Arendt, being a citizen also defines what it means to be "human" (15). In today's modern societies, while groups other than foreigners and those deprived of their rights are recognized as citizens, the inclusion of groups other than free men in politics fundamentally relies on a process of exclusion through inclusion and inclusion through exclusion. Refugees, LGBTI+ individuals, women,

children, older adults, people with mental illnesses, those deprived of their liberty, and ultimately nature and animals are groups that, in terms of the right to life, have, in Arendt's words, "lost the right to have rights" (16). Mechanisms that define humanity through exclusion, on the other hand, are based on describing all life and vitality from an anthropocentric perspective. Animals and the animal realm are also rejected and excluded, in an attempt to disregard their place in human life and the psyche.

So, what does all this have to do with a vacuum cleaner commercial or with being a mother to a dog or any other animal? Quite a lot, in my opinion. Because here, we encounter the desire of the cultural order, of the dominant power, to define motherhood. This desire goes beyond stripping motherhood of its psychological dimensions and reducing it to biological references; it is a perspective that seeks to define motherhood by excluding it from the construction of the social. Forming a maternal bond is fundamentally linked, in the psychic realm, to the feminine aspect of psychic bisexuality. The cultural order, which seeks to determine who will be a mother and how one becomes a mother, sets out to define motherhood through its control over the female body and sexuality. This accepted definition of motherhood is also fundamentally linked to the rejection of the feminine. The exclusion and rejection of the feminine element, which is embedded in the psyche of every individual regardless of gender, is a cornerstone of the patriarchal social order and its cultural structures such as religion and morality. From Kristeva's perspective, this exclusion is made possible by the coding of everything related to the maternal bond and the feminine—such as childbirth, menstrual blood, breast milk, vomit, and feces—as repulsive, and by keeping them at a distance through fear (17). On the other hand, this exclusion at the foundation of the symbolic order is not, in fact, a complete expulsion. It is a process of inclusion through exclusion. Giorgio Agamben traces this exclusionary inclusion mechanism in the construction and functioning of the dominant power structure in the political sphere of today's modern societies (18). This mechanism, which is carried out by suspending rights everywhere—in the social sphere, in the establishment of the domestic and public sphere, the family and the political scene—defines the transformation of the "state of exception" into the rule (18,19). In this context, motherhood is defined as a sharply limited "social role" for women; it is internalized through exclusion and transformed into a "sacred life" under the determining authority and domination of sovereign power and the cultural order. In his discussions of the "state of exception," Agamben draws on the concept of "homo sacer," which has its roots in Roman law (18). "Homo sacer" is a concept that describes individuals who can be killed but cannot be sacrificed. Killing them goes unpu-nished, but sacrificing them through rituals is also forbidden. This is because a sacrifice is an entity included within the divine realm. "Homo sacer," or in this case "femina sacer," is transformed into a "cursed sacred" that must remain outside the divine realm. Just as is the case today with women, children, LGBTQ+ individuals, refugees, and animals living on the streets. This patriarchal system designates itself as the ultimate arbiter of what constitutes a "life worth living."

A woman who forms a maternal bond with an animal, or anyone who forms such a bond, is also defying the dictates of the ruling government. Yet under this system, a woman—who has no sexual desire, who gives birth to and raises as many children as desired, in whatever way is desired, and who provides care but does not fall in love—is permitted to lead a life in which she appears to have a place in society but is actually excluded if she does not conform. So why are both animals and the bonds we form with them so often targeted by hatred? Many arguments can be put forward from various perspectives. I believe this hatred is more closely linked to the "rejection of the feminine." Those who strive to reject the feminine element within themselves project this hatred onto external objects by denying and excluding it. The hatred awakened by a bond with a dog is likely related to the earliest feeling of "basic insecurity," stemming from an envy of the animal's evoked "unbridled" freedom, vitality, and the capacity for bonding that implies a libidinal investment in an object of affection.

Returning to the reactions to the ad and the fact that censorship is at work here, launching an inves-

tigation and subjecting it to a social media firestorm amounts to saying, "I'll decide whose mother she is!" At the same time, this is a discourse about a patrilineal system that is excessively fearful of anything that evokes matrilineality. According to this, acceptable motherhood is tied to a cultural order that is nurturing, clean, and excludes everything that evokes feminine sexual desire in particular. Acceptable motherhood and womanhood are constructed through the exclusion of the feminine—which is met with revulsion and fear (17). For socialization to occur, the bond with the mother must be severed, yet at the same time, this bond can never be completely severed. In contemporary societies, there is a transition to a symbolic order in which the social is established only through the rejection of this bond. At this point, it is impossible not to see that this is not a complete transition, but rather is linked to remaining at a threshold or a boundary. Perhaps for this reason, today we are witnessing the rejection of an autonomous society and the construction and maintenance of a heteronomous society (20), that is, a society dependent on the other.

Where did the associations evoked by the "A True Story of Motherhood" ad take us? Today, we live in an era where the rejection of femininity, its exclusion and encoding as unclean, dangerous and frightening in the social sphere, extends to those whose lives are dominated, ignored and destroyed in cities that have turned into concentration camps (21,22). This is an age in which there is no object as the Other, in which disgust and exclusion function as a psychic object, in which the process of subject formation has been crippled, and in which psychic structures are becoming increasingly dominant. Therefore, we witness not only the inability to connect with the object, the other, through a libidinal investment, but also the dominance of attacking this libidinal bond with hatred. However, repeatedly confronting the fact that humans can never be complete, that the nature from which we come and in which we live is based on the chaos that persists in our unconscious, can open up much more space for human existence and for knowing ourselves. When this space is opened up, it becomes possible to find and rediscover ways to coexist and form bonds not only with nature, animals, and our planet but also with those who are different within the social sphere. True connection is only possible through respect for the right to life and every form of existence. So let's ask: Excuse me, whose mother are you?

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REFERENCES

1. Freud S. Haz İlkesinin Ötesinde, Ben ve İd. Babaoğlu AN, çeviren. İstanbul: Metis Yayınları; 2001.

2. Freud S. Bir Yanılsamanın Geleceği. Şipal K, çeviren. İstanbul: Say Yayınevi; 1986.

3. Freud S. Uygarlığın Huzursuzluğu. Barışcan H, çeviren. İstanbul: Metis Yayınları; 1999.

4. Erikson EH. Childhood and society. New York: W. W. Norton & Company; 1994.

5. Winnicott DW. The theory of the parent-infant relationship. International Journal of Psychoanalysis. 1960;41(6):585-595.

6. Abrevaya E. Kadınlığın Uzun ve Dolambaçlı Yolu. İstanbul: Bağlam Yayınları; 2013.

7. Abrevaya E. Psikanalizde Kadınlık, Arzu ve Yüceltme. Ülgen Kurtul P, çeviren. İstanbul: Bağlam Yayınları; 2025.

8. Freud S. Cinsellik Kuramı Üzerine Üç Deneme. İçinde: Kapkın E, çeviren. Cinsellik Üzerine. İstanbul: Payel Yayınları; 2006.

9. Freud S. Female Sexuality. International Journal of Psychoanalysis. 1932;13:281-297.

10. Freud S. Analysis Terminable and Interminable. International Journal of Psychoanalysis. 1937;18:373-405.

11. Perelberg RJ. Psychic Bisexuality: A British-French Dialogue. Lemma A, editör. New York: Routledge; 2018.

12. Kristeva J. Some Observations on Female Sexuality. Annual of Psychoanalysis. 2004;32:59-68.

13. Kestemberg E. "Astrid": Ou homosexualité, identité, adolescence. Quelques propositions hypothétiques. İçinde: Adolescence à vif. Paris: Presses Universitaires de France; 1999. s. 239–265.

14. Freud S. Totem ve Tabu. Sel S, çeviren. İstanbul: Sosyal Yayınlar; 1984.

15. Arendt H. İnsanlık Durumu. Şener BS, çeviren. İstanbul: İletişim Yayınları; 2021.

16. Arendt H. Totalitarizmin Kaynakları/2: Emperyalizm. Şener BS, çeviren. İstanbul: İletişim Yayınları; 2011.

17. Kristeva J. Korkunun Güçleri: İğrençlik Üzerine Deneme. Tutal N, çeviren. İstanbul: Ayrıntı Yayınları; 2014.

18. Agamben G. Kutsal İnsan: Egemen İktidar ve Çıplak Hayat. Türkmen İ, çeviren. İstanbul: Ayrıntı Yayınları; 2020.

19. Agamben G. İstisna Hali. Atakay K, çeviren. İstanbul: Ayrıntı Yayınları; 2020.

20. Castoriadis C. Dünyaya, İnsana ve Topluma Dair. Tanrıöver HU, çeviren. İstanbul: İletişim Yayınları; 2021.

21. Hayvanları Koruma Kanununda Değişiklik Yapılmasına Dair Kanun, 7527 Sayılı. T.C. Resmî Gazete, 32620 (1 Ağustos 2024). Erişim adresi: https://www.turmob.org.tr/arsiv/mbs/resmigazete/32620-2.pdf

22. İstanbul Sözleşmesi: Kadınlara Yönelik Şiddet ve Ev İçi Şiddetin Önlenmesi ve Bunlarla Mücadeleye Dair Avrupa Konseyi Sözleşmesi. 2011. Erişim adresi: https://istanbulsozlesmesi.org/sozlesmenin-tam-metni/

Linking craving to addiction severity in alcohol use disorder: The mediating impact of psychological flexibility

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SUMMARY

Objective: Alcohol Use Disorder (AUD) is a long-term mental health condition marked by alcohol use that is hard to regulate and accompanied by persistent cravings, both of which contribute to increased addiction severity and relapse risk. Psychological flexibility, a critical component of Acceptance and Commitment Therapy (ACT), has been shown to help individuals tolerate cravings without resorting to substance use.

Method: This study investigated the hypothesis that psychological flexibility serves as a mediator in the relationship between alcohol craving and addiction severity in individuals with AUD. The sample consisted of 86 individuals diagnosed with AUD who completed the Penn Alcohol Craving Scale, the Acceptance and Action Questionnaire–Substance Abuse, and the Addiction Profile Index. The potential mediating effect of psychological flexibility was analyzed using a mediation model.

Results: Craving was positively correlated with addiction severity and negatively correlated with psychological flexibility. Psychological flexibility significantly predicted lower addiction severity and partially mediated the relationship between craving and addiction severity, accounting for 29% of the total effect.

Discussion: The findings indicate that psychological flexibility plays a mitigating role in the relationship between craving and addiction severity in AUD. The effectiveness of psychosocial interventions, particularly ACT-based treatments, may be enhanced by targeting psychological flexibility. Further longitudinal and multicenter studies are warranted to confirm these mechanisms and inform clinical practice.

Key Words: Alcohol use disorder, Craving, Psychological flexibility, Addiction severity, Acceptance and Commitment Therapy

INTRODUCTION

Alcohol use disorder (AUD) is a chronic and relapsing psychiatric condition characterized by compulsive alcohol use, impaired control, and withdrawal symptoms (the experience of negative emotional and physical symptoms when not drinking). According to DSM-5, meeting at least two of eleven criteria establish the diagnosis, which can range from mild to severe (1–4).

One key concept in understanding the consequences of AUD is the severity of addiction. Factors influencing addiction severity include the number of diagnostic symptoms present, the degree to which alcohol use impairs daily functioning, the intensity of craving, the type and quantity of substance used, the frequency of use, and the individual's motivation to quit (5) Craving, defined as a strong and persistent urge to consume alcohol or other substances—often accompanied by physiological symptoms—has been recognized as a central feature of AUD. It plays a significant role not only in predicting relapses but also in determining addiction severity (6,7).

Alcohol use disorder (AUD) is recognized as the most common subtype of substance use disorders (SUDs) globally and associated with substantial psychiatric, physical, social, and economic burdens, including millions of deaths annually and signifi-

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cant healthcare costs (8–11). These alarming figures underscore the urgent need for effective clinical interventions and increased research efforts aimed at mitigating the impact of AUD. A comprehensive understanding and classification of alcohol-related issues is essential, especially given the diverse and multifaceted nature of these problems (12–14).

In recent years, psychological flexibility has emerged as a promising therapeutic target in the treatment of AUD and other SUDs. Within the framework of Acceptance and Commitment Therapy (ACT), psychological flexibility involves maintaining awareness of the present moment while engaging in purposeful, value-driven behavior, despite the presence of distressing internal states (15). In contrast, psychological rigidity—particularly in the form of experiential avoidance, which involves efforts to escape or suppress unwanted internal experiences—is viewed as a core pathological process in the development and maintenance of substance and alcohol use disorders. From this perspective, substance use often functions as a maladaptive coping mechanism aimed at diminishing emotional discomfort or psychological distress (16). In such cases, individuals may use alcohol or drugs to temporarily alleviate these aversive internal states. However, although this strategy may offer short-term relief, it tends to perpetuate a harmful cycle in which reliance on substances increases over time. This process undermines the development of more adaptive emotional regulation skills and contributes to heightened psychological inflexibility (17).

Enhancing psychological flexibility is thought to contribute to reduced substance use by improving an individual's ability to tolerate distress and by fostering motivation for behavior change (18,19). Support for this hypothesis comes from interventions like ACT, which have shown significant efficacy in treating individuals with SUDs (20–23). Ulusoy et al. reported that psychological flexibility mediated the relationship between depressive symptomatology and addiction severity, implying that enhanced psychological flexibility may enable individuals to cope with depressive experiences without turning to substances (24).

While previous research has explored the associations between craving and addiction severity, as well as between addiction severity and psychological flexibility, the role of psychological flexibility as a potential mediator in the link between craving and addiction severity remains unexamined. Given that psychological flexibility helps individuals reduce experiential avoidance and engage in meaningful behaviors despite internal discomfort, it may serve as a protective factor that moderates the impact of craving on addiction severity. Therefore, this study aims to investigate the potential mediating role of psychological flexibility in the relationship between craving and addiction severity among individuals with AUD.

METHODS

Sample and Procedure

The study was conducted in a specialized outpatient clinic for alcohol use disorder (AUD) at the Research, Treatment, and Training Center for Alcohol and Substance Dependence (AMATEM) within our hospital. The study sample composed of 86 individuals diagnosed with AUD based on DSM-5 criteria who met the inclusion criteria, agreed to participate voluntarily, and presented to the clinic between May and December 2024. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Ethical approval was granted by the Clinical Research Ethics Committee of a local training and research hospital (Decision No: 2024-05-22, dated March 18, 2024).

An a priori power analysis was performed using the G*Power 3.1 software. The alpha error level was set at .05, the desired statistical power at .80, and the effect size ($f^2 = 0.20$) was determined in accordance with Cohen's (1988) conventional benchmarks and a review of the relevant literature, which indicated an effect size between medium and large. The f^2 value was derived from the contribution of craving and psychological inflexibility to the explained variance in multiple regression models predicting addiction severity. As a result of the

analysis, the required sample size was determined to be 59 participants. However, to account for potential attrition and enhance the study's sensitivity, we recruited a total of 86 participants. A post-hoc power analysis confirmed that this final sample size provided a power level of 0.94, ensuring high statistical robustness for the mediation analysis.

Inclusion criteria were: being between 18 and 65 years of age, having a current diagnosis of AUD based on DSM-5 criteria, not receiving treatment for AUD at the time of application, not meeting diagnostic criteria for any disorder likely to impair judgment (e.g., psychotic disorders or delirium), not being intoxicated during the evaluation, not having any mental or physical condition likely to impair comprehension or data reliability, and not meeting the criteria for another substance use disorder.

Participants were thoroughly briefed on the study procedures and provided with information regarding the content of the questionnaires. Informed consent was obtained from individuals who voluntarily agreed to take part in the research. Alongside the sociodemographic questionnaire, the following psychometric instruments were administered to eligible participants: the Penn Alcohol Craving Scale (PACS), the Acceptance and Action Questionnaire–Substance Abuse (AAQ-SA), and the Addiction Profile Index (API).

Measurements

Sociodemographic data form: Participants' demographic characteristics were obtained through a semi-structured sociodemographic questionnaire developed by the researchers, which included items regarding age, gender, educational background, and marital status.

The Penn Alcohol Craving Scale (PACS): PACS is a frequently employed self-assessment tool developed to measure the extent, recurrence, and duration of alcohol craving during the previous seven days. Developed by Flannery et al. (1999), the PACS consists of five items covering key dimensions of craving, providing a brief but psychometrically sound instrument for both clinical and research settings (25). The scale is suitable for monitoring changes in craving during treatment and assessing the relationship between craving and alcohol use outcomes. It has shown high validity in different populations. Evren et al. (2011) conducted a Turkish adaptation of the PACS and reported that the scale had good internal consistency (Cronbach's alpha = 0.91) and strong test-retest reliability (26). Their findings also supported the construct validity of the scale and confirmed its suitability for use in Turkish-speaking clinical and research populations.

Acceptance and Action Questionnaire-Substance Abuse (AAQ-SA): AAQ-SA was employed to evaluate levels of psychological flexibility. The AAQ-SA is a self-report scale that evaluates psychological flexibility in individuals with substance use problems (27). This 17-item instrument was specifically designed for individuals with substance use disorders (SUDs), comprising two subscales. The first subscale, “Willingness” assesses the individual’s openness to and acceptance of substance-related thoughts, feelings, and urges. The second subscale, “Action” measures the degree of engagement in value-driven behaviors and commitment to change despite internal difficulties. Elevated scores on the scale indicate greater psychological flexibility, whereas lower scores reflect increased psychological rigidity. The Turkish adaptation, including validity and reliability analyses, was carried out by Uygur et al. (28).

Addiction Profile Index (API): Addiction severity was measured using the Addiction Profile Index (API), a 37-item instrument developed by Ögel et al. (5). The scale comprises five subdimensions: patterns of substance use, diagnostic criteria for substance use disorders, the impact of substance use on daily functioning, craving, and motivation to cease substance use. The patterns of substance use subscale assesses the type, frequency, and variety of substances used, as well as problems associated with use. The diagnostic criteria subscale corresponds to core DSM-based addiction indicators, such as tolerance, withdrawal, and loss of control. The impact on daily functioning subscale evaluates the negative consequences of substance use on various life domains, including work, education, family, social relationships, financial status, and legal

issues. The craving subscale measures the intensity of the desire to use substances, reflecting the strength and persistence of urges. Finally, the motivation to cease substance use subscale assesses the individual's readiness and willingness to quit, which is considered a key factor in treatment engagement and recovery While each subscale can be evaluated independently, a weighted total score can also be calculated. Scores below 12 suggest low addiction severity, whereas scores above 12 reflect more severe levels of addiction.

Statistical Analysis

The data were analyzed using the Statistical Package for the Social Sciences (IBM SPSS Statistics, Version 26) for descriptive and correlational analyses, and Jamovi software for mediation analysis. Descriptive statistics were applied to summarize the sample characteristics. To test the main hypothesis of the study, a mediation analysis was performed using the medmod module in Jamovi. The analysis aimed to explore the mediating role of psychological flexibility in the association between alcohol craving and addiction severity. All statistical inferences were based on a significance threshold of $p < 0.05$, and 95% confidence intervals were calculated for the parameter estimates.

RESULTS

A total of 86 individuals participated in the study. Of the participants, 10 (11.6%) were women and 76 (88.4%) were men. The mean age was 45.2±11 years. Among the 86 participants, 42 (48.8%) were married and 23 (26.7%) were single. Fifty-two participants (60.5%) reported no previous treatment history. Detailed socio-demographic characteristics are presented in Table 1.

According to skewness and kurtosis values, all scales exhibited a normal distribution.

As shown in Table 2, Pearson correlation analysis indicated a significant negative correlation between addiction severity (API) and Willingness (AAQ-SA) ($r = -0.557$, $p < 0.001$), as well as a significant positive correlation between addiction severity and alcohol craving (PACS) ($r=0.514$, $p<0.001$). Willingness (AAQ-SA) was negatively correlated with alcohol craving ($r=-0.347$, $p< 0.01$). However, the correlations between Action (AAQ-SA) and the other variables were not statistically significant.

Table 1: Sociodemographic characteristics of the participants

Age (Mean–SE)	45.2–11	
	N	%
Sex		
Female	10	11.6%
Male	76	88.4%
Education Level		
Primary School	23	26.7%
Middle School	25	29.1%
High School	29	33.7%
University	8	9.3%
Marital Status		
Married	42	48.8%
Single	23	26.7%
Having Children		
Yes	58	67.4%
No	27	31.4%
Previous Treatment		
Yes	33	38.4%
No	52	60.5%

To further clarify the potential mediating effect of psychological flexibility on the relationship between alcohol craving and addiction severity, a mediation analysis was conducted. Since the "action" subscale did not correlate with addiction severity, it was not included in subsequent analyses, and the mediation analysis was performed using the "willingness" subscale. The model explained 51% of the variance observed in addiction severity. The findings revealed that alcohol craving was significantly associated with lower psychological flexibility ($\beta= -0.347$, 95% CI: -0,97 to -0.27, $p< 0.001$), while psychological flexibility showed a significant association with addiction severity ($\beta=-0.431$, 95% CI: -0.15 to -0.06, $p < 0.001$). Furthermore, alcohol craving demonstrated a significant direct positive effect on addiction severity ($\beta=0.365$, 95% CI: 0.09 to 0.23, $p< 0.001$).

Findings from the mediation analysis indicated that psychological flexibility served as a partial mediator in the relationship between alcohol craving and addiction severity (indirect effect: $\beta=0.150$, 95%

Table 2: Relationships between scale scores (Pearson correlation coefficients)

	API	Action (AAQ-SA)	Willingness (AAQ-SA)	PACS
API	-			
Action (AAQ-SA)	0,021	-		
Willingness (AAQ-SA)	-0,557***	-0,140		
PACS	0,514***	-0,129	-0,347**	-

p<0,01,*p<0,001, API: Addiction Profile Index, AAQ-SA:Acceptance and Action Questionnaire-Substance Abuse, PACS: The Penn AlcoholCraving Scale

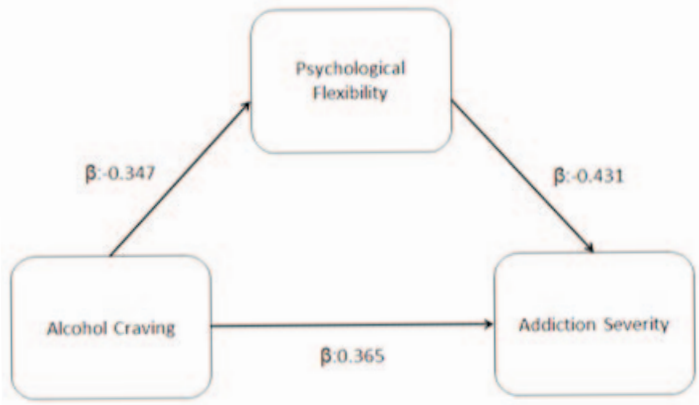

Figure 1. The standardized path coefficients of the tested model.

CI 0.02 to 0.11, p=0.005), explaining 29% of the overall effect. The remaining 71% was attributable to the direct influence of alcohol craving on addiction severity. A comprehensive summary of the mediation model results is presented in Table 3.

Figure 1 illustrates the standardized path coefficients of the tested model. The direct relationship between alcohol craving and addiction severity remained significant. The Sobel test confirmed the significance of the mediation effect (one-tailed $p < 0.001$; two-tailed $p < 0.001$).

DISCUSSION

Current literature shows that craving is a significant challenge for patients with AUD and is directly related to clinical severity as observed in other substance use disorders (6,7,29,30). Within this framework, the current findings are consistent with existing literature, revealing a significant positive relationship between craving and the severity of addiction. Furthermore, the results support the notion that craving functions as a significant predictor of addiction severity, in line with previous empirical evidence (5–7,29,31). While the link between craving and AUD is well-documented, the psychological mechanisms that sustain or intensify this relationship are not yet fully understood. Existing literature suggests that psychological flexibility is negatively associated with the severity of addiction (17,24). To date, empirical investigations have not directly addressed the potential mediating role of psychological flexibility in the association between alcohol craving and addiction severity. The present study, utilizing a clinical sample of individuals diagnosed with AUD, provides evidence that psychological flexibility significantly mediated this relationship, suggesting a potential psychological pathway contributing to addiction severity in the context of craving. In our study, psychological flexibility partially mediated the relationship between alcohol craving and addiction severity, explaining 29% of the total effect. Notably, elevated craving levels were linked to reduced psychological flexibility. Furthermore, an inverse association was observed between psychological flexibility and the severity of addiction.

Psychological rigidity—a core construct within Acceptance and Commitment Therapy (ACT)—refers to attempts to avoid or suppress unpleasant internal experiences(32). This concept overlaps with experiential avoidance and difficulties engaging in valued behavior (33). Both have been linked to alcohol/substance use disorders. From this perspective, craving—defined as an overwhelming urge to use alcohol accompanied by relief-oriented thoughts—may lead individuals to use substances to escape internal experiences. Such avoidance can disrupt value-based action (16,17). Willingness and acceptance represent the functional alternative within the psychological flexibility model (32,33). In our study, the AAQ-SA scores, particularly the willingness subscale, were negatively associated with craving and addiction severity, which supports this theoretical interpretation.

Several studies highlight the role of experiential avoidance in substance use. Forsyth et al. suggested

Table 3: Results of indirect and direct effects from the mediation analysis model

				95% CI				
Model	Model Pathway	Estimate	SD	Lower	Upper	Beta	Z	p
Indirect Effect	A.C.>P.F.>A.S	0.0653	0.0232	0.0200	0.1107	0.150	2.82	0.005
Components	A.C.>P.F.	-0.6153	0.1793	-0.9667	-0.2640	-0.347	-3.43	< .001
	P.F. > A.S.	-0.1062	0.0214	-0.1482	-0.0642	-0.431	-4.95	< .001
Direct Effect	A.C.>A.S	0.1594	0.0380	0.0849	0.2338	0.365	4.19	< .001
Total Effect	A.C.> A.S	0.2247	0.0406	0.1450	0.3043	0.514	5.53	< .001

A.C.: Alcohol Craving, P.F.: Psychological Flexibility, A.S: Addiction Severity

that avoidance of distressing internal states increased substance use among veterans (34). Stewart et al. found that experiential avoidance predicted coping-motivated alcohol use (35). The short-term effectiveness of using substances to avoid distressing internal experiences is well-documented, as it provides immediate relief from aversive thoughts and emotions, thereby reinforcing the behavior (36). In line with this perspective, Ulusoy et al. demonstrated that psychological inflexibility mediated depressive symptoms and addiction severity (24). A meta-analysis (2025) also reported a moderate positive association between experiential avoidance and substance use (37). Although craving was not directly examined in those studies, these findings collectively indicate that avoidance-based processes are relevant in AUD. Our findings further support earlier studies by demonstrating an inverse relationship between psychological flexibility and the severity of addiction.

AUD is defined as a psychiatric disorder that involves intense craving for alcohol, difficulty coping with these cravings, physical symptoms, and impairment in functioning in areas of one's life while attempting to avoid these challenges or the effects of alcohol (4). Within this definition, craving is explicitly included, along with indications of experiential avoidance and psychological rigidity. The severity of addiction increases as the number and intensity of these DSM-5 diagnostic criteria increase (4). Furthermore, the AUD literature consistently shows that the severity of craving predicts the severity of addiction (5). In this regard, the primary outcome of our research suggests that psychological flexibility plays a significant mediating role in linking craving to increased addiction severity, thereby helping explain how craving may relate to clinical impairment.

In current study, psychological flexibility partially mediated the relationship between alcohol craving and addiction severity, explaining 29% of the total effect. This effect was particularly evident in the willingness subscale. The remaining 71% can be attributed to the direct effect between alcohol craving and addiction severity and other possible mediating factors. These include factors found in the literature such as impulsive behavior, compulsive drinking, and deficiencies in emotion regulation skills (38–40). However, other sub-dimensions of psychological attachment that have not yet been sufficiently researched, such as cognitive fusion, rigid attachment to the conceptual self, and weak contact with the present moment, may also mediate this relationship. It is clear that more research is needed in this area.

These findings may contribute to a deeper understanding of psychosocial intervention mechanisms and highlight flexibility-targeted approaches as clinically relevant. In particular, ACT-based interventions may complement craving-reduction strategies by helping individuals tolerate internal experiences rather than suppress them. Through these interventions, individuals may move toward value-directed living and benefit from abstinence or harm reduction efforts more effectively.

This research is not without limitations. First, the use of a cross-sectional design restricts the ability to draw conclusions about causal relationships within the tested mediation model. Employing a longitudinal approach in future studies would provide a clearer understanding of the directional links among variables. Another methodological limitation concerns the exclusive use of self-report measures to assess addiction severity and related psychological constructs. While these tools are practical and widely used, relying solely on self-reports introduces potential biases—including social desirability, underreporting of substance use, and individual differences in insight—which may affect the accuracy of the findings. Also, the exclusive use of self-report measures may contribute to conceptual overlap between experiential constructs, which should be considered when interpreting the mediation effect. Additionally, the study was conducted in a single clinical center, which may limit the generalizability of the results due to potential sample homogeneity, treatment culture effects, or regional clinical practices that might differ from other settings. A further constraint is the limited representation of female participants, which restricted the ability to examine gender-specific effects. Although the overall findings were statistically significant, the small number of women in the sample prevented a meaningful analysis of gender differences. The limited number of female participants—and the lower-than-expected female-to-male ratio—constitutes a

limitation both in terms of representing all women diagnosed with AUD and in terms of accurately reflecting the overall sample. Moreover, the study did not explore the distinct dimensions of psychological flexibility as potential mediators in the relationship between craving and addiction severity, which represents an additional limitation. Including these components in future research with larger samples may provide more precise insights to guide the development of new treatment and relapse-prevention strategies. Future studies should also incorporate larger, multicenter, and cross-cultural samples to strengthen the generalizability and applicability of the findings to broader populations.

In conclusion, this study highlights psychological flexibility as a key mediating factor linking craving to the severity of addiction in individuals with AUD. Our findings suggest that individuals with intense cravings are more predisposed to psychological rigidity, which increases addiction severity. Our study adds to the growing body of literature emphasizing the importance of acceptance-based approaches such as ACT in AUD treatment by identifying psychological flexibility as one of the key mechanisms underlying this relationship. Our results highlight the potential benefits of targeting psychological flexibility in therapeutic interventions aimed at reducing craving-related functional impairment and enhancing treatment outcomes in AUD. Future longitudinal and multicenter research is warranted to elucidate the underlying mechanisms more thoroughly, thereby informing the development of effective interventions and relapse prevention strategies.

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REFERENCES

1. Koob GF. Alcohol use disorder treatment: problems and solutions. Annu Rev Pharmacol Toxicol 2024; 64(1):255–275.

2. Koob GF, Volkow ND. Neurobiology of addiction: a neurocircuitry analysis. Lancet Psychiatry 2016; 3(8):760–773.

3. Koob GF, Powell P, White A. Addiction as a coping response: hyperkatifeia, deaths of despair, and COVID-19. American Journal of Psychiatry 2020; 177(11):1031–1037.

4. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. American Psychiatric Association; 2013.

5. Ögel K, Evren C, Karadağ F, Gürol DT. The development, validity, and reliability of the Addiction Profile Index (API). Turk Psikiyatri Derg 2012; 23(4):263–275.

6. World Health Organization. The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines. World Health Organization; 1992. 362 p.

7. Cavicchioli M, Vassena G, Movalli M, Maffei C. Is craving a risk factor for substance use among treatment-seeking individuals with alcohol and other drugs use disorders? A meta-analytic review. Drug Alcohol Depend 2020; 212:108002.

8. Centers for Disease Control and Prevention (CDC). Alcohol and Public Health: Alcohol-Related Disease Impact (ARDI). Annual Average for United States (2011–2015). Alcohol-attributable deaths due to excessive alcohol use, all ages. 2020 Dec.

9. World Health Organization. World Health Organization. Global status report on alcohol and health 2018.

10. GBD 2016 Alcohol and Drug Use Collaborators. The global burden of disease attributable to alcohol and drug use in 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Psychiatry. 2018 Dec;5(12):987-1012. doi: 10.1016/S2215-0366(18)30337-7. Epub 2018 Nov 1. Erratum in: Lancet Psychiatry. 2019 Jan;6(1):e2. doi: 10.1016/S2215-0366(18)30488-7. PMID: 30392731; PMCID: PMC6251968.

11. Mutlu E. Cultural evolution of addiction. Dusunen Adam J Psychiatr Neurol Sci 2024; 37(1):1-4

12. Esser MB, Sherk A, Liu Y, Naimi TS, Stockwell T, Stahre M, Kanny D, Landen M, Saitz R, Brewer RD. Deaths and Years of Potential Life Lost From Excessive Alcohol Use - United States, 2011-2015. MMWR Morb Mortal Wkly Rep. 2020 Oct 2;69(39):1428-1433. doi: 10.15585/mmwr.mm6939a6. PMID: 33001874; PMCID: PMC7537556.

13. Ohtani Y, Ueno F, Kimura M, Matsushita S, Mimura M, Uchida H. Highly endorsed screening and assessment scales for alcohol problems: a systematic review. Neuropsychopharmacol Rep 2023; 43(4):470–481.

14. Sacks JJ, Gonzales KR, Bouchery EE, Tomedi LE, Brewer RD. 2010 National and state costs of excessive alcohol consumption. Am J Prev Med 2015; 49(5): 73–79.

15. Hayes SC, Luoma JB, Bond FW, Masuda A, Lillis J. Acceptance and commitment therapy: model, processes and outcomes. Behaviour Research and Therapy 2006; 44(1):1–25.

16. Wilson KG, Hayes SC, Byrd MR. Exploring compatibilities between acceptance and commitment therapy and 12-step treatment for substance abuse. Journal of Rational-Emotive and Cognitive-Behavior Therapy 2000; 18(4):209–234.

17. Luciano C, Paez-Blarrina M, Valdivia-Salas S. Acceptance and Commitment Therapy (ACT) in substance consumption as

an experiential avoidance strategy. International Journal of Clinical and Health Psychology 2010; 10(1):141–165.

18. Ii T, Sato H, Watanabe N, Kondo M, Masuda A, Hayes SC, Akechi T. Psychological flexibility-based interventions versus first-line psychosocial interventions for substance use disorders: systematic review and meta-analyses of randomized controlled trials. J Contextual Behav Sci. 2019; 13:109–120.

19. Hayes SC, Strosahl KD, Wilson KG. Acceptance and commitment therapy: the process and practice of mindful change. 2nd edition. New York, NY: The Guilford Press; 2012.

20. Smout MF, Longo M, Harrison S, Minniti R, Wickes W, White JM. Psychosocial treatment for methamphetamine use disorders: a preliminary randomized controlled trial of cognitive behavior therapy and acceptance and commitment therapy. Subst Abus 2010; 31(2):98–107.

21. Heffner M, Eifert GH, Parker BT, Hernandez DH, Sperry JA. Valued directions: acceptance and commitment therapy in the treatment of alcohol dependence. Cogn Behav Pract 2003; 10(4):378–383.

22. Osaji J, Ojimba C, Ahmed S. The use of acceptance and commitment therapy in substance use disorders: a review of literature. J Clin Med Res 2020; 12(10):629–633.

23. Krotter A, Aonso-Diego G, González-Menéndez A, González-Roz A, Secades-Villa R, García-Pérez Á. Effectiveness of acceptance and commitment therapy for addictive behaviors: a systematic review and meta-analysis. J Contextual Behav Sci 2024; 32:100773.

24. Ulusoy S, Ramakan ED, Gulec V, Alniak I, Yavuz KF. Do psychological inflexibility and self-criticism mediate the relationship between depression and addiction severity? Dusunen Adam J Psychiatr Neurol Sci 2022; 35(2):130-137.

25. Flannery BA, Volpicelli JR, Pettinati HM. Psychometric properties of the penn alcohol craving scale. Alcohol Clin Exp Res 1999; 23(8):1289–1295.

26. Evren C, Umut G, Agachanli R, Evren B, Bozkurt M, Can Y. Validation study of the turkish version of the craving typology questionnaire (CTQ) in male alcohol-dependent patients. Dusunen Adam J Psychiatr Neurol Sci 2016; 29(3):219-226.

27. Luoma J, Drake CE, Kohlenberg BS, Hayes SC. Substance abuse and psychological flexibility: the development of a new measure. Addiction Research & Theory 2011; 19(1):3–13.

28. Uygur H, Yavuz KF, Eren I, Uygur O, Selcuk M, Varsak N, et al. Reliability and validity of the turkish version of the acceptance and action questionnaire-substance abuse (AAQ-SA) on a clinical sample. Psychiatry and Clinical Psychopharmacology 2021; 30(1):47–54.

29. Kuerbis AN, Shao S, Treloar Padovano H, Jadanova A, Selva Kumar D, Vitale R, Nitzburg G, Vadhan NP, Morgenstern J. Context and craving among individuals with alcohol use disorder attempting to moderate their drinking. Exp Clin Psychopharmacol. 2020 Dec;28(6):677-687. doi: 10.1037/pha0000349. Epub 2020 Jan 23. PMID: 31971419; PMCID: PMC7375899.

30. Balcı MM, Pak ŞC, Erdoğan A, Eryılmaz MM. The relationship of remission with functionality, quality of life and craving in patients with opiate use disorder. Journal of Clinical Psychiatry 2022; 25(1):67–74.

31. Sliedrecht W, de Waart R, Witkiewitz K, Roozen HG. Alcohol use disorder relapse factors: a systematic review. Psychiatry Res 2019; 278:97–115.

32. Bond FW, Hayes SC, Barnes-Holmes D. Psychological flexibility, ACT, and organizational behavior. In: Acceptance and Mindfulness at Work. 1st ed. 2006. p. 25–54.

33. Wolgast M. What does the acceptance and action questionnaire (AAQ-II) really measure? Behav Ther. 2014; 45(6):831–839.

34. Forsyth JP, Parker JD, Finlay CG. Anxiety sensitivity, controllability, and experiential avoidance and their relation to drug of choice and addiction severity in a residential sample of substance-abusing veterans. Addictive Behaviors 2003; 28(5):851–870.

35. Stewart SH, Zvolensky MJ, Eifert GH. The Relations of anxiety sensitivity, experiential avoidance, and alexithymic coping to young adults' motivations for drinking. Behav Modif 2002; 26(2):274–296.

36. Hayes SC, Wilson KG, Gifford E V., Follette VM, Strosahl K. Experiential avoidance and behavioral disorders: a functional dimensional approach to diagnosis and treatment. J Consult Clin Psychol 1996; 64(6):1152–1168.

37. Barrado-Moreno V, Serrano-Ibáñez ER, Esteve R, Ramírez-Maestre C, Sánchez-Meca J. The role of psychological flexibility and inflexibility in substance addiction, abuse, or misuse: a systematic review and meta-analysis. Int J Ment Health Addict 2025 https://doi.org/10.1007/s11469-025-01468-4

38. Petit G, Luminet O, Maurage F, Tecco J, Lechantre S, Ferauge M, Gross JJ, de Timary P. Emotion Regulation in Alcohol Dependence. Alcohol Clin Exp Res. 2015 Dec;39(12):2471-9. doi: 10.1111/acer.12914. Epub 2015 Nov 28. PMID: 26613633.

39. Liu Z, Luo R, Fu R, Yuan C, Xu X, Zhou D, Zhao M, Yuan TF, Du J. The Influences of Impulsivity and Education Levels on Severity of Alcohol Dependence. Front Psychiatry. 2020 Aug 5;11:737. doi: 10.3389/fpsyt.2020.00737. PMID: 32848917; PMCID: PMC7419695.

40. Sánchez E, Cruz Fuentes CS, Benjet C, Medina-Mora ME. Impaired control in heavy drinking and its association with alcohol craving and alcohol use disorder severity. Salud Mental 2020; 43(4):151–157.

The effect of psychodrama group therapy on anxiety levels in parents of children with anorectal malformations

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SUMMARY

Objective: Evaluating the quality of life and anxiety levels of parents of children diagnosed with anorectal malformations (ARM) and to examine the effect of psychodrama group therapy on anxiety levels.

Method: The study was conducted with parents of children with ARM who participated in the ARM Expert Family Meeting organized in collaboration with Izmir University of Economics Faculty of Medicine. Participants were first administered a demographic information form, the Hamilton Anxiety Scale (HAM-A), and the EUROHIS Quality of Life Scale. Following these assessments, three structured psychodrama group therapy sessions, each lasting 60–90 minutes, were conducted. After the completion of the psychodrama sessions, the HAM-A scale was administered again to the participants to evaluate the effect of the intervention on anxiety levels. The data obtained were evaluated using the Wilcoxon signed-rank test and Spearman correlation analysis.

Results: 22 parents (11 men, 11 women) participated in the study. The mean age of the participants was 35.2 ±11.7 (19-65). A statistically significant difference was found between anxiety levels before and after psychodrama group therapy ($p<0.05$). Furthermore, a moderate, negative, and significant correlation was found between EUROHIS quality of life scores and initial and final HAM-A anxiety levels ($r=-0.53$; $p<0.05$; $r=-0.57$, $p<0.05$, respectively).

Discussion: Psychodrama group therapy was effective in reducing anxiety levels in parents of children with ARM and revealed a significant relationship between quality of life and anxiety level. These findings indicate that psychodrama can be an applicable and beneficial intervention method for this specific group.

Key Words: Anorectal malformation, parent, psychodrama, anxiety

INTRODUCTION

Anorectal malformation (ARM) is a general term used for various diseases often referred to as imperforate anus. Patients with this diagnosis do not have a normal anal opening; instead, a fistula tract opens into the perineum or adjacent anatomical structures located anterior to the anal muscle complex. In men, the fistula tract opens into the urinary system, while in women it opens into gynecological structures (1). The clinical picture can range from simple anomalies such as anal stenosis to more complex structural abnormalities such as cloacal malformation. Although the etiology of ARM is not fully known, it has been reported to be associated with genetic predisposition and syndromes such as VACTERL, Townes-Broks, Currarino's, and Pallisten-Hall. In addition, factors such as adriamycin, etretinate, and vitamin A deficiency have also been reported to play a role in the development of ARM (2-5). Its incidence is approximately 1/5000 live births (6). The risk of ARM occurring in subsequent children of parents with an ARM baby is stated as 1% (7). Prenatal diagnosis is rarely made, mostly based on other anomalies accompanying serious cases. The majority of cases are diagnosed in the early postnatal period (8). All these processes can directly affect the quality of life of parents. Anorectal malformation, a rare disease, is an unexpected situation for parents, and it is a process in which they try to learn every stage and need to learn from the experiences of parents who have experienced similar situations. Therefore, the supportive role of the Anorectal

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Malformation Association, which consists of parents of children with anorectal malformations, in the lives and quality of life of parents is noteworthy (9).

Quality of life is defined by the World Health Organization as the way a person perceives their functioning in physical, psychological, social, and environmental areas. Parents of children with chronic illnesses experience intense stress from the moment of diagnosis. In cases requiring surgical intervention, such as ARM, the uncertainty of the disease, the treatment process, possible complications, the burden of daily care, and limitations encountered in social life can negatively affect the quality of life of parents (10). The literature indicates that parents of children with ARM experience significant decreases in quality of life, especially in psychological and social areas, and that this situation continues even after surgical interventions (11). Parents are at emotional risk due to their children's body image problems, disease periods, complications, daily care needs, stigma, psychosocial barriers, and uncertainties (12). Furthermore, it has been shown that the younger the child, the higher the parents' anxiety levels (13), while individuals who receive professional psychological support have stronger coping skills (14). Therefore, it is of great importance to consider not only physical but also psychosocial dimensions in assessments of quality of life.

Accordingly, psychosocial interventions applied to parents of children with chronic illnesses aim to alleviate the emotional burden of individuals, increase their coping skills, and support their quality of life (15,16). Psychoeducation, individual therapy, counseling, and group work are among these interventions; group-based approaches, in particular, provide significant benefits through sharing and social support (9,17).

Psychodrama holds a special place among these group-based interventions. Developed by Moreno, psychodrama is a therapeutic method that addresses individuals' experiences through role-playing, dramatization, and creative expression, aiming for insight and emotional relief (18). Originally defined as "psychodramatic sociometric group therapy," in this approach, psychodrama refers to the concretization of experiences on stage, sociometry refers to the evaluation and regulation of intragroup relationships, and group therapy refers to the sharing and support processes (19). The literature shows that psychodrama is not limited to psychosocial effects but can also create changes at the neurobiological level (20,21). It is emphasized that the action-based structure of the method is crucial, especially in terms of the role of action in neurobiological changes; through multi-layered neural integration, psychodrama can create healing effects not only at the psychological but also at the biological level (22). This multidimensional structure has enabled the use of psychodrama in a variety of settings, including education, healthcare, industry, and social fields (19,23,24), with its effectiveness reported in several studies (18,23).

In this context, the literature on psychosocial support practices for parents of children with ARM is quite limited. While existing studies generally focus on the psychological effects of diagnosis and treatment processes (25, 26); there is no study in the literature that evaluates the effect of structured group interventions, especially psychodrama-based applications, on anxiety in parents of children with ARM. Accordingly, the aim of this study is to evaluate the quality of life and anxiety levels of parents of children diagnosed with ARM and to examine the effectiveness of psychodrama group therapy on anxiety levels. In this respect, the study aims to fill an important gap in the literature by both making visible the psychological burden experienced by parents in the face of a rare health condition and revealing the transformative effect of psychodrama-based group therapies on this burden.

METHODS

Study Design and Ethics

This study was conducted at Izmir University of Economics, Faculty of Medicine on September 6, 2024. The ethical suitability of this cross-sectional study was approved by the Izmir University of Economics Ethics Committee with decision number B.30.2.IEUSB.0.05-20-301 dated September 17, 2024. The research was conducted in accor-

dance with ethical rules based on the principles of the Helsinki Declaration.

Sample Size Calculation

The sample size was determined using G*Power software (version 3.1, Heinrich Heine University, Düsseldorf, Germany) with the following input data (27). A t-test was used to assess the difference between two dependent groups. Input data such as 80% statistical power, 0.05 significance level (α), and effect size 0.627 obtained from previous studies were used. As a result of these values, the predicted total sample size was obtained as 22.

Participants, Inclusion and Exclusion Criteria

The study sample consisted of parents (mothers and/or fathers) who attended the "Anorectal Malformation Expert Family Meeting" from different cities in Turkey. Inclusion criteria included having a child aged 0-18 years diagnosed with anorectal malformation, being the primary caregiver for the child, being able to read, write, and communicate in Turkish, and volunteering for psychodrama group therapy. Participants were also considered to have no prior or current diagnosis of anxiety or mood disorders and not receiving active psychiatric medication for these disorders. Exclusion criteria were: participating only as an observer (passive) in psychodrama group therapy, being in or receiving treatment for an acute episode of schizophrenia or other primary psychotic disorders listed in the International Classification of Diseases and Related Health Problems (ICD-11) section on mental disorders, and the participant's child having a primary illness other than ARM.

Data Collection

The data collection process in this study was carried out in two stages. In the first stage, all participants were administered the Hamilton Anxiety Scale (HAM-A) and the European Health Impact Scale (EUROHIS) before the psychodrama group therapy. In the second stage, structured psychodrama group therapy was conducted with the participants. After the psychodrama process was completed, the HAM-A was administered again to all participants to evaluate the effect of psychodrama group therapy on anxiety levels. The measurement tools used in the study and the application process of psychodrama group therapy are explained in detail below.

European Health Impact Scale (EUROHIS): The EUROHIS quality of life scale is a general purpose index quality of life scale derived from the WHO-QOL-Bref, a short version of the World Health Organization's quality of life scale. The scale consists of 8 questions, two of which are ge-neral assessments. All questions are answered using a 5-point Likert scale, and the quality of life level increases as the scores increase. The first two questions assess general quality of life and general health perception, respectively. It is not recommended to calculate the total score if either of these two questions is left unanswered. The other six questions relate to energy level, daily life satisfaction, self-satisfaction, social relationships, financial situation, and living conditions. Only one of these six questions can be left unanswered; in case of a missing answer, the average of the remaining questions is used for scoring. The scale is scored based on the sum of the answers given to the questions. A study on the validity of the Turkish version of the EUROHIS scale was conducted by Eser et al. (Cronbach α = 0.85) (28).

Hamilton Anxiety Scale (HAM-A): The Hamilton Anxiety Scale (HAM-A) is a semi-structured scale developed to assess a person's anxiety level over the past 72 hours. It is also widely used in monitoring treatment for anxiety disorders. The scale consists of 14 items that include both mental and physical symptoms of anxiety. The assessment is carried out by scoring each item from "0" (none) to "4" (very severe), and the total anxiety score is obtained from the sum of all items. The total score of the scale ranges from 0 to 56. A study on the validity of the Turkish version of the HAM-A scale was conducted by Yazıcı et al. (Inter-rater reliability coefficient = 0.94) (29). The reason for choosing the Hamilton Anxiety Scale in our research is that it allows the participant to express themselves during the application while also including the clinician's observations in the assessment. It is considered important to consider the therapist's observation

and the individual's self-reports together in evaluating the effectiveness of therapy (30).

Psychodrama Group Therapy

The psychodrama group therapy applied within the scope of the research was conducted by the responsible researcher and was based on a structured group work model. The responsible researcher, who is the psychodrama director, has managed numerous psychodrama groups in various clinical fields and is still actively conducting group work (31-33). In addition, she received a psychodrama director certificate from a psychodrama institute affiliated with the Ministry of National Education in 2008 and continues to receive supervision from the same institute.

The psychodrama group therapy was planned as three sessions with ten-minute breaks and to be completed on the same day. In this process, a safe environment was provided for parents to express their feelings about their child's illness; anxiety levels, coping strategies, and social support needs were addressed. The psychodrama process was structured as follows:

1. Session – Warm-up Phase

In this session, a trusting environment was created among the group members and warm-up exercises were carried out. Participants' emotional expressions were strengthened by relating them to the sharing of other members who had similar feelings. At the end of the session, it was observed that many participants expressed the feeling of "I am not alone." In psychodrama, the warm-up phase constitutes the beginning and preparation phase of the session; it aims to establish a trust-based bond between the therapist and the group members, to initiate group interaction, and to reduce the participants' hesitancy towards sharing experiences (34). This process allows for a gradual increase in spontaneity and the preparation of the protagonist for deep work. Warm-up is not only cognitive but also a multidimensional preparation process encompassing physical, emotional, and social aspects (20).

2. Session – Action Phase

In this session, participants were enabled to express the situations that caused their anxieties by concretizing them. Using the sociodrama technique, factors that increase and decrease anxiety were made visible on stage through verbal expressions that could direct the body. With the support of the facilitator, participants became aware of factors that reduce anxiety (e.g., trusting their doctor, the presence of recovered individuals, having knowledge about the illness, feeling that they are not alone), understood their importance, and had the opportunity to freely express situations that increase anxiety (e.g., feelings of guilt, inadequacy, self-judgment). This process contributed to the reduction of anxiety and the acquisition of awareness regarding coping strategies that can be used in daily life. The action phase was supported by an imagination exercise performed with music, allowing participants to experience the reduction of anxiety, and the session was concluded with this exercise. The fact that group members can have different experiences in this phase facilitates the transfer of awareness to daily life (19). At the neurobiological level, the action phase supports the recall of bodily memories, the emotional stimulation of the limbic system, and the integration between the prefrontal cortex and the right hemisphere by creating simultaneous activation in various regions of the brain (20, 21). This process facilitates the expression of emotions; The calming of the amygdala and the decrease in cortisol levels contribute to an increased sense of security.

3. Session – Sharing and Feedback

In the final session, participants who came to the stage were encouraged to express their experiences by relating them to their lives. Care was taken to ensure that group members expressed themselves without coercion and within the framework of equal speaking rights, in accordance with the democratic structure of psychodrama. The sharing phase allows intense emotions to be expressed in a safe environment, spontaneous reactions to be put into words, and learning processes to be reinforced through group support. Identification among group members facilitates individuals' approach to their own themes, contributing to the development of

Table 1. Session Structure and Techniques Used in Psychodrama Group Therapy.

Session	Process Phase	Purpose	Psychodrama Techniques Used	Content/Emotional Themes
First Session	Warming	-Building Trust -Prepearing to Express emotions	- Warm Up Exercises - Connection	-Recognising Simular Experiences -Increasing Feeling of Trust
Second Session	Action	-Ensuring a holistic approach to anxiety. - Identifying coping strategies - Experiencing a reduction in anxiety	- Sociodrama - Imagination accompanied by music	- Discovering factors that increase/decrease anxiety - The courage to try - Being able to feel a reduction in anxiety and a sense of relaxation
Third Session	Sharing and feedback	- Synthesis of experiences -Gaining insight - Increasing the feeling of social support	- Sharing -Giving and taking feedback	- A sense of unity and strength within the group - Understanding what has been experienced at a cognitive level

insight. This phase creates an integrative effect at the emotional, cognitive, and social levels (22).

Throughout the entire process, empathy and support within the group were reinforced, each participant was encouraged to express themselves, and care was taken to ensure that the sessions proceeded in a safe environment. Although psychodrama groups are mostly implemented as ongoing processes, it is seen in the literature that structured psychodrama groups can be implemented with different numbers of sessions and frequencies (35, 36). The fact that participating families from various regions of Turkey can only come together once a year is the most important factor determining the choice to conduct three consecutive sessions in a single day in this study.

Statistical Analysis

The obtained data were first analyzed using visual (histogram and scatter plots) and statistical (Kolmogorov-Smirnov and Shapiro-Wilk tests) methods. Due to the non-normal distribution of the data, median and interquartile range (IQR) values were reported in the descriptive analyses. As part of hypothesis testing, the Wilcoxon signed-rank test was applied to evaluate the difference between anxiety levels before and after psychodrama. Finally, Spearman correlation analysis was used to examine the relationship between the participants' quality of life levels and anxiety levels. In all comparisons, a $p<0.05$ value was considered statistically significant. Statistical analyses were performed using R software (version 4.2.2) (37)

RESULTS

22 parents (11 men, 11 women) participated in the study. The mean age of the participants was 35.2±11.7 (19-65 years).

A statistically significant difference was found between anxiety levels before and after psychodrama group therapy ($p<0.001$) (Figure 1 and Figure 2).

Figure 1 shows the pre-test and post-test HAM-A scores of each participant as a line graph. Each line represents a participant.

A decrease in anxiety levels was observed in the vast majority of participants, indicating that the intervention had positive results in most individuals.

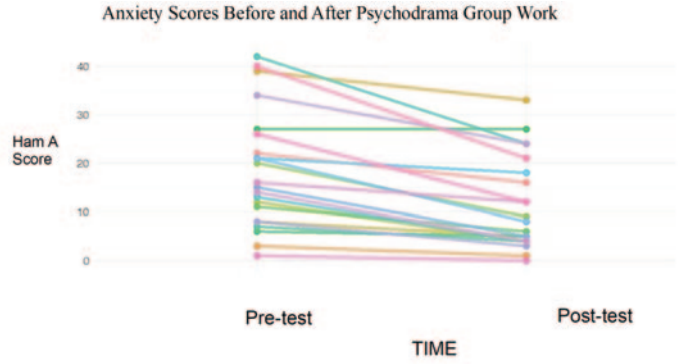

Figure 1. Comparison of participants' HAM-A (Hamilton Anxiety Scale) scores before and after psychodrama group therapy at the individual level.

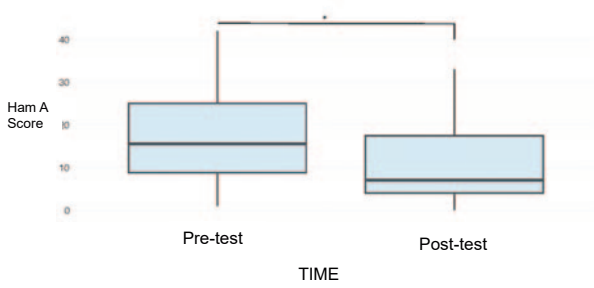

Figure 2. Box plot showing the distribution of Hamilton Anxiety Scale (HAM-A) scores before and after psychodrama.

Figure 2 shows the distribution of HAM-A scores of individuals participating in psychodrama group work in the pre-test and post-test periods using a box plot. While the median anxiety score was higher in the pre-test period at 15.5 (16,25), this value decreased significantly in the post-test period 7 (13,5). This supports the effectiveness of the intervention.

A moderate, negative, and statistically significant correlation was found between participants' EUROHIS quality of life scores and their initial HAM-A scale scores ($r = -0.53$, $p < 0.05$).

A moderate, negative, and statistically significant correlation was found between participants' EUROHIS quality of life scores and their post-test HAM-A scale scores ($r = -0.57$, $p<0.05$).

DISCUSSION

This study aimed to examine the effect of psychodrama group therapy on the anxiety levels of parents of children with ARM and its relationship with their quality of life. The findings showed a significant decrease in anxiety levels of parents after the application of psychodrama group therapy, and this effect occurred with a high effect size. In addition, a moderate negative relationship was found between the parents' quality of life and anxiety levels.

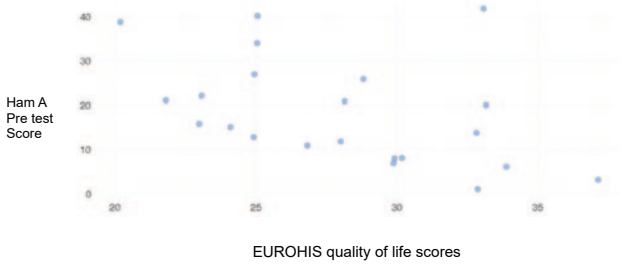

Figure 3. Scatter plot showing the relationship between EUROHIS quality of life scores and HAM-A pre-test anxiety scores.

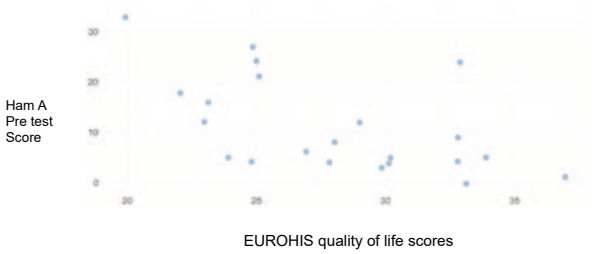

Figure 4. Scatter plot showing the relationship between EUROHIS quality of life scores and HAM-A post-test anxiety scores.

Although studies on postoperative anal function and quality of life in patients with ARM are abundant, evidence regarding the quality of life and mental health of parents of children with ARM remains limited. Moreover, compromised parental well-being may adversely influence the child's adaptation to treatment and psychological development (26, 38–42). The present study addresses this gap by evaluating parental quality of life, mental health, and the effects of psychodrama group therapy.

Previous studies have shown that the care burden, especially for mothers, is negatively related to quality of life, with quality of life decreasing as the care burden increases (14, 43). Similarly, in our study, we observed that the quality of life scores were low in the parents of children with ARM. An important element that distinguishes our study is that female and male parents were equally represented in the sample. While previous studies generally showed that mothers were predominantly represented in the sample (13, 18, 44), in this study, female and male parents were equal. This equality allowed for a more homogeneous collection of data and independent evaluation of gender.

Numerous studies in national and international literature have shown that psychodrama group therapy reduces anxiety in different disease groups and their relatives (18, 45-50). Group-based interventions are known to provide psychological relief through sharing, emotional support, and gaining insight (51). Although there are studies showing that support groups for parents of children with ARM reduce anxiety (25, 44), there are no findings regarding the application of psychodrama group therapy in this specific sample.

Research conducted in Turkey shows that psy-

chodrama clinical applications are widespread and effective on various psychological outcomes. Psychodrama group therapy strengthens the perception of social support in the field of psycho-oncology and supports mental health (52). In a study conducted with university students, psychodrama significantly increased hope, life satisfaction, and subjective well-being (53). In online psychodrama applications conducted during the pandemic, it was shown that depression and anxiety levels decreased and psychological resilience increased (54). There are also findings that psychodrama contributes to the improvement of psychosomatic symptoms (55). In addition, review studies conducted in Turkey have shown that art therapy and psychodrama-based interventions support psychological well-being in adult and adolescent samples (56). However, these studies in the existing Turkish literature focus on different clinical populations and do not include psychodrama applications for parents of children with ARM. Therefore, our study is the first to examine the effect of psychodrama on parents under a special caregiving burden.

In the context of the current literature, our study demonstrated a significant decrease in anxiety levels among parents of children with ARM after the psychodrama intervention. This indicates that the anxiety-reducing effect of psychodrama group therapy, an action-based method, is not merely a momentary scale finding but a real-life effect. Regardless of the persistence of the anxiety-reducing effect, it has also been stated in the literature that psychodrama, especially the action phase, leads to neurobiological changes (20, 21).

In relation to quality of life, participants who demonstrated lower post-intervention anxiety in the psychodrama group had reported higher baseline quality of life scores prior to the intervention. This finding suggests a possible relationship between quality of life and psychological resilience. Although studies directly examining this relationship are limited in the literature, the findings of Jing Li et al. show that social support reduces stress and that this improves quality of life (44,57,58). These results are consistent with the observation in our study at the theoretical level.

This study has some limitations. The fact that the sociodemographic characteristics of the participants, other than their status as primary caregivers of a child with ARM, were not assessed in detail, limited the comparison of the findings in terms of these variables. Another significant limitation is that the psychodrama intervention was conducted in an open group format, consisting of only three sessions and limited to a single day, making it difficult to evaluate the long-term effects of the intervention. In line with the literature indicating that significant changes in quality of life mostly occur as a result of long-term and multi-session interventions, a scale-based assessment of this dimension was not conducted after the psychodrama.

Finally, to more clearly demonstrate the specific and lasting effects of psychodrama on anxiety, future studies with larger sample groups, including follow-up measurements and control groups, are needed. In this context, it is important to carefully interpret the findings and support the results with more comprehensive, multi-session, longitudinal research.

This study revealed that psychodrama group therapy is effective in reducing anxiety levels in parents of children with ARM and that there is a significant relationship between quality of life and anxiety. The findings highlight the importance of psychosocial support interventions for parents and show that psychodrama can be an applicable method in this area. Future studies need to use follow-up scales to determine how long the effect of psychodrama group therapy on the anxiety level of parents of children with ARM lasts. Data obtained from these scales will contribute to revealing how frequently psychodrama group therapy should be applied to provide a more lasting and sustainable effect in reducing anxiety.

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REFERENCES

1. Smith CA, Avansino J. Anorectal Malformations. StatPearls. Treasure Island (FL):Copyright © 2025, StatPearls Publishing LLC.; 2025.

2. Bakal Ü, Gürbaz MT, Kazez A. Çocuklarda Anorektal Malformasyonlar. Firat Tip Dergisi. 2015;20(2).

3. Coran AG, Adzick NS, Krummel TM, Laberge J-M, Shamberger R, Caldamone A. Pediatric Surgery E-Book: Expert Consult-Online and Print: Elsevier Health Sciences; 2012.

4. Davies MC, Creighton SM, Wilcox DT. Long-term outcomes of anorectal malformations. Pediatric Surgery International. 2004;20(8):567-72.

5. Levitt MA, Peña A. Anorectal malformations. Orphanet journal of rare diseases. 2007;2(1):33.

6. Okur MH, Çiğdem MK, Önen A, Otçu S. Anorektal malformasyonlu olgularda klinik deneyimimiz: 115 olgunun analizi. Dicle Tıp Dergisi. 2014;41(2):294-7.

7. Önel AE, Akçay Didişen, N. Anorektal Malformasyonu Olan Çocuk Hastada Roy Adaptasyon Modeline Göre Hemşirelik Yaklaşımı: Olgu Sunumu. Journal of Infant, Child and Adolescent Health. 2022;2(3):189-203.

8. Hakalmaz AE, Tekant GT. Anorectal malformations and late-term problems. Turkish Archives of Pediatrics. 2023;58(6):572.

9. Ryan G, Vyrostek S, Aminoff D, Booth K, Driesbach S, Fisher M, Gerberick J, Haanen M, Mullins C, Parker L, Schwarzer N. Importance of education and the role of the patient and family in the care of anorectal malformations. Semin Pediatr Surg. 2020 Dec;29(6):150990. doi: 10.1016/j.sempedsurg.2020.150990. Epub 2020 Nov 9. PMID: 33288139.

10. Witvliet MJ, Bakx R, Zwaveling S, van Dijk TH, van der Steeg AF. Quality of life and anxiety in parents of children with an anorectal malformation or hirschsprung disease: the first year after diagnosis. European Journal of Pediatric Surgery. 2016;26(01):002-6.

11. Bhartiya S, Kumar R, Sen A, Ranjan Debnath P, Kundal V, Sahu SS, Prafful K. Evaluation of psychosocial burden on parents of children with anorectal malformation. J Int Med Sci Acad. 2019;32(3):144-50.

12. Nicholas DB, Otley A, Smith C, Avolio J, Munk M, Griffiths AM. Challenges and strategies of children and adolescents with inflammatory bowel disease: a qualitative examination. Health and quality of life outcomes. 2007;5(1):28.

13. Akin Sari B, Demiroğullari B, Ozen O, İseri E, Kale N, Başaklar C. Quality of life and anxiety in T urkish patients with anorectal malformation. Journal of Paediatrics and Child Health. 2014;50(2):107-11.

14. Pruthi GK, Mohta A. Psychosocial burden and quality of life in parents of children with anorectal malformation. Journal of Indian Association of Pediatric Surgeons. 2010;15(1):15-8.

15. Çöp E, Dinç GŞ, Kültür SEÇ. Kronik hastalığı olan çocukların annelerinde başetme becerilerinin psikiyatrik belirtiler ile ilişkisi: bir ön çalışma. Turkish Journal of Pediatric Disease. 2016;10(3):170-6.

16. Oğuzhan M, Erden G, editors. Kronik ve Ölümcül Hastalığı Olan Çocuklarda ve Ailelerinde Ortaya Çikan Sorunlar ve Psikososyal Müdahalenin Önemi. Yeni Symposium; 2012.

17. McFarlane WR, Dixon L, Lukens E, Lucksted A. Family psychoeducation and schizophrenia: A review of the literature. Journal of marital and family therapy. 2003;29(2):223-45.

18. Şarlak D, Öztürk E. Psikodrama Temelli Müdahale Programları: Sistematik Bir Değerlendirme. Karya Journal of Health Science. 2021;2(1):21-9.

19. Enstitüsü UP. Psikodrama [Available from: https://umutpsikodrama.com/psikodrama-nedir/.

20. Bilik E. Neuropsychodrama: What is happening in our brains in psychodrama? Revista Brasileira de Psicodrama. 2019;27(2):165-73.

21. Orkibi H. Psychodrama: A Creative Method to Survive and Thrive: Cambridge University Press; 2025.

22. Çakar HN, Tamam L. Psikodrama ve Nörobilim: Duygu, Eylem ve Beyin Arasındaki Köprü.

23. Altınay D. Psikodramada çağdaş yaklaşımlar: Sistem Yayıncılık; 2010.

24. Đurić Z, Veljković J, Tomić M. Psychodrama: A beginner's guide: Jessica Kingsley Publishers; 2006.

25. Diseth TH, Emblem R, Vandvik IH. Adolescents with anorectal malformations and their families: Examples of hidden psychosocial trauma. Family Systems Medicine. 1995;13(2):215.

26. Ying B, Wu F, Wang Y, Feng W, Hou J, Liu R. Negative emotions and quality of life of parents with children diagnosed with anorectal malformations. Pediatric Surgery International. 2023;39(1):190.

27. Kang H. Sample size determination and power analysis using the G* Power software. Journal of educational evaluation for health professions. 2021;18.

28. Eser E, Lağarlı T, Baydur H, Akkurt V, Akkuş H, Arslan E, et al. EUROHIS (WHOQOL-8. Tr) Türkçe sürümünün Türk toplumundaki psikometrik özellikleri. Turkish Journal of Public Health. 2010;8(3):136-52.

29. MK Y. Hamilton anxiety rating scale: interrater reliabilty and validity study. Turk J Psychiatry. 1998;9:114-7.

30. Maier W, Buller R, Philipp M, Heuser I. The Hamilton Anxiety Scale: reliability, validity and sensitivity to change in anxiety and depressive disorders. Journal of affective disorders. 1988;14(1):61-8.

31. Eslek A, Mizmlioğlu E, Mete AL, Aktener AY, Limon Ö. Psikodrama Grup Çalışmasının Şefkat Yorgunluğu Ve Yaşam Kalitesi Üzerine Etkisi. 9 Psikiyatri Zirvesi & 16 Anksiyete Kongresi2024.

32. Eslek A, Özen B, Aktener AY. Bir Olgu Üzerinden: Müzikle İmajinasyon Tekniğinin Kullanıldığı Bir Monodrama Çalışmasının Kanser Hastasının Anksiyetesi ve Ağrısına Etkisine Dikkat Çekilmesi. 60 Ulusal Psikiyatri Kongresi2024.

33. Eslek A, Şahin S, Aktener AY. Düzenli Psikodrama Gruplarına Katılımın Alkole Bağlı Demansta İşlevsellik Ve

Yaşam Kalitesinde Düzelmeye Yol Açması: Bir Olgu Sunumu. 13 Ulusal Alkol Ve Madde Bağımlılığı Kongresi 2022.

34. López-González MA, Morales-Landazábal P, Topa G. Psychodrama group therapy for social issues: A systematic review of controlled clinical trials. International Journal of Environmental Research and Public Health. 2021;18(9):4442.

35. Maya J, Pérez-Berbel M, Giraldo-Arroyave L, Hurtado I. Psychodrama: implementation, study design and effectiveness: a systematic review. BMC Complementary Medicine and Therapies. 2025;25:232.

36. Pramann R. Benefits, limitations, and potential harm in psychodrama. Utah: Shepherd's Staff Christian Counselling Centre; 2008.

37. Team RC. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. http://www R-project org/. 2016.

38. Funakosi S, Hayashi J, Kamiyama T, Ueno T, Ishii T, Wada M, Amae S, Yoshida S, Hayashi Y, Matsuoka H. Psychosocial liaison-consultation for the children who have undergone repair of imperforate anus and Hirschsprung disease. J Pediatr Surg. 2005 Jul;40(7):1156-62. doi: 10.1016/j.jpedsurg.2005.03.059. PMID: 16034762.

39. Grano C, Aminoff D, Lucidi F, Arpante A, Violani C. Self-efficacy, postoperative care satisfaction, body image and sexual functioning in ARM patients. Pediatric surgery international. 2008;24(11):1201-5.

40. Hassink EA, Brugman-Boezeman AT, Robbroeckx LM, Rieu PN, van Kuyk EM, Wels PM, Festen C. Parenting children with anorectal malformations: implications and experiences. Pediatr Surg Int. 1998 Jul;13(5-6):377-83. doi: 10.1007/s003830050344. PMID: 9639622.

41. Judd-Glossy L, Ariefdjohan M, Curry S, Ketzer J, Pena A, Bischoff A. A survey of adults with anorectal malformations: perspectives on educational, vocational, and psychosocial experiences. Pediatric surgery international. 2019;35(9):953-61.

42. Ludman L, Spitz L. Psychosocial adjustment of children treated for anorectal anomalies. Journal of pediatric surgery. 1995;30(3):495-9.

43. Dinçer Ş. Anorektal malformasyonlu çocukların ve annelerinin yaşam deneyimleri, yaşam kaliteleri ve bakım yükünün annelerin yaşam kalitesine etkisi: Ege Üniversitesi; 2024.

44. Li J, Gao W, Zuo W, Liu X. Relationship between quality of life and social support in parents of children with congenital anorectal malformations in China. Journal of Pediatric Nursing. 2020;53:e87-e92.

45. Kooraki M, Hashemi SE, Mehrabizadeh Honarmand M, Peymannia B. Effectiveness of Integrated Cognitive-Behavioral Psychodrama Group Therapy on The Fear of Negative and Positive Evaluation and Social Anxiety in Socially Anxious Adolescents: a Randomized Clinical Trial. Counseling Culture and Psycotherapy. 2024;15(60):87-120.

46. Mojahed A, Zaheri Y, Moqaddam MF. Effectiveness of group psychodrama on aggression and social anxiety of children with attention-deficit/hyperactivity disorder: A randomized clinical trial. The Arts in Psychotherapy. 2021;73:101756.

47. Oğuzhanoğlu NK, Bayraktutan M, Varma GS, Uğurlu TT. Sosyal anksiyete bozukluğunda aleksitimi ve sempatik deri yanıtları üzerine ilaç ve psikodrama grup terapisinin etkileri. Klinik Psikiyatri Dergisi. 2019;22(4).

48. Samadi H, Mahdiyan H, Ghasemi M. Comparison of the Effectiveness of Psychodrama and Group Therapy Based on Acceptance and Commitment on Students' Depression with Social Anxiety Disorder. Medical Journal of Mashhad university of Medical Sciences. 2021;64(1):2496-510.

49. Soygür H, Çelikel B, Aydemir Ç, Bozkurt S. Hasta yakınları ile gerçekleştirilen psikodrama yönelimli destekleyici-eğitici grup psikoterapisinin kronik şizofreni gidişi üzerinde etkisi. Düşünen Adam. 1998;11(4):5-11.

50. Varma GS, Oğuzhanoğlu NK, Ateşci FÇ, Karagöz N, Apa F. Alzheimer hastasına bakım veren yakınlarında psikodramatik grup terapisi. Anadolu Psikiyatri Derg. 2018;19:567-76.

51. Khalili FN, Swilem S. The efficiency of a group counseling program based on psychodrama in enhancing self-awareness and reducing tension among tenth grade students in Qalqilia City. Education in the Knowledge Society (EKS). 2021;22:e23921-e.

52. İren Akbiyik D, Soygür H, Karabulut E. Psiko-onkoloji ve aile hekimliğinde ruh sağlığını güçlendirme: Sosyal destek algısı ve psikodrama grup terapisi uygulamaları. Anatolian Journal of Psychiatry/Anadolu Psikiyatri Dergisi. 2012;13(3).

53. Gökkaya F, Gülser Z, Günak G, Köse B, Güleç M, Günel E, Sandıkcıoğlu B, İpek AK, Özkez Y. Psikodrama yöntemiyle gerçekleştirilen grup uygulamalarının üniversite öğrencilerinin umut, yaşam doyumu ve öznel iyi oluşları üzerindeki etkisinin incelenmesi. Gençlik Araştırmaları Dergisi. 2019;7(19):83-104.

54. Kurt P, Sarıoğlu M, Parlak S. Pandemi Sürecinde Çevrimiçi Psikodrama Grup Terapisinin Depresyon, Anksiyete Ve Psikolojik Dayanıklılık Üzerine Etkisi/the Effect of Online Psychodrama Group Therapy on Depression, Anxiety and Psychological Resilience During the Pandemic. Education & Youth Research. 2021;1(2):108-21.

55. Bal PN, Şener Ö. Psikosomatik hastaliklarin iyileştirilmesinde psikodramanin etkisi. Uluslararası Eğitim Bilimleri Dergisi. 2024(5):310-23.

56. Gökkaya F, Zorluoğlu E, Işık İ, Önkür B, Bozdemir T, Kızıltan R, Mıh C, Salıkyüz S, Deniz C. Türkiye'de bilişsel davranışçı grup terapisi, psikodrama ve sanat terapisi kullanılarak yapılmış etkililik çalışmalarının incelenmesi. Psikiyatride Güncel Yaklaşımlar. 2020;12(2):258-73.

57. Lubinga SJ, Levine GA, Jenny AM, Ngonzi J, Mukasa-Kivunike P, Stergachis A, Babigumira JB. Health-related quality of life and social support among women treated for abortion complications in western Uganda. Health Qual Life Outcomes. 2013 Jul 15;11:118. doi: 10.1186/1477-7525-11-118. PMID: 23855524; PMCID: PMC3718758.

58. Yilmaz MS, Piyal B, Akdur R. Social support and quality of life in a group of cancer patients (Ankara, Turkey). Turkish journal of medical sciences. 2017;47(3):732-7.

Reliability and validity of the Turkish version of the quick delay questionnaire for adults with attention-deficit/hyperactivity disorder

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SUMMARY

Objective: Delay-related processes refer to individuals' affective, cognitive, and behavioral responses to waiting situations, often characterized by impatience, frustration, and a preference for immediate rewards. The aim of this study was to evaluate the Turkish version's validity and reliability of the Quick Delay Questionnaire for Adults (QDQ-A), a self-report tool developed to assess delay-related characteristics in adults with ADHD.

Method: The study included 109 adults diagnosed with ADHD (mean age = 26.30 ± 7.19) and 79 controls (mean age = 29.85 ± 6.95). Participants completed the Adult ADHD Self-Report Scale (ASRS), the Hospital Anxiety and Depression Scale (HADS), and the QDQ-A.

Results: Confirmatory factor analysis revealed a two-factor structure consistent with the original version; delay aversion and delay discounting. Cronbach's alpha coefficients indicated good internal consistency: .85 for the delay aversion subscale and .70 for the delay discounting subscale. Test–retest analysis demonstrated acceptable reliability ($p < .001$). Within the ADHD group, QDQ-A subscale scores were positively correlated with ASRS subscales, a weak but statistically significant correlation was observed between the delay discounting subscale and HADS depression scores ($\rho = .193$, $p = .045$).

Discussion: The present findings support the Turkish version of the QDQ-A as a valid and reliable tool for use in adult populations.

Key Words: Attention-Deficit/Hyperactivity Disorder, reliability, validity, delay discounting, delay aversion

INTRODUCTION

Although Attention-Deficit/Hyperactivity Disorder (ADHD) is most commonly diagnosed during childhood, current evidence indicates that the disorder or its symptoms may persist into adulthood in a substantial proportion of cases (1). Due to developmental differences and frequent comorbidities, the clinical presentations and functional impairments observed in adults differ considerably from those seen in children (2). Increasing recognition that adult ADHD is a common, impairing, and frequently underdiagnosed condition has led to the development of screening tools for use in community and workplace settings (3).

One of the major challenges affecting quality of life in ADHD is impulsivity, which can be defined as the tendency to act suddenly without considering potential consequences, engage in behaviors that may be harmful, and experience difficulty in delaying gratification or waiting for rewards (4,5). Adults with ADHD often experience difficulties both in waiting for rewards (6) and in functioning effectively in situations involving prolonged delays (7). Two main concepts are prominent in the relationship between ADHD and reward processing. The first is delay discounting that refers to the tendency for the perceived value of a reward to decrease as the delay to its receipt increases. As the waiting time lengthens, the individual perceives the reward as less valuable. Second, delay aversion reflects the discomfort or negative affect associated with waiting for a reward, leading adults to prefer a smaller immediate reward over a larger delayed one. When there is an opportunity to reduce the delay, delay-averse adults are likely to choose the

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option that provides immediate gratification, even at the cost of losing part of the reward (8,9). In short, the pre-ference for "smaller-sooner" over "larger-later" rewards is commonly observed in such adults (10).

On the other hand, meta-analytic evidence suggests that delay discounting functions as a transdiagnostic process across psychiatric disorders, with variability across conditions rather than a uniform increase in all diagnoses. Within this dimensional framework, ADHD appears to be characterized by particularly pronounced delay-related decision-making difficulties, supporting the relevance of delay discounting as a meaningful construct for assessment and intervention in adult ADHD populations (11).

To date, delay-related behaviors have generally been assessed using neuropsychological tests; however, these instruments were primarily designed for use in children and may not be suitable for adults. Furthermore, they are often time-consuming and require substantial resources. In this context, the Quick Delay Questionnaire for Adults (QDQ-A), which has been translated into several languages and psychometrically validated, stands out as a promising assessment tool (12,13).

The purpose of the present study was to evaluate the Turkish validity and reliability of the QDQ-A, a self-report instrument developed to assess delay-related behaviors in adults with ADHD, and to provide a practical tool that can facilitate diagnosis and treatment follow-up.

In addition to serving as a supportive instrument for the assessment and monitoring of patients, this scale aims to enhance understanding of the severity of specific delay-related symptoms observed in adults with ADHD and to facilitate its application in diverse research contexts.

METHOD

Translation process

The study was reviewed and approved by the Clinical Research Ethics Committee (Approval No: I10-732-23). Following the approval by the ethics committee, the original English version of the QDQ-A was independently translated into Turkish by two members of the research team. The preliminary Turkish version was then administered to a pilot sample consisting of 20 healthy controls and 20 adults with ADHD in order to assess clarity and comprehensibility. Subsequently, the Turkish form was back-translated into English by an independent expert. Based on the feedback obtained from the back-translation process, necessary adjustments were made, and the final version of the scale was used by the research team.

Participant characteristics

The study included patients aged 18 to 65 who were diagnosed with ADHD according to DSM-5 criteria, and who applied to the Department of Psychiatry at Ankara University Faculty of Medicine. ADHD diagnoses were established by experienced psychiatrists based on a comprehensive clinical psychiatric evaluation. The study included 109 adults diagnosed with ADHD and 79 healthy controls. A control group consisting of adults without active psychiatric complaints and with no current use of psychiatric medication was also recruited. Patients with intellectual disability (IQ < 80), those diagnosed with schizophrenia or schizoaffective disorder, and patients with bipolar disorder currently experiencing depressive, manic, or hypomanic episodes were excluded. The study was conducted online, and informed consent was obtained electronically before participants accessed the scales. Participants completed three self-report scales along with a sociodemographic data form: QDQ-A, the Adult ADHD Self-Report Scale (ASRS), and the Hospital Anxiety and Depression Scale (HADS). Differences between groups were examined using statistical analyses, and Spearman correlation analyses were conducted to investigate the relationships between QDQ-A scores and ADHD, depression, and anxiety symptoms.

To evaluate the construct validity of the questionnaire, confirmatory factor analysis was applied. The suitability of the data for factor analysis was tested using the Kaiser-Meyer-Olkin (KMO) measure and Bartlett's test of sphericity. Factors with eigenvalues greater than 1 were extracted, and item loadings above .50 were considered acceptable.

Internal consistency reliability of the scale and its subscales (Delay Aversion and Delay Discounting) was assessed using Cronbach's alpha coefficients, with values above .70 considered acceptable.

Measures

Adult ADHD self-report scale: The Adult ADHD Self-Report Scale was developed by the World Health Organization (WHO) for screening purposes (14). The scale consists of two subscales with nine items each: inattention and hyperactivity/impulsivity. The items assess the frequency of symptoms experienced over the past six months. The ASRS measures 18 DSM-5-based symptoms of ADHD. The Turkish validity and reliability study of the scale was conducted in 2009 (15).

Hospital anxiety and depression scale: The Hospital Anxiety and Depression Scale was developed by Zigmond and Snaith in 1983(16). It is a self-report measure developed to identify the risk and severity of anxiety and depression, as well as to monitor changes over time. It comprises 14 items — seven assessing anxiety and seven assessing depression — rated on a four-point Likert scale. The Turkish validity and reliability study of the scale was conducted by Aydemir et al. The cutoff scores were determined as 10/11 for the anxiety subscale and 7/8 for the depression subscale in Turkish version of HADS (17).

Quick delay questionnaire: The Quick Delay Questionnaire was developed by Clare et al. as a 10-item self-report questionnaire for adults. It aims to measure two aspects of delay-related behavior: delay aversion and delay discounting. The items describe various scenarios and responses related to waiting and delay in daily adult life, including themes such as waiting in line, preference for short-term outcomes over long-term benefits, and tolerance for waiting periods. Participants respond using a 5-point Likert scale ranging from "very much like me" (1) to "not like me at all" (5). Items 6–10 are reverse-scored in the original version (18).

The psychometric properties of the QDQ-A have been shown to distinguish adults with ADHD from healthy or clinical controls. Logistic regression analyses conducted by Thorell et al. demonstrated that the QDQ-A exhibited high specificity but moderate sensitivity in differentiating adults with ADHD from non-clinical controls. QDQ-A scores have been found to correlate not with experimental delay discounting measures, but rather with functional impairments such as substance use, criminal behavior, and financial mismanagement. These findings support the use of the QDQ-A as a reliable complementary tool rather than a replacement for experimental assessments. Furthermore, results suggest that adults with higher ADHD subscale scores are at greater risk for real-life problems related to impulsivity and delay-related behaviors (13).

Data analysis

Confirmatory factor analysis was performed to test the original two-factor structure of the QDQ. The DWLS estimator was used due to the ordinal nature of the data. Model fit was evaluated using chi-square statistics, factor loadings, AVE, and reliability coefficients. Internal consistency was evaluated using Cronbach's α coefficients for the total scale, subscales test–retest reliability was assessed in a subsample of participants from both the ADHD and control groups who completed the QDQ-A twice with a four-week interval. Spearman's rank correlation coefficients were calculated to determine the strength of the relationships between the first and second administrations of each subscale and the total score.

Convergent validity was evaluated using Spearman's correlation analyses between the QDQ-A and ASRS. For discriminant validity, Mann–Whitney U tests were used to compare QDQ-A scores between the ADHD and control groups. Non-parametric tests were preferred due to non-normal score distributions. Statistical significance was set at $p < .05$ for all analyses.

Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) version 23 (SPSS Inc.).

Table 1. Demographic characteristics of participants by group

Variables	ADHD Group (n = 109)	Control Group (n = 79)	Statistical Test	*p* value
Age (Mean – SD)	26.30 – 7.19 (18-55)	29.85 – 6.95 (18-65)	*t* = -3.36, *df* = 186	<.001[a]
Gender n (%):			x† = 1.45,*df* = 1	.22[b]
Female	58 (53.2)	49 (62.0)		
Male	51 (46.8)	30 (38.0)		
Marital Status n (%):			x† = 6.47,*df* = 2	.03[b]
Single	86 (78.9)	49 (62.0)		
Married	23 (21.1)	30 (38.0)		
Education n (%):			x† = 32.74,*df* = 4	< .001[b]
Primary school	3 (2.7)	-		
High school	51 (55.9)	15 (19.0)		
University	45 (41.3)	64 (81.0)		
Occupation n (%):			x† = 15.57,*df* = 3	.001[b]
Unemployed	12 (11.0)	2 (2.5)		
Student	40 (36.7)	14 (17.7)		
Civil servant	56 (51.4)	62 (78.5)		
Other	1 (0.9)	1 (1.3)		

Note: Group comparisons revealed that the ADHD and control groups differed significantly in age, marital status, education level and occupation. Abbreviations: SD = Standard Deviation a:Independent sample t test, b: Chi square test

RESULTS

Demographic characteristics of participants

A total of 109 adults diagnosed with ADHD and 79 healthy controls participated in the study. The mean age of the ADHD group was 26.3 ± 7.19 years (range = 18–55), whereas the mean age of the control group was 29.85 ± 6.95 years (range= 18–65), showing a statistically significant difference ($t = –3.36$, $df = 186$, $p < .001$). Gender distribution was 53.2% female and 46.8% male in the ADHD group, and 62.0% female and 38.0% male in the control group ($x^2=1.45$, df=1, p= .22). Marital status differed significantly between groups, with 78.9% single and 21.1% married in the ADHD group, compared to 62.0% single and 38.0% married in controls ($x^2= 6.47$, df=2, p=.03).

Regarding education, 2.7% of the ADHD group were primary school graduates, 55.9% high school graduates, and 41.3% university graduates, whereas in the control group, 19.0% were high school graduates and 81.0% were university graduates (x^2 =32.74, df=4, p<.001). The results are summarized in Table 1.

Validity

Factor analysis

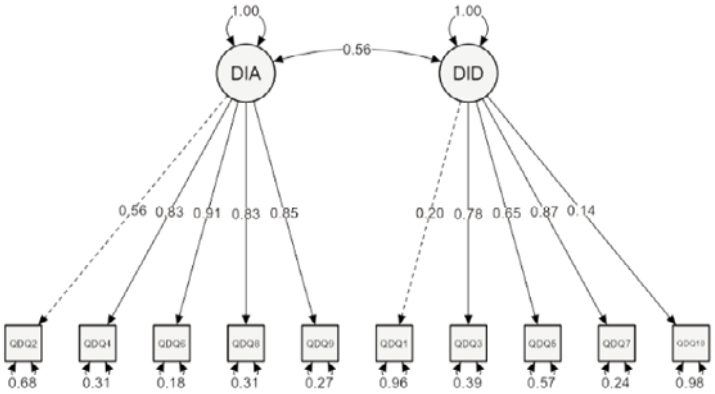
A confirmatory factor analysis was conducted to examine the original two-factor structure of the Quick Delay Questionnaire. The results indicated that the proposed two-factor model demonstrated acceptable model fit ($x^2(34) = 220.46$, p<.001, CFI = .825, TLI = .769, GFI = .947, RMSEA= .226, 90% CI [.198, .255]). The standardized factor loadings ranged from .562 to .908 for the Delay Aversion factor and from .136 to .870 for the Delay Discounting factor. Most factor loadings were statistically significant (p<.001), while item QDQ1 showed marginal significance (p=.051) and item QDQ10 showed a relatively low but statistically significant loading (p=.029). The correlation between the two latent factors was moderate and statistically significant (r=0.56, p<.001), indicating that although the factors are related, they represent dis-

Table 2. Confirmatory factor analysis of the QDQ-A

Items	Delay Aversion	Delay Discounting
1. I won't give up if it's important to me, even if I have to wait a long time for something.	-	.197
2. I am usually calm when I have to wait in line.	.562	-
3. I prefer a task because it is beneficial in the long run, although I usually do not get immediate rewards.	-	.778
4.I feel comfortable waiting for something.	.830	-
5.I usually give up things that I can't have right away.	-	.653
6.I hate waiting for things.	.908	-
7.I try to avoid tasks that will only benefit me in the long run and that do not have immediate benefits.	-	.870
8. I feel constrained when I have to wait for someone else to get ready before I can do something	.829	-
9.Having to wait for things makes me feel stressed and nervous.	.853	-
10.The future is not important to me, I only think about the immediate consequences of my actions.	-	.136

Note: Factor labels were determined through content analysis. The table displays the factor loadings of the QDQ-A items across the two-factor structure.

Figure 1. Confirmatory factor analysis of the Turkish version of the Quick Delay Questionnaire showing standardized factor loadings



Standardized factor loadings of the two-factor model of the Quick Delay Questionnaire. DIA=Delay Aversion; DID=Delay Discounting.

tinct dimensions of delay-related behaviors. The CFA model with standardized factor loadings is presented in Figure 1.

The factor structure of the QDQ-A for the entire sample is presented in Table 2.

Correlation analysis

Since the data in the ADHD group were not normally distributed (Kolmogorov –Smirnov test, $p < .05$), Spearman's rank correlation coefficients (ρ) were used to examine the convergent and discriminant validity of the QDQ-A. Correlation analyses were conducted between total QDQ-A scores and ASRS scores and subscales in the full sample. A positive and significant correlation was observed between the two variables. Spearman's rho coefficients (ρ) and two-tailed p-values are summarized in Table 3.

Within the ADHD group, correlations between the subscales of the QDQ-A and the HADS were examined to assess discriminant validity. According to the Spearman correlation analysis, except for the correlation between the delay discounting subscale and the HADS depression subscale ($\rho = .193$, $p = .045$), no statistically significant associations were found between anxiety or depression scores and the QDQ-A subscales and total score ($p > .05$). Additionally, in the healthy control group, the mean HADS anxiety score was 6.90 ± 4.27 (0–19) and the mean HADS depression score was 5.19 ± 3.39 (0–15). In the ADHD group, the mean HADS anxiety score was 12.89 ± 5.27 (1–25) and the mean HADS depression score was 9.52 ± 4.55 (1–20). Mann–Whitney U test revealed significant differences between the groups for both HADS anxiety ($U = 1649.00$, $Z = -7.228$, $p < .001$) and HADS depression scores ($U = 1977.50$, $Z = -6.337$, $p < .001$).

Discriminant validity analysis

The results of the Mann-Whitney U test, indicate that the QDQ-A subscales and total scores of the ADHD group differ significantly compared to the control group. The ADHD group scored significantly higher than the control group on all QDQ-A subscales and the total score ($p < .001$). Specifically, adults with ADHD had higher scores in delay aversion ($U = 2880.000$, $Z = -3.878$, $p < .001$) and delay discounting ($U = 1974.000$, $Z = -6.282$, $p < .001$), as well as in the total QDQ-A score ($U = 2057.500$, $Z = -6.046$, $p < .001$). The results are presented in Table 4.

Reliability

Internal consistency analysis

Internal consistency analyses showed that the Delay Aversion subscale had good reliability, with

Table 3. Spearman Correlation Coefficients Between the QDQ Turkish Version and ASRS

Variables	QDQ-A-Delay Aversion	QDQ-A-Delay Discounting	QDQ-Total Score
ASRS-Inattention	p= 371, *p*<.001	p= .598, *p*<.001	p= .580, *p*<.001
ASRS-Hyperactivity/ Impulsivity	p=.378, *p* < .001	p = .494, *p*<.001	p = .515, *p*<.001
ASRS-Total Score	p=.391, *p*< .001	p = .568, *p*<.001	p= .569, *p*<.001

Note. Spearman s rank-order correlation coefficients (p) were calculated to examine the relationships between QDQ-A and ASRS scores in the full sample. All reported correlations are two-tailed. Abbreviations: QDQ-A=Quick Delay Questionnaire for Adults; ASRS=Adult ADHD Self-Report Scale.

Table 4. Mann-Whitney U Test results for QDQ-A scores of ADHD and control groups

Subscales	ADHD Group Median	Control Group Median	Mann-Whitney U	Wilcoxon W	Z value	p
Delay Aversion	18.0	14.0	2880.000	6040.000	-3.878	<.001
Delay Discounting	15.0	10.0	1974.000	5134.000	-6.282	<.001
QDQ-A Total Score	33.5	24.0	2057.500	5217.500	-6.046	<.001

Note: Mann-Whitney U test results comparing measurement subscales between ADHD and control groups are presented. Significant differences were found between groups in all subscales (p <.001). Abbreviation: QDQ-A = Quick Delay Questionnaire for Adults

a Cronbach's alpha of .857 and McDonald's omega of .888. The Delay Discounting subscale demonstrated acceptable internal consistency, with a Cronbach's alpha of .707 and McDonald's omega of .507. The total QDQ score showed good reliability, with a Cronbach's alpha of .773 and McDonald's omega of 0.916. Item–total statistics are summarized in Table 5.

Test-retest correlation

To evaluate the temporal stability of the scale, a test-retest procedure was conducted with 15 control and 31 ADHD adults, with a 4-week interval between the two administrations.

Test–retest reliability was evaluated using Spearman rank-order correlations. In the control group(n = 15), the delay aversion subscale showed a significant but moderate correlation ($\rho = .34$, $p < .001$), indicating moderate temporal stability. The delay discounting subscale demonstrated higher reliability ($\rho = 0.59$, $p < .001$), suggesting stronger consistency over time.

For the ADHD group (n = 31), a strong and significant correlation was found between the test and retest scores of the delay aversion subscale ($\rho = .721$, $p < .001$), and a moderate-to-high correlation for the delay discounting subscale ($\rho = .680$, $p < .001$). The total QDQ-A scores also showed a strong test–retest correlation ($\rho = .751$, $p < .001$), indicating high overall temporal reliability of the scale. The test–retest correlation coefficients for both groups are summarized in Table 6.

Table 5. Internal consistency analysis results for QDQ-A subscales

Factor	Cronbach α	McDonald's ω	AVE
Delay Aversion	.857	.888	.648
Delay Discounting	.707	.507	.369
Total	.773	.916	–

Cronbach's α and McDonald's ω coefficients were calculated to assess internal consistency. Average variance extracted (AVE) values were calculated to evaluate convergent validity.
Note. Corrected item–total correlations and Cronbach's α if deleted values are presented for each subscale. Higher corrected item–total correlations indicate stronger relationships between the subscale and the total QDQ-A score. Cronbach's α if deleted reflects the change in internal consistency when the corresponding subscale is removed.

DISCUSSION

The present study aimed to examine the validity and reliability of the Turkish version of the QDQ-A in adults with ADHD. The findings demonstrated that the Turkish version of the scale retained the original two-factor structure consisting of delay aversion and delay discounting. In addition, the scale showed satisfactory internal consistency, significant correlations with ASRS scores supporting convergent validity, and strong test–retest reliability. Furthermore, the QDQ-A scores significantly differentiated adults with ADHD from healthy controls, supporting its discriminative validity. Previous research has shown that delay discounting in adults with ADHD is associated with adverse real-life outcomes, including academic underachievement, occupational difficulties, and impaired financial decision-making, highlighting the clinical relevance of assessing delay-related behaviors in this population. (19). Findings on emotion regulation difficulties in adults with ADHD complement evidence from delay-related decision-making research, together pointing to broader self-regulatory challenges that are relevant for clinical assessment (20). These behavioral tendencies are central to the motivational framework of ADHD and provide a theoretical rationale for instruments such as the QDQ-A, which aim to quantify delay-related decision-making processes. Recognizing and addressing these mechanisms is essential for clinicians seeking to improve both social and academic outcomes in adults with ADHD.

Table 6. Test–retest reliability of the QDQ-A

Scale	Group	n	Spearman ρ	p
Delay Aversion	ADHD	31	.721	< .001
Delay Discounting	ADHD	31	.680	< .001
Total QDQ-A	ADHD	31	.751	< .001

Abbreviation: QDQ-A: Quick Delay Questionnaire-Adult version; ρ: Spearman correlation coefficient.

Regarding the psychometric properties of the Turkish version of the QDQ-A in adults with ADHD, findings demonstrated that the two-factor structure of the scale—delay aversion and delay discounting—was retained in the Turkish sample and showed satisfactory levels of validity and reliability. The CFA results indicated that the original factor structure was largely consistent with the Turkish sample. Some relatively lower factor loadings or lack of statistical significance for certain items may be attributed to differences in cultural characteristics, educational background, or sample characteristics. The high discriminative power between groups, the significant correlations with ASRS subscales, and the consistent test–retest results can be considered among the strengths of this study.

In the present study, a statistically significant but weak association was observed between delay discounting and depressive symptoms. Although the magnitude of this correlation was small, it may still have clinical relevance in adults with ADHD, given the high prevalence of comorbid depressive disorders in this population. Previous studies have suggested that depressive symptoms may influence motivational processes and reward sensitivity, which could partially explain the relationship between depressive symptoms and delay-related decision-making (21,22). Therefore, the observed association may reflect overlapping mechanisms between mood regulation and delay-related behavioral tendencies.

Additionally, anxiety and depression levels were found to be significantly higher in the ADHD group compared to the control group. These differences should be considered as potential confounding factors when interpreting group comparisons in delay-related behaviors. Future studies may benefit from controlling for mood symptoms when examining delay-related processes in adults with ADHD. Although a statistically significant relationship was found between depression and delay discounting, this association was weak in magnitude and reflected a weak correlation, suggesting that delay-related processes captured by the QDQ-A are largely independent from depressive symptomatology. Given that comorbidity is frequently observed in adults diagnosed with ADHD, it is important for the QDQ-A to demonstrate strong discriminative ability for ADHD.

Future research should evaluate the Turkish version of the QDQ-A in different clinical populations, such as adults with substance use or mood disorders, to further investigate its discriminant validity. Additionally, integrating behavioral or experimental paradigms alongside self-report measures may enhance the ecological validity of the instrument.

This study has several limitations. First, the sample consisted exclusively of adults diagnosed and treated at the Department of Psychiatry, Ankara University Faculty of Medicine, and a group of volunteer healthy controls. While one previous validity and reliability study of the QDQ-A included similar healthy control and ADHD groups (12), another study included healthy individuals, patients with ADHD, and individuals with other psychiatric conditions (13). This may limit the generalizability of the findings to the broader population. Second, the ADHD and control groups differed significantly in age and educational level, which may have influenced the comparisons between groups. Third, all data were obtained through self-report instruments. Fourth, the study employed a cross-sectional design, which prevents conclusions regarding changes in QDQ-A scores over time or in response to treatment. Longitudinal research is needed to evaluate the sensitivity of the instrument to treatment outcomes and temporal changes in delay-related behaviors. Finally, test–retest reliability was assessed in a relatively small subsample. Replication with larger samples would provide stronger evidence for the temporal stability of the scale.

In conclusion, the Turkish version of the Self-Report QDQ-A scores appears to be reliable; however, as suggested by previous QDQ reliability and validity study (13), this instrument should be considered a complement to laboratory measures rather than a substitute for them. Access to the Turkish version of the Self-Report QDQ-A is available upon request from the authors via e-mail.

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REFERENCES

1. Turgay A, Goodman DW, Asherson P, Lasser RA, Babcock TF, Pucci ML, Barkley R; ADHD Transition Phase Model Working Group. Lifespan persistence of ADHD: the life transition model and its application. J Clin Psychiatry. 2012 Feb;73(2):192-201. doi: 10.4088/JCP.10m06628. Epub 2012 Jan 10. PMID: 22313720.

2. Öncü B. Erişkinde DEHB'yi fark etmek! Psikiyatride Güncel. 2016;6(4):265–275.

3. Ustun B, Adler LA, Rudin C, Faraone SV, Spencer TJ, Berglund P, Gruber MJ, Kessler RC. The World Health Organization Adult Attention-Deficit/Hyperactivity Disorder Self-Report Screening Scale for DSM-5. JAMA Psychiatry. 2017 May 1;74(5):520-527. doi: 10.1001/jamapsychiatry.2017.0298. Erratum in: JAMA Psychiatry. 2017 Dec 1;74(12):1279. doi: 10.1001/jamapsychiatry.2017.3375. Erratum in: JAMA Psychiatry. 2019 Nov 1;76(11):1213. doi: 10.1001/jamapsychiatry.2019.3111. PMID: 28384801; PMCID: PMC5470397.

4. Türkiye Psikiyatri Derneği. Erişkinlerde dikkat eksikliği ve hiperaktivite bozukluğu tanı ve tedavi kılavuzu. Ankara: Türkiye Psikiyatri Derneği Yayınları; 2018. Öncü B. Kavramsal açıdan DEHB: Kavramsal açıdan DEHB ve tarihçe. In: Semerci B, Aksoy UM, editors. Erişkinlerde dikkat eksikliği ve hiperaktivite bozukluğu tanı ve tedavi kılavuzu. Ankara: Türkiye Psikiyatri Derneği Yayınları; 2018. p. 3-15. (in Turkish)

5. Thapar A, Cooper M. Attention deficit hyperactivity disorder. Lancet. 2016;387(10024):1240–1250. doi:10.1016/S0140-6736(15)00238-X

6. Marco R, Miranda A, Schlotz W, Melia A, Mulligan A, Müller U, Andreou P, Butler L, Christiansen H, Gabriels I, Medad S, Albrecht B, Uebel H, Asherson P, Banaschewski T, Gill M, Kuntsi J, Mulas F, Oades R, Roeyers H, Steinhausen HC, Rothenberger A, Faraone SV, Sonuga-Barke EJ. Delay and reward choice in ADHD: an experimental test of the role of delay aversion. Neuropsychology. 2009 May;23(3):367-80. doi: 10.1037/a0014914. PMID: 19413450.

7. Scime M, Norvilitis JM. Task performance and response to frustration in children with attention-deficit/hyperactivity disorder. Psychol Sch. 2006;43(3):377–386. doi:10.1002/pits.20150

8. Bitsakou P, Antrop I, Wiersema JR, Sonuga-Barke EJS. Probing the limits of delay intolerance: Preliminary young adult data from the Delay Frustration Task (DeFT). J Neurosci Methods. 2006;151(1):38–44. doi:10.1016/j.jneumeth.2005.06.039

9. Sonuga-Barke EJS. Psychological heterogeneity in AD/HD: A dual pathway model of behaviour and cognition. Behav Brain Res. 2002;130(1–2):29–36. doi:10.1016/S0166-4328(01)00432-6

10. Sonuga-Barke EJS. The dual pathway model of AD/HD: An elaboration of neuro-developmental characteristics. Neurosci Biobehav Rev. 2003;27(7):593–604. doi:10.1016/j.neubiorev.2003.08.005

11. Amlung M, Marsden E, Holshausen K, Morris V, Patel H, Vedelago L, Naish KR, Reed DD, McCabe RE. Delay Discounting as a Transdiagnostic Process in Psychiatric Disorders: A Meta-analysis. JAMA Psychiatry. 2019 Nov 1;76(11):1176-1186. doi: 10.1001/jamapsychiatry.2019.2102. Erratum in: JAMA Psychiatry. 2023 Jan 1;80(1):96. doi: 10.1001/jamapsychiatry.2022.3755. PMID: 31461131; PMCID: PMC6714026.

12. Chen C, Zhang S, Hong H, Qiu S, Zhou Y, Zhao M, Pan M, Si F, Dong M, Li H, Wang Y, Liu L, Sonuga-Barke EJS, Qian Q. Psychometric properties of the Chinese version of the Quick Delay Questionnaire (C-QDQ) and ecological characteristics of reward-delay impulsivity of adults with ADHD. BMC Psychiatry. 2024 Apr 2;24(1):251. doi:10.1186/s12888-024-05706-2. PMID: 38566048; PMCID: PMC10988885.

13. Thorell LB, Sjöwall D, Mies GW, Scheres A. Quick Delay Questionnaire: Reliability, validity, and relations to functional impairments in adults with attention-deficit/hyperactivity disorder (ADHD). Psychol Assess. 2017 Oct;29(10):1261-1272. doi: 10.1037/pas0000421. Epub 2016 Dec 19. PMID: 27991822.

14. Kessler RC, Üstün TB. The World Mental Health Survey Initiative version of the World Health Organization Composite International Diagnostic Interview (CIDI). Int J Methods Psychiatr Res. 2004;13(2):93–121. doi:10.1002/mpr.168

15. Doğan S, Öncü B, Varol-Saraçoğlu G, Küçükgöncü S. Erişkin Dikkat Eksikliği Hiperaktivite Bozukluğu Kendi Bildirim Ölçeği (ASRS-v1.1): Türkçe formunun geçerlilik ve güvenilirliği. Anadolu Psikiyatri Derg. 2009;10(2):77–87.

16. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand. 1983;67(6):361–370. doi:10.1111/j.1600-0447.1983.tb09716.x

17. Aydemir Ö, Güvenir T, Küey L, Kültür S. Hastane Anksiyete ve Depresyon Ölçeği Türkçe formunun geçerlilik ve güvenilirliği. Türk Psikiyatri Derg. 1997;8(4):280–287.

18. Clare S, Helps S, Sonuga-Barke EJS. The Quick Delay Questionnaire: A measure of delay aversion and discounting in adults. ADHD Atten Def Hyp Disord. 2010;2(1):43–48. doi:10.1007/s12402-009-0015-0

19. Beauchaine TP, Ben-David I, Sela A. Attention-deficit/hyperactivity disorder, delay discounting, and risky financial behaviors: A preliminary analysis of self-report data. PLoS One. 2017;12(5):e0176933. doi:10.1371/journal.pone.0176933

20. Soler-Gutiérrez AM, Pérez-González JC, Mayas J. Evidence of emotion dysregulation as a core symptom of adult ADHD: A systematic review. PLoS One. 2023;18(1):e0280131. doi:10.1371/journal.pone.0280131

21. Takahashi T, Oono H, Inoue T, Boku S, Kako Y, Kitaichi Y, Kusumi I, Masui T, Nakagawa S, Suzuki K, Tanaka T, Koyama T, Radford MH. Depressive patients are more impulsive and inconsistent in intertemporal choice behavior for monetary gain and loss than healthy subjects--an analysis based on Tsallis' statistics. Neuro Endocrinol Lett. 2008 Jun;29(3):351-8. PMID: 18580849.

22. Garzón B, Polania R, Hare TA. Resource-rational adaptations to different intertemporal choice environments affect evidence accumulation and encoding-related processes. Preprint. doi: 10.21203/rs.3.rs-8387640/v1

Short-term vital sign changes following sedative psychotropic initiation in hospitalized patients: A retrospective cohort study

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SUMMARY

Objective: Sedative psychotropic medications, such as olanzapine, quetiapine, mirtazapine, and trazodone, are commonly used in hospitalized patients to manage psychiatric symptoms, such as insomnia, restlessness, and agitation. Despite their widespread use, data on their short-term effects on vital signs in medically complex patients are limited. Understanding these effects is crucial for optimizing patient safety in acute care settings. This retrospective cohort study aimed to assess the effect of olanzapine, quetiapine, mirtazapine, and trazodone on vital signs (systolic and diastolic blood pressure, heart rate, oxygen saturation, and body temperature) in non-intensive care unit hospitalized patients.

Method: Among 871 screened consultation episodes, 184 patients met eligibility criteria and were included in the final analysis. Vital signs were collected at six standardized time points, 24 h before and after medication initiation. Linear mixed-effects models with subject-specific random intercepts were used to examine the treatment group, phase (pre–post), time of the day, and group-by-phase interactions. Multiple tests across the five primary phase effects were conducted using the Holm correction.

Results: Across all vital sign outcomes, fixed-effect estimates were small and indicated minimal physiological change. Heart rate showed a modest unadjusted decrease from pre- to post-exposure ($\beta = -1.72$ beats/min, 95% CI -3.11 to -0.33; $p = .017$); however, this association did not remain statistically significant after adjustment for multiple comparisons (Holm-adjusted $p = .083$). No statistically significant phase effects or group-by-phase interaction effects were observed for systolic blood pressure, diastolic blood pressure, or oxygen saturation.

Discussion: In this medically complex inpatient cohort, commonly used sedative psychotropic agents (olanzapine, quetiapine, mirtazapine, and trazodone) did not produce clinically meaningful short-term changes in the vital signs.These findings support the cautious but routine use of these agents in inpatients, with standard monitoring. Further prospective studies are recommended to explore the long-term outcomes and potential drug interactions.

Key Words: Hospitalized patients, non-benzodiazepine psychotropic sedatives, short-term effects, vital signs

INTRODUCTION

Psychiatric consultations are integral to the care of hospitalized patients in the medical and surgical wards. The demand for such consultations varies, with studies indicating that approximately one-third of hospitalized patients require psychiatric evaluation during their hospital stay (1,2). The primary reasons for psychiatric consultations in these settings include a spectrum of acute psychiatric disturbances including agitation, delirium, depression, anxiety, and substance withdrawal (3,4).

Addressing psychiatric symptoms in medically and surgically hospitalized patients is clinically important. Untreated psychiatric symptoms can complicate the management of primary medical and surgical conditions. For instance, severe anxiety, depression, or agitation may impede patient compliance with medical regimens and postoperative care instructions, thereby influencing recovery outcomes (5,6). Moreover, psychiatric conditions such as delirium are associated with increased morbidity and mortality rates, contributing to prolonged hospital stays, increased healthcare expenditures, and elevated risks of long-term cognitive impairment

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(1). Additionally, untreated psychiatric disorders may exacerbate physiological stress responses, adversely affecting cardiovascular and immune functions, which are critical for the recovery process in medically and surgically ill patients (7). Effective management of psychiatric symptoms enhances patient satisfaction and quality of life and optimizes clinical outcomes (8). Therefore, integrating psychiatric care into comprehensive patient management strategies is essential to improve health outcomes and optimize healthcare resource utilization.

In this context, commonly utilized psychiatric medications in medical and surgical wards include traditionally categorized antipsychotics, antidepressants, and sedative hypnotics. Medications such as olanzapine and quetiapine are favored for their sedative properties and efficacy in managing agitation and delirium, with a reduced risk of extrapyramidal side effects compared with older antipsychotics (9). Medications such as trazodone and mirtazapine, renowned for their sedative effects, are beneficial for treating insomnia and anxiety, particularly in older adults, owing to their favorable side effects (10).

Olanzapine and quetiapine exert their therapeutic effects through the complex interplay of receptor antagonism. For example, olanzapine antagonizes dopamine D2, serotonin 5-HT2A, histamine H1, and alpha-1 adrenergic receptors. These actions contribute to the sedative properties and potential for orthostatic hypotension due to vasodilation (11). Quetiapine similarly antagonizes serotonin 5-HT2A and alpha-1 adrenergic receptors, affecting the heart rate and blood pressure regulation (12). Trazodone antagonizes serotonin 5-HT_2A, histamine H_1, and α_1-adrenergic receptors, thereby contributing to its sedative and hypnotic properties. In hospitalized or older adults, while it is less likely to cause major direct respiratory suppression or marked thermoregulatory disruption, vigilance regarding oxygen saturation, body temperature changes, and orthostatic hypotension is still warranted, given the sedative and adrenergic blockade-related effects (13,14). Mirtazapine primarily antagonizes central presynaptic adrenergic autoreceptors/heteroreceptors and histamine H_1 receptors (and additionally 5-HT_2A/5-HT_2C/5-HT_3 receptors), leading to sedative and hypnotic effects. Its peripheral α_1-adrenergic antagonism and sedative burden contribute to the potential for orthostatic hypotension, especially in vulnerable hospitalized or geriatric patients (15). These receptor interactions, particularly adrenergic and histaminergic antagonism, underscore the potential for immediate physiological changes in vital signs, including blood pressure, heart rate, oxygen saturation, and body temperature, which are critical for monitoring complex patients. Although these drugs are effective in the management of psychiatric symptoms and are chosen because of their favorable side-effect profiles, case reports have shown that even at low single doses, they can cause life-threatening conditions such as hypotension, bradycardia, and hypothermia (16-21).

However, there is a scarcity of real time studies examining the effects of these selected agents on vital signs such as blood pressure, heart rate, body temperature, and oxygen saturation in medically complex patients, a population often excluded from clinical trials (22). Most studies have focused on long-term outcomes or specific adverse events rather than immediate physiological responses. Understanding acute physiological effects is critical because any significant changes in vital signs could indicate adverse reactions or interactions with other medications used to treat primary medical conditions. Given the current gap in the literature, this study aimed to retrospectively investigate the short-term effects of olanzapine, quetiapine, mirtazapine, and trazodone on the vital signs of hospitalized patients. This study aimed to enhance the safety and efficacy of psychiatric interventions in medically complex hospitalized patients by providing insights into the real-time effects of these psychotropic agents on vital signs.

METHODS

Participants

This study was approved by the Ethics Committee of Koc University (protocol number: 2025.204.IRB2.091). This retrospective study screened 871 consultation cases from Koc University Hospital, hospitalized over a 7-month period, and referred for psychiatric evaluation. The reasons for psychiatric consultation included sleep problems, anxiety, depression, delirium, and agitation.

Table 1. Reasons for ineligibility among screened consultation episodes (n=680)

Reason for ineligibility	n	% of ineligible (n=680)	% of screened (n=871)
ICU consultations	6	0.9	0.7
Discharge prescription only	74	10.9	8.5
Repeat consultation within 7 days	45	6.6	5.2
Already receiving a target study medication (not a new start)	94	13.8	10.8
Behavioral recommendations and/or melatonin only	75	11.0	8.6
Initiated non-sedating antidepressant (excluding trazodone/mirtazapine) or a mood stabilizer	248	36.5	28.5
Initiated benzodiazepine (non-target)	31	4.6	3.6
Initiated antipsychotic other than quetiapine/olanzapine	107	15.7	12.3

Note: Counts are mutually exclusive by construction (one primary ineligibility reason per screened episode).

The main selection criterion was the administration of olanzapine, quetiapine, trazodone, or mirtazapine after psychiatric consultation. Patients who were not advised to use one of these medications or who had already been using one of the selected drugs were excluded from the study. If the same patient consulted more than once in the same week, only the first consultation was considered. Consultations from the intensive care unit were also excluded because of possible instability in the vital signs.

Of the 871 screened consultation episodes, 680 were deemed ineligible after applying prespecified criteria, primarily because the consultation did not result in a new initiation of a target sedative psychotropic. The most common ineligibility reason was initiation of a non-target antidepressant or a mood stabilizer (n=248; 36.5% of ineligible), followed by initiation of a non-target antipsychotic (n=107; 15.7%), and cases in which the patient was already receiving a target study medication prior to consultation (n=94; 13.8%). Additional ineligible episodes included consultations resulting in behavioral recommendations and/or melatonin only (n=75; 11.0%), consultations for discharge prescription only (n=74; 10.9%), initiation of a benzodiazepine (n=31; 4.6%), repeat consultations within 7 days (n=45; 6.6%), and ICU consultations (n=6; 0.9%). A complete breakdown is provided in Table 1.

After screening, 191 cases were eligible; 7 eligible cases were excluded because the recommended target medication was not administered, yielding a final analytic sample of 184.

Extracted data and variables

Patient files were examined for recorded vital signs including diastolic blood pressure, systolic blood pressure, heart rate, body temperature, and oxygen saturation. Vital signs were collected during the 24 h immediately preceding the first dose of psychotropic medication and during the 24 h immediately following the first dose at corresponding standardized time points. Six standardized time points (1AM, 6AM, 10AM, 1PM, 6PM, and 10 PM) were selected to capture comprehensive diurnal variations in vital signs and align with standard hospital vital sign monitoring protocols, ensuring consistency in data collection both pre and post medication initiation (Figure 1).

In addition, age, biological sex, primary diagnoses, known chronic illnesses, daily drug regimens, consultation dates, and consultation notes were recorded for each participant. As the major diagnosis for hospitalization may affect the vital signs, the major comorbidities/diagnoses were divided into three categories: oncological diseases, infectious diseases, and other disorders (cardiovascular diseases, pulmonary diseases, endocrine and metabolic diseases, neurological diseases). Patients were administered one of four psychotropic medications (olanzapine, quetiapine, mirtazapine, or

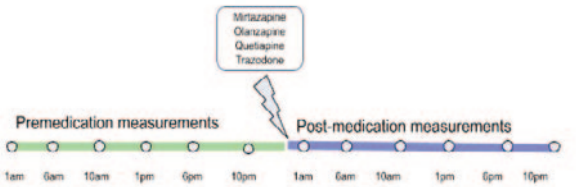

Figure 1. Time points when vital signs were recorded before and after medication initiation

trazodone), as prescribed by the psychiatric consultation service. The initial dose ranges used were mirtazapine, 15 mg, olanzapine 2.5–5 mg, quetiapine 12.5–25 mg, and trazodone, 25–50 mg. All medications were administered orally, typically once daily, for the first 24 hours of observation. In addition, the current usage of antihypertensive drugs (diuretics, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and their combinations) was recorded, and 184 patients were divi-ded into two groups: those who used antihypertensive drugs (n=85) and those who did not (n=99).

Statistical Analysis

Descriptive statistics were computed for demographic and clinical variables, including means, medians, and standard deviations for continuous variables and frequencies and percentages for categorical variables. Baseline continuous variables were compared across treatment groups using one-way analysis of variance (ANOVA) or the Kruskal-Wallıs test, and categorical variables were compared using chi-square or Fisher's exact tests, as appropriate based on distributional assumptions. We performed repeated measurements of five physiological outcomes (systolic blood pressure, diastolic blood pressure, heart rate, oxygen saturation, and temperature) using linear mixed-effects models. For each outcome, the fixed effects structure included group, phase (post vs. pre), time (within-day order), and group x phase interaction. Subject-specific random intercepts accounted for heterogeneity between the subjects. Models were estimated with maximum likelihood for likelihood ratio testing, and standard errors were used to compute Wald's 95% confidence intervals for parameter estimates. For block-wise inference on fixed effects, we computed likelihood ratio tests by comparing the full models with reduced models that omitted the term of interest. Because we examined the phase effect across the five outcomes, we controlled for multiple comparisons using Holm's method (family wise error rate, =0.05).

Missing repeated-measures data were handled within a mixed-model framework that accommodated unbalanced longitudinal data without imputation. The post-medication 1:00 AM time point had a higher rate of missing observations (~50%), consistent with the overnight clinical workflow, where vital signs may not be recorded if patients are sleeping and clinically stable. As this represented the earliest physiological response window after medication administration, it was retained for the primary analysis. Missingness at all other time points ranged from 10 to 30%.

RESULTS

Sample Characteristics

Of the 871 consultation episodes screened, 680 were ineligible after applying prespecified criteria, leaving 191 eligible episodes. Seven eligible episodes were excluded because the recommended target medication was not administered, resulting in a final analytic cohort of 184 patients. The primary reasons for hospitalization in the study sample were oncological disorders (n=109), infectious diseases (n=31), neurological disorders (n=10), cardiovascular diseases (n=8), renal and hepatic insufficiency (n=10), pulmonary diseases (n=8), orthopedic surgery (n=4), and non-oncological abdominal surgery (n=4). The mean age was 68.2±14.4 (median =70, min=20, max=100), and 40.2% of the sample were females. Of the patients, 21.4% had a diagnosis of delirium, and 16.9% had an ongoing infection. Of the patients, 46.2% were taking antihypertensive medications. The most

	Total	Mirtazapine	Olanzapine	Quetiapine	Trazodone	p
Sample size N (%)	184 (100)	86 (46.8)	17 (9.2)	58 (31.5)	23 (12.5)	
Age (mean–SD)	68.24–14.37	65.9–14.83	66.1–12.87	73.3–12.65	65.7–15.31	0.025
Sex						
Male	110 (59.8%)	50(58.1%)	10(58.8%)	39 (67.2%)	11(47.8%)	0.46
Female	74 (40.2%)	36(41.9%)	7(41.2%)	19(32.8%)	12(52.2%)	
Accompanying Diagnosis						
Oncological Disease	109 (59.2%)	61(70.9%)	6(35.3%)	28(48.3%)	14(60.9%)	p<0.001
Infectious Disease	31(16.8%)	8(9.3%)	4(23.5%)	16(27.6%)	3(13%)	0.024
Delirium	40(21.7%)	5 (5.9%)	11(64.7%)	22(37.9%)	2(8.7%)	p<0.001
Other comorbidities	136 (73.9%)	59(68.6%)	13(76.5%)	46(79.3%)	18(78.3%)	0.32
Antihypertensive use						
No	99 (53.8%)	51 (59.3%)	11(64.8%)	26(44.8%)	11(47.9%)	
Yes	85 (46.2%)	35 (40.7%)	6 (35.2%)	32(55.2%)	12(52.1%)	0.25

Table 2. Sample characteristics of the total sample and study groups

commonly prescribed drugs were mirtazapine (46.8%), quetiapine (31.5%), trazodone (12.5%), and olanzapine (9.2%). The demographic and clinical variables of the total sample and the medication groups are shown in Table 2.

In the comparative analysis of mean age across drug groups, the quetiapine group exhibited a significantly higher mean age than the other groups, with no significant age differences observed among the remaining drug groups (Kruskal-Wallis variance analysis, p=0.025). The prevalence of oncological disorders was notably higher in the mirtazapine group (70.9%) and lower in the olanzapine group (35.3%) (p<0.001). The occurrence of delirium also differed significantly between the groups (p<0.001), with the olanzapine group demonstrating a markedly higher incidence (64.71%). Additionally, significant group differences were observed in the occurrence of infection (P =0.024), with the quetiapine group having the highest rate (28.07%) and the mirtazapine group having the lowest (9.3%). No significant differences were identified between the groups with respect to other comorbidities (p=0.32). Antihypertensive use did not differ significantly between groups (p=0.25).

Linear Mixed-Effects Models

For systolic and diastolic blood pressure, oxygen saturation, and temperature, neither the phase main effect nor the group x phase interaction indicated a systematic pre–post change; confidence intervals spanned the null, and omnibus model tests were non-significant. Random-intercept mixed-effects models demonstrated an adequate fit, suggesting that individual-level variability was appropriately modeled.

The 1.00 am post-dose timepoint had ~50% missing data (vs. 10–30% at other time points), reflecting overnight workflow patterns rather than a systematic loss. This time point was retained given its clinical relevance as the first post-dose observation and mixed-model tolerance for unbalanced data.

In summary, while heart rate exhibited a modest unadjusted decline from pre-to post-intervention, multiplicity-adjusted analyses did not provide definitive evidence of a consistent physiological change across outcomes. The full numeric results, including estimates, standard errors, CIs, omnibus tests, and fit indices, are available in the tables and figures.

DISCUSSION

The findings of this retrospective analysis provide valuable insights into the effects of commonly prescribed sedative psychotropic medications (olanzapine, quetiapine, mirtazapine, and trazodone) on the vital signs of a cohort of hospitalized patients. Given the increasing reliance on these medications to manage psychiatric symptoms in medically complex populations, understanding their physiological effects is crucial to ensure patient safety and optimize therapeutic outcomes.

The primary outcome of this study indicated that there were no significant changes in vital signs, including systolic and diastolic blood pressure, heart rate, oxygen saturation, and body temperature, within 24 h of the administration of the selected psychotropic medications. This is a noteworthy finding, especially considering the high prevalence of comorbidities within the study population, where nearly 60% of the patients had an oncological disease. While previous research has highlighted various adverse events associated with sedative hypnotics, such as drowsiness and dizziness, there

Table 3. Linear Mixed-Effects Model Estimates for Vital Sign Outcomes

Outcome	Effect	Estimate (Beta)	95% CI	Wald x†/F	p	Holm-adjusted p	Interpretation
Heart rate	Phase (Post vs Pre)	-1.72	-3.11 to -0.33	5.67	0.017	0.083	Trend; NS after correction
Systolic BP	Phase (Post vs Pre)	0.42	-1.50 to 2.35	0.21	0.65	0.65	No effect
Diastolic BP	Phase (Post vs Pre)	0.36	-1.10 to 1.82	0.16	0.7	0.7	No effect
Oxygen saturation	Phase (Post vs Pre)	0.01	-0.10 to 0.12	0.33	0.56	0.56	No effect
Temperature	Phase (Post vs Pre)	0.02	-0.03 to 0.06	1.02	0.31	0.31	No effect

Estimates represent fixed effects for the post-phase versus pre-phase change. Holm correction was applied across the five primary phase tests. NS = non-significant after correction.

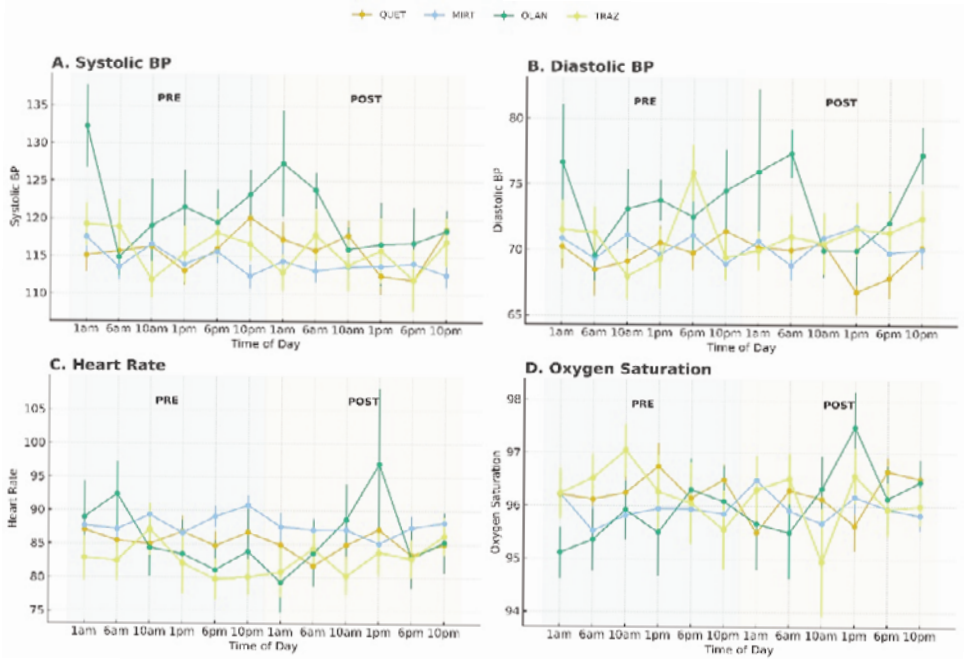

Figure 2. Vital sign trajectories before (PRE) and after (POST) psychotropic medication administration across four drug classes. The blue and orange shaded areas represent the PRE and POST post-medication periods, respectively. The lines show group means with standard errors. Groups: MIRT-mirtazapine; OLAN-olanzapine; QUET -quetiapine; TRAZ-trazodone.

has been limited empirical data specifically examining their impact on vital signs, such as blood pressure, heart rate, and oxygen saturation (23). Our study fills this gap by providing empirical data on the short-term hemodynamic and respiratory effects of these drugs in a clinical setting. For practitioners, these results suggest that routine vital sign monitoring, which is already the standard for hospitalized patients, is sufficient to detect rare adverse events.

The lack of significant differences in the vital signs between the medication groups in this study may be attributed to several factors. First, the patient population had a high prevalence of comorbid conditions, which could have influenced the stability of vital signs, despite the use of sedative hypnotics. Second, the dosages of the medications were tailored to minimize adverse effects, reflecting the clinical practice of cautious prescribing.

Published case reports have described serious cardiopulmonary and hemodynamic events following single-dose exposure to several of the study medications. Examples include bradycardia after a single 30 mg dose of mirtazapine (16), bradycardia and hypotension reported with olanzapine at doses of 2.5–10 mg even in otherwise healthy individuals (24-26), cardiopulmonary arrest after a single 25 mg dose of quetiapine and sustained hypotension after initiation at 50 mg (18,27), and bradycardia after a 50 mg dose of trazodone (21,28). Although these reports underscore potential idiosyncratic vulnerability and the importance of clinical monitoring, causal inference is limited by their design and the frequent presence of baseline medical risk factors and co-medications. In contrast, evidence from larger observational cohorts and synthesis studies has generally not corroborated a high incidence of severe acute physiological instability at therapeutic doses in monitored settings (29-31). The results of our study confirm previous studies suggesting that psychotropic drugs are frequently associated with adverse events in the elderly, severe hemodynamic instability is less common than feared when low doses are used (32,33). For instance, a meta-analysis by (9) regarding antipsychotics in delirium treatment highlighted that while sedation is a frequent side effect, severe cardiovascular events requiring discontinuation are relatively rare compared with placebo administration.

The patient population included in the study comprised elderly patients hospitalized for diseases, such as cancer, delirium, and serious infections. In general, this population requires sedative medications for insomnia, agitation, and anxiety. In this population, drug selection is challenging because of comorbid diseases, polypharmacy, and unstable

vital signs due to critical illness. Benzodiazepines are not a good choice in this group because of the risk of increasing confusion and depressing respiration. Instead, antidepressants and antipsychotics with sedative-hypnotic effects are preferred by many psychiatrists (34). In this study, mirtazapine was prescribed more frequently in the oncologic patient group, which is understandable considering the antiemetic and appetite-enhancing effects of mirtazapine, since these patients usually complain of nausea and lack of appetite, most of them being cachectic. In the delirium group, quetiapine was the preferred drug. Considering that these patients often have hyperactive delirium and symptoms, such as agitation, visual hallucinations, and delusions, it is rational to prefer an antipsychotic with a shorter half-life (35). Although trazodone is a reliable sedative antidepressant with a short half-life and anxiolytic properties, it is less preferred than mirtazapine for several reasons. First, mirtazapine has additional antiemetic properties, and its antihistaminic effects are more pronounced (36). Second, the sublingual form of mirtazapine is available as an advantage for patients with swallowing difficulties and nausea while taking the drug. The fact that olanzapine is less preferred than quetiapine, despite being a cardiac-safe and highly effective drug for acute agitation, may be due to the preference for drugs with shorter half-lives because of the risk of excessive sedation in this patient group.

Despite these promising findings, several limitations of this study remain to be acknowledged. The retrospective nature of the study inherently limits control over confounding variables and restricts the ability to draw definitive causal conclusions regarding the relationship between medication administration and vital sign changes. Because eligibility required a new initiation of a target sedative psychotropic and excluded ICU consultations, the analytic cohort represents a selected subset of consulted inpatients. Accordingly, these results should be interpreted within the context of a selected consultation-based cohort, and may not generalize to all medically complex inpatients. Second, the lack of a similar number of patients in the drug groups, and the small number of patients in the trazodone and olanzapine groups may have affected the results in terms of comparison. Additionally, the sample size, although adequate for preliminary analysis, may limit the generalizability of the findings. Future prospective studies or randomized controlled trials could help validate our findings and assess whether certain patient populations (e.g., those with cardiovascular diseases) are more vulnerable to adverse effects. Long-term outcomes were associated with psychotropic-induced vital sign changes, particularly in relation to mortality, length of hospital stay, and rehospitalization.

Another limitation is the lack of detailed information regarding the concurrent use of other medications, particularly those that could influence the cardiovascular parameters. The interactions between psychotropic medications and other pharmacological agents remain underexplored and understanding these interactions is essential for optimizing patient safety. Importantly, the first post-dose time point (1:00 AM) exhibited higher missingness (~50%), which is consistent with routine overnight nursing practices in medically stable patients. Because this represents the earliest physiological window following medication administration, exclusion removes clinically meaningful information. The retention of this time point and the use of mixed-effects modeling minimized bias and preserved interpretability. Sensitivity analyses excluding the 1:00 AM time point yielded similar findings, supporting the robustness of the results (available upon request).

In conclusion, this retrospective analysis contributes to the growing body of the literature on the use of psychotropic medications in hospitalized patients. These findings indicate that olanzapine, quetiapine, mirtazapine, and trazodone have a minimal impact on vital signs within the first 24 h of administration, suggesting that these medications can be safely utilized in acute care settings when used at conservative doses. However, vigilant monitoring of vital signs, particularly in patients with comorbidities, remains paramount. Our findings and current literature mainly highlight the impact of interindividual differences, emphasizing that factors such as comorbid cardiac conditions, age, concurrent medications, and variables influencing drug absorption play a crucial role. As psychiatric care becomes increasingly integrated into the management of hospitalized patients, further research

is essential to refine our understanding of the physiological implications of psychotropic medications, ultimately enhancing patient safety and therapeutic efficacy in acute care settings.

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All authors reviewed and approved the final version of the manuscript and agree to be accountable for all aspects of the work in accordance with ICMJE authorship criteria.

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REFERENCES

1. Oldham MA, Desan PH, Lee HB, Bourgeois JA, Shah SB, Hurley PJ, Sockalingam S; Council on Consultation-Liaison Psychiatry. Proactive Consultation-Liaison Psychiatry: American Psychiatric Association Resource Document. J Acad Consult Liaison Psychiatry. 2021 Mar-Apr;62(2):169-185. doi: 10.1016/j.jaclp.2021.01.005. Epub 2021 Jan 29. PMID: 33970855.

2. Rivelli SK, Shirey KG. Prevalence of psychiatric symptoms/syndromes in medical settings. In: Summergrad P, Kathol R, editors. Integrated Care in Psychiatry. New York: Springer; 2014. doi:10.1007/978-1-4939-0688-8_2

3. Grover S, Sahoo S, Aggarwal S, Dhiman S, Chakrabarti S, Avasthi A. Reasons for referral and diagnostic concordance between physicians/surgeons and the consultation-liaison psychiatry team. Indian J Psychiatry. 2017;59(2):170. doi:10.4103/psychiatry.indianjpsychiatry_305_16

4. Hasan HM, Althomali BA, Msolly MS, Amaway MA. Consultation-liaison psychiatry in a tertiary general hospital in Saudi Arabia: A retrospective analysis. Middle East Curr. Psychiatry 2025;32:80. doi:10.1186/s43045-025-00579-x

5. McBride KE, Solomon MJ, Bannon PG, Glozier N, Steffens D. Surgical outcomes for people with serious mental illness: systematic review and meta-analysis. Med J Aust. 2021;214(8):379-85. doi:10.5694/mja2.51009

6. Chen H, Devine M, Khan W, Khan IZ, Waldron R, Barry MK. The impact of psychiatric comorbidities on emergency general surgical patients' outcomes. Surgeon. 2023;21(5):289-94

7. Segerstrom SC, Miller GE. Psychological stress and the human immune system: a meta-analytic study of 30 years of inquiry. Psychol Bull. 2004;130(4):601-30

8. Lanini I, Amass T, Calabrisotto CS, Fabbri S, Falsini S, Adembri C, et al. The influence of psychological interventions on surgical outcomes: a systematic review. J Anesth Analg Crit Care. 2022;2(1):31

9. Kishi T, Hirota T, Matsunaga S, Iwata N. Antipsychotic medications for delirium: systematic review and meta-analysis of RCTs. J Neurol Neurosurg Psychiatry. 2016;87(7):767-74

10. MOC C. Insomnia in older adults: A review of treatment options. Cleve Clin J Med. 2025;92(1):43

11. Kolli P, Kelley G, Rosales M, Faden J, Serdenes R. Olanzapine pharmacokinetics: A clinical review. Pharmgenomics Pers Med. 2023;16:1097-1108. doi:10.2147/PGPM.S391401

12. Nemeroff CB, Kinkead B, Goldstein J. Quetiapine: preclinical studies, pharmacokinetics, drug interactions, and dosing. J Clin Psychiatry. 2002;63(13):5-11

13. Yamadera H, Suzuki H, Nakamura S, Endo S. Effects of trazodone on polysomnography and temperature in healthy volunteers. Psychiatry Clin Neurosci. 1999;53(2):189-91

14. Haria M, Fitton A, McTavish D. Trazodone: pharmacology and therapeutic use in depression. Drugs Aging. 1994;4(4):331-55

15. Hassanein EHM, Althagafy HS, Baraka MA, Abd-Alhameed EK, Ibrahim IM. Pharmacological update of mirtazapine: a narrative literature review. Naunyn Schmiedebergs Arch Pharmacol. 2024 May;397(5):2603-2619. doi: 10.1007/s00210-023-02818-6. Epub 2023 Nov 9. PMID: 37943296; PMCID: PMC11074035.

16. Demir-Gundogmus P, Gundogmus I, Olcu EB, Karagoz A, Algul A. Therapeutic single-dose mirtazapine-induced bradycardia: A case report. Dusunen Adam. 2018;31:304-7

17. Nakamura M, Seki M, Sato Y, Nagamine T. Quetiapine-induced bradycardia and hypotension in the elderly. Innov Clin Neurosci. 2016;13(1-2):34-6

18. Chia P, Poh LC, Ong J, Ong S. Cardiopulmonary arrest after a single 25-mg quetiapine dose: case report. J Crit Care Med.

2020;6(4):253-8

19. Lee TW, Tsai SJ, Hwang JP. Severe cardiovascular side effects of olanzapine in an elderly patient: case report. Int J Psychiatry Med. 2003;33(4):399-401

20. Rasnayake LR, Wimalarathne H, Jayapala RK, Gamage CD, Dassanayake DL, Ratnayake SL, Colombage A, Nandadeva D, Nelumdeniya AN. An unusual case of hypothermia associated with therapeutic doses of olanzapine: a case report. J Med Case Rep. 2011 May 18;5:189. doi: 10.1186/1752-1947-5-189. PMID: 21592373; PMCID: PMC3117824.

21. Karaman E. Bradycardia following a single dose of trazodone. Maltepe Med J. 2020;12(1):16-8

22. Halstead S, Yap CX, Warren N, Agarwal SM, Brand BA, Chan SKW, Cipriani A, Correll CU, Crossley N, D'Ambrosio E, Emsley R, Firth J, Gaughran F, Gee S, Hahn M, Hayes JF, Heald A, Howes OD, Kane JM, Kapi M, Leucht S, Meyer N, O'Donoghue B, Okeke E, Perry BI, Solmi M, Sommer IE, Srivastava V, Taipale H, Taylor D, Tiihonen J, Young AH; Lancet Psychiatry Physical Health Commission Consortium; McCutcheon RA, Siskind D, Pillinger T. Holistic prevention and management of physical health side-effects of psychotropic medication: second report of the Lancet Psychiatry Physical Health Commission. Lancet Psychiatry. 2025 Sep;12(9):673-699. doi: 10.1016/S2215-0366(25)00162-2. PMID: 40812961.

23. Onyeaka HK, Beach SR, Huffman JC, Stern TA. Side effects of psychotropic medications. In: Massachusetts General Hospital Psychopharmacology and Neurotherapeutics. 2024:130

24. Markowitz JS, DeVane CL, Boulton DW, Liston HL, Risch SC. Hypotension and bradycardia in a healthy volunteer following a single 5 mg dose of olanzapine. J Clin Pharmacol. 2002;42(1):104–106. doi:10.1177/009127000204200113.

25. Sachdeva V, Ashraf S, Inam S, Shah K, Singla A, Mansuri Z, Jain B. Olanzapine-induced bradycardia. Prim Care Companion CNS Disord. 2023;25(4):22cr03453. doi:10.4088/PCC.22cr03453.

26. Lee TW, Tsai SJ, Hwang JP. Severe cardiovascular side effects of olanzapine in an elderly patient: case report. Int J Psychiatry Med. 2003;33(4):399–401. doi:10.2190/U99G-XDML-0GRG-BYE0.

27. Bharadwaj RS, Slade TB. Sustained hypotension with initial low dose of quetiapine in a middle-aged man receiving an antihypertensive agent. Prim Care Companion CNS Disord. 2010;12(6):PCC.10l00981yel. doi:10.4088/PCC.10l00981yel

28. Li TC, Chiu HW, Ho KJ, Tzeng DS. Bradycardia following a single low dose of trazodone. Asian J Psychiatr. 2011;4(1):77–79. doi:10.1016/j.ajp.2010.03.003.

29. El-Saifi N, Moyle W, Jones C, Tuffaha H. Quetiapine safety in older adults: a systematic literature review. J Clin Pharm Ther. 2016;41(1):7–18. doi:10.1111/jcpt.12357.

30. Allen ND, Leung JG, Palmer BA. Mirtazapine's effect on the QT interval in medically hospitalized patients. Ment Health Clin. 2020;10(1):30–34. doi:10.9740/mhc.2020.01.030.

31. Liu SB, Liu S, Gao K, Wu GZ, Zu G, Liu J. Olanzapine for the treatment of ICU delirium: a systematic review and meta-analysis. Ther Adv Psychopharmacol. 2023;13:20451253231152113. doi:10.1177/20451253231152113.

32. Seifert J, Reinhard MA, Bleich S, Erfurth A, Greil W, Toto S, Grohmann R, Glocker C. Psychotropic drug-induced adverse drug reactions in 462,661 psychiatric inpatients in relation to age: results from a German drug surveillance program from 1993-2016. Ann Gen Psychiatry. 2024 Nov 18;23(1):47. doi: 10.1186/s12991-024-00530-0. PMID: 39558338; PMCID: PMC11575432.

33. Calvi A, Fischetti I, Verzicco I, Belvederi Murri M, Zanetidou S, Volpi R, Coghi P, Tedeschi S, Amore M, Cabassi A. Antidepressant Drugs Effects on Blood Pressure. Front Cardiovasc Med. 2021 Aug 3;8:704281. doi: 10.3389/fcvm.2021.704281. PMID: 34414219; PMCID: PMC8370473.

34. Casey MF, Elder NM, Fenn A, Niznik J, Khoujah D, Cole JB, Cardon Z, Ding M, Goukasian N, Moreton E, Koehl JL, Magidson PD, Skains RM, Tyler K, Liu SW; Geriatric Emergency Department Guidelines Medication Safety Group. Comparative Safety of Medications for Severe Agitation: A Geriatric Emergency Department Guidelines 2.0 Systematic Review. J Am Geriatr Soc. 2025 Sep;73(9):2893-2904. doi: 10.1111/jgs.19485. Epub 2025 Apr 24. PMID: 40275439; PMCID: PMC12460960.

35. Hawkins S, Bucklin M, Muzyk A. Quetiapine for the treatment of delirium. J Hosp Med. 2013;8(4). doi:10.1002/jhm.2019.

36. Friesen K, Falk J, Bugden S. The safety of meperidine prescribing in older adults: a longitudinal population-based study. BMC Geriatr. 2016;16:1.

The impact of Attention-Deficit/Hyperactivity Disorder and comorbid anxiety disorder on neuropsychological test performance: A retrospective clinical sample study

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SUMMARY

Objective: Attention-Deficit/Hyperactivity Disorder (ADHD) is characterized by executive dysfunction, particularly in working memory, inhibitory control, and attention. Anxiety disorders frequently co-occur with ADHD and may exacerbate or obscure these deficits. This study aimed to retrospectively evaluate neuropsychological test performance in ADHD with and without comorbid anxiety.

Method: This retrospective, cross-sectional study was conducted at the Child and Adolescent Psychiatry Outpatient Clinic of Kartal Dr Lutfi Kirdar City Hospital. Clinical records of patients aged 6–18 years presenting with inattention between January 2023 and April 2024 were reviewed. Performance on the Stroop Color–Word Test, d2 Test of Attention, Digit Span, and Porteus Maze Test was analyzed. Participants were categorized into six groups based on DSM-5 diagnoses: ADHD, ADHD + anxiety, ADHD + other diagnoses, anxiety only, other psychiatric diagnoses, and non-diagnosed.

Results: A total of 159 participants (53.5% male; mean age = 14.07±2.42 years) were included. Digit Span scores were significantly higher in the non-diagnosed group compared with all diagnostic groups ($p<0.01$). d2 error rates were highest in the ADHD group ($p<0.01$). Stroop 4, Stroop 5, and total completion times were significantly longer in the ADHD and ADHD + anxiety groups ($p<0.01$). Stroop correction scores were elevated in ADHD groups.

Discussion: Findings confirmed impairments in working memory, selective attention, and processing speed in ADHD and comorbid groups. Anxiety did not exert a protective effect on inhibitory control but appeared to impose additional burden on working memory. These results underscore the importance of considering anxiety when assessing executive dysfunction in ADHD.

Key Words: ADHD, anxiety disorder, neuropsychological tests, working memory, Stroop, d2 attention

INTRODUCTION

Attention-Deficit/Hyperactivity Disorder (ADHD) is a prevalent neurodevelopmental disorder affecting approximately 5% of children and is associated with persistent, long-term adverse effects on academic achievement, social relationships, and overall adaptive functioning (1,2). Executive dysfunction has been consistently identified as a hallmark feature of ADHD by empirical studies and meta-analyses, with moderate impairments documented in inhibitory control, working memory, and cognitive flexibility (3,4). These deficits exert a significant impact on functional outcomes and account for much of the heterogeneity that characterizes the clinical presentation of ADHD.

Anxiety disorders represent one of the most common comorbidities in ADHD. Current epidemiological and clinical studies report that between approximately one-third and nearly half of children with ADHD either meet the diagnostic criteria for at least one anxiety disorder or exhibit clinically significant anxiety symptoms (5,6,7,8). However, the impact of anxiety on executive functions in ADHD is theoretically complex, and empirical findings remain inconsistent (9,10,11). These inconsistencies are attributed to several factors, including

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methodological differences in the measurement of working memory and inhibition (e.g., scales and neuropsychological tests), the manner in which anxiety is assessed (dimensional / trait measures), the failure to control for concurrent ADHD symptoms and other comorbidities, and the confounding of adult and pediatric samples (12).

Some of these studies propose that anxiety exacerbates deficits in attentional control and working memory within ADHD by increasing cognitive load and impairing processing efficiency (13,14,15,16). Conversely, other findings suggest that anxiety may transiently enhance inhibitory performance through arousal-based mechanisms, potentially leading to performance gains under specific conditions (17,18). Furthermore, a recent study indicated that trait anxiety is generally not associated with executive function impairments in children with ADHD. Consequently, comorbid anxiety may alleviate certain executive dysfunctions while exacerbating others, resulting in a multidimensional cognitive profile that differs from the isolated presentation of either disorder (12,19,20). These divergent results underscore the need for a more nuanced investigation into how anxiety modulates executive functioning within diagnostically heterogeneous pediatric samples.

Despite the extensive literature examining executive function in ADHD, a significant research gap persists regarding how neuropsychological tests commonly used in real-world clinical settings differentiate between ADHD, ADHD with comorbid anxiety, and isolated anxiety disorders. Most existing studies rely on highly controlled research samples, which often possess limited ecological validity. In contrast, outpatient child and adolescent psychiatry clinics frequently evaluate children with overlapping symptoms, varying levels of functional impairment, and complex patterns of comorbidity. Determining whether these diagnostic groups exhibit distinct performance patterns in routine neuropsychological assessments is of critical importance for the accurate interpretation of test results and for guiding clinical decision-making processes.

The present study addresses this research gap by examining the performance of children presenting with complaints of inattention on neuropsychological measures routinely administered in an outpatient clinical setting. By comparing groups diagnosed with ADHD, ADHD with comorbid anxiety, and anxiety disorders, we aimed to elucidate how these conditions reflect differentiated profiles of executive function and attentional performance within an ecologically valid, naturalistic clinical sample.

The hypotheses of our study are as follows:

1. Children diagnosed with ADHD are expected to demonstrate significantly more pronounced impairments in working memory and inhibitory control compared to those diagnosed with isolated anxiety disorders.

2. Children with ADHD + anxiety comorbidity are predicted to exhibit relatively superior inhibitory control compared to those with ADHD only.

3. The ADHD + anxiety group is expected to show more severe working memory impairments relative to the ADHD-only group.

4. Children with isolated anxiety disorders are expected to display relatively preserved executive function performance in comparison to both ADHD groups.

METHOD

This retrospective, cross-sectional study was conducted at the Child and Adolescent Psychiatry Outpatient Clinic of Kartal Dr Lutfi Kirdar City Hospital. Records of neuropsychological assessments routinely administered to patients presenting with complaints of inattention were obtained from electronic health records and archived files within the specified period (01 January 2023–01 April 2024). Ethical approval was obtained from the Institutional Non-Interventional Clinical Research Ethics Committee of Kartal Dr Lutfi Kirdar City Hospital (Decision No: 010.99/39). The study was carried out in accordance with the principles outlined in the Declaration of Helsinki.

Sample and Grouping

Inclusion criteria were as follows:

1. Age between 6 and 18 years;

2. Presentation to the outpatient clinic with complaints of inattention and/or a provisional diagnosis of ADHD;

3. Attainment of valid scores on at least two neuropsychological assessments (Stroop, d2, Porteus, Digit Span) within the same evaluation period;

4. Clinical assessment conducted in accordance with Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria.

Exclusion criteria included:

1. Presence of intellectual disability (Intelligence Quotient (IQ) < 70);

2. Neurological disorders, epilepsy, or chronic medical conditions;

3. Diagnosis of autism spectrum disorder;

4. İncomplete or insufficient neuropsychological test records.

Participants were categorized into six groups based on clinical evaluations conducted according to DSM-5 diagnostic criteria: ADHD, ADHD with comorbide anxiety disorder, ADHD with other psychiatric diagnoses, anxiety disorders, other psychiatric disorders, and a non-diagnosed group.

The "non-diagnosed group" consisted of individuals who presented with complaints of inattention but did not meet criteria for any psychiatric disorder according to DSM-5 following clinical assessment. We emphasize that the non-diagnosed group in this study does not represent a community-based healthy control sample. Thus, this group should not be interpreted as a true healthy control group; rather, it reflects a "clinically referred, non-diagnosed" comparison group. Although not a healthy control sample, this group was used as the reference category for comparative analyses within the study.

All neuropsychological assessments were conducted prior to the initiation of any pharmacological treatment. In our clinical protocol, medication is introduced only after neuropsychological testing is completed; therefore, none of the participants were using psychotropic medication at the time of assessment.

The Stroop Color-Word Test (SCWT): SCWT, originally developed by John Stroop in 1935, is sensitive to frontal lobe functioning. It assesses the ability to inhibit cognitive interference, which occurs when the processing of one attribute of a stimulus disrupts the simultaneous processing of another attribute. In addition to interference control, the test is used to evaluate other cognitive processes, including selective attention, processing speed, cognitive flexibility, and working memory. Longer completion times and increased error rates indicate difficulties in inhibitory control (21,22).

The test comprises four cards presented in five different conditions. During the first two cards, participants are instructed to read words, whereas in the third, fourth, and fifth cards, they are asked to name colors. Both completion time and the number of errors/corrections are recorded. Scoring is conducted in three ways: total errors, total corrections, and the time elapsed from the "start" command to the reading of the last stimulus (23).

d2 Test of Attention: The d2 Test of Attention, developed by Rolf Brickenkamp, is a paper-and-pencil measure designed to assess selective attention, concentration, and processing speed. Participants are required to accurately and rapidly identify target symbols among distractors. The test consists of 14 rows, each containing 47 characters. For each row, participants are given 20 seconds to cross out all instances of the "d" with two marks. Missed targets are recorded as Error 1 (E1), while incorrectly marked characters are recorded as Error 2 (E2). The sum of E1 and E2, divided by the

total number of processed items and multiplied by 100, yields the error percentage, which was used as the primary outcome measure in the present study. Error percentage was calculated based on raw performance data, and no age-normed or education-adjusted standardization was applied, as the primary aim of the study was to compare relative attentional accuracy across diagnostic groups rather than to determine performance relative to normative reference samples. Error percentage represents an established outcome parameter in the d2 literature and is commonly used as an index of accuracy-based selective attention and inhibitory control independent of processing speed (24).

The d2 Test has been shown to measure selective attention and concentration with high reliability (25).

Digit Span Subtest (WISC-IV): The Digit Span subtest is part of the Wechsler Intelligence Scale for Children – Fourth Edition (WISC-IV), one of the updated versions of the Wechsler scales developed to assess the cognitive abilities of children aged 6 to 16 years (26). In recent years, the WISC-IV has been standardized in Türkiye, and this updated form has been widely implemented in clinical and research settings (27).

In the present study, the Digit Span subtest of the WISC-IV was employed to evaluate short-term memory and verbal working memory. The forward digit span primarily measures short-term memory capacity, whereas the backward digit span is more sensitive to executive functioning and information manipulation processes (28).

In the present study, Digit Span was analyzed as a single composite score. This methodological decision was necessitated by the wide age range of the sample and the use of age-adjusted WISC-IV scaled scores. According to the WISC-IV standardization, reliable and comparable scaled scores are provided for the total Digit Span score across different age groups; however, age-adjusted scaled scores for the forward and backward components separately are not consistently available. Accordingly, all analyses were conducted using age-adjusted WISC-IV scaled scores rather than raw scores (28,29).

Porteus Maze Test: The Porteus Maze Test, originally developed by Porteus and later adapted into Turkish by Toğrol, is a non-verbal assessment tool requiring participants to complete progressively complex mazes without lifting the pencil or crossing the lines (30). The test is designed to evaluate executive functioning, planning ability, visuospatial skills, and adaptability to novel situations (31).

Statistical Analysis

Statistical analyses were conducted using NCSS (Number Cruncher Statistical System) 2020 Statistical Software (NCSS LLC, Kaysville, Utah, USA). In evaluating the study data, quantitative variables were summarized using descriptive statistics (mean, standard deviation, median, minimum, and maximum), while qualitative variables were presented as frequencies and percentages. Normality of distribution was assessed through skewness–kurtosis values and Box Plot visual inspection.

For comparisons of executive function scores across diagnostic groups, sex, age, and grade level were entered as covariates (adjusted), and ANCOVA was applied. When significant main effects were detected, Bonferroni-adjusted post-hoc tests were used to determine the source of group differences. In addition, the assumption of homogeneity of regression slopes was evaluated by testing interaction terms between diagnostic group and each covariate (age, sex, and grade level). None of the interaction terms were statistically significant (all $p > .05$), indicating that the assumption was met for all ANCOVA models.

Results were evaluated within a 95% confidence interval, with statistical significance set at $p < .05$.

Interpretation of Partial Eta Squared (32):

0.01-0.05	Small effect size
0.06-0.14	Medium effect size
≥0.14	Large effect size

Table 1. Distribution of descriptive characteristics

		n (%)
Gender	Male	85 (53.5)
	Female	74 (46.5)
Age	*Mean – SD*	14.07–2.42
	Median (Min□Max)	14.2 (6.5-17.9)
Education Level	Primary school	13 (8.2)
	Middle school	51 (32.1)
	High school	95 (59.7)
Diagnosis	Clinically referred, non-diagnosed group	16 (10.1)
	ADHD	62 (39.0)
	ADHD +Anxiety	18 (11.3)
	ADHD +Other psychiatric disorders	35 (22.0)
	Anxiety disorders	17 (10.7)
	Other psychiatric disorders	11 (6.9)

Note. The clinically referred, non-diagnosed group does not represent a healthy control sample; participants in this group were clinically evaluated for attentional complaints but did not meet criteria for a psychiatric diagnosis.

Cohen proposed these benchmarks for eta squared (η^2). Partial eta squared (η^2p) values are commonly interpreted using the same criteria, as emphasized by Richardson (2011), who states: "Partial eta squared values are commonly interpreted using Cohen's benchmarks for η^2" (32,33).

RESULTS

The study was conducted with a total of 159 participants, of whom 46.5% (n = 74) were female. Participants' ages ranged from 6.5 to 17.9 years, with a mean age of 14.07 ± 2.42 years. The descriptive characteristics of the participants are presented in Table 1.

In the ADHD + Other Diagnoses group, comorbid conditions accompanying ADHD included oppositional defiant disorder in 8.8%, depression in 4.4%, learning disorder in 2.5%, conduct disorder in 1.9%, tic disorder in 1.3%, obsessive compulsive disorder in 1.3%, trichotillomania in 0.6%, primary nocturnal enuresis in 0.6%, and encopresis in 0.6% of the total sample. In the Other Psychiatric Disorders group, diagnoses consisted of depression in 2.5%, obsessive–compulsive disorder in 1.3%, conduct disorder in 1.3%, adjustment disorder in 1.3%, and eating disorder in 0.6% of the total sample.

The mean and median scores of the psychometric assessments administered to the participants are presented in Table 2.

Comparisons of psychometric test performance across diagnostic groups are presented in Table 3. When age, sex, and grade level were controlled as covariates, no significant differences were observed for the Porteus Maze Test ($F(5, 153) = 1.81$, $p = 0.367$, partial $\eta^2 = 0.037$).

When age, sex, and grade level were controlled as covariates, Digit Span scores differed significantly across diagnostic groups. ANCOVA revealed a significant main effect of diagnostic group on Digit Span performance ($F (5, 153) = 32.95$, $p = 0.001$, partial $\eta^2 = 0.534$). The clinically referred, non-diagnosed group had significantly higher Digit Span scores compared with the ADHD, ADHD +anxiety, ADHD +other diagnoses, anxiety disorders, and other psychiatric disorders groups (respectively: $p = 0.001$; $p = 0.001$; $p = 0.001$; $p = 0.001$; $p = 0.001$; $p < 0.01$). Additionally, participants in the "other psychiatric disorders" group scored higher than those in the ADHD group ($p = 0.010$; $p < 0.05$). The effect size was calculated as 0.663.

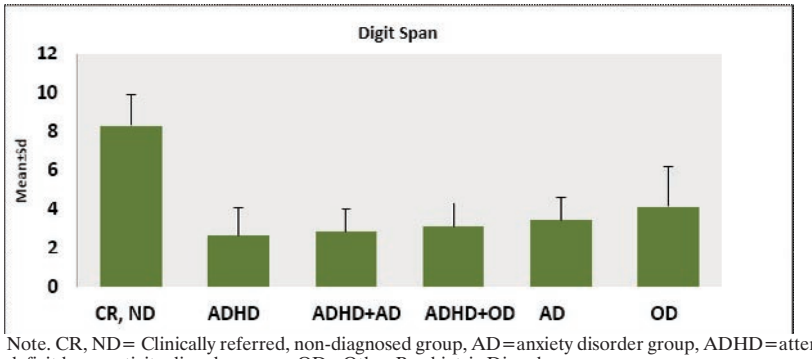
The distribution of Digit Span scores across diagnostic groups is illustrated in Figure 1.

Table 2. Distribution of scores on psychometric tests

Measure	*Mean ± SD*	Median (Min-Max)
The Porteus Maze Test	94.75±14.48	96 (43-127)
Digit Span	3.52±2.15	3 (1-10)
d2 Test of Attention (error percentage)	11.29±7.22	10.2 (0.3-40)
Stroop 1 time	9.56±2.41	9 (6-20)
Stroop 2 time	10.80±3.76	10 (6-33)
Stroop 3 time	14.80±4.58	14 (7-35)
Stroop 4 time	19.56±5.67	19 (10-47)
Stroop 4 errors	0.06±0.40	0 (0-4)
Stroop 4 corrections	0.40±0.76	0 (0-5)
Stroop 5 time	29.99±10.22	28 (14-84)
Stroop 5 errors	0.63±2.27	0 (0-18)
Stroop 5 corrections	1.45±1.50	1 (0-7)
Total Stroop time	84.71±21.91	80 (46-204)

Note. Time values are presented in seconds. Digit Span values represent age-adjusted WISC-IV scaled scores. Although the theoretical scaled score range is 1-19, the observed range in the present sample was 1-10.

Figure 1. Distribution of Digit Span scores across diagnostic groups



Note. CR, ND= Clinically referred, non-diagnosed group, AD=anxiety disorder group, ADHD=attention deficit hyperactivity disorder group, OD=Other Psychiatric Disorder group

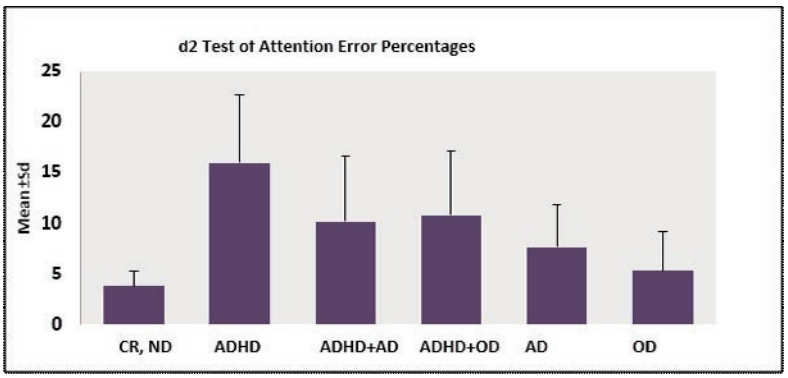
ANCOVA revealed a significant main effect of diagnostic group on d2 Test of Attention error percentages after adjusting for age, sex, and grade level ($F(5, 153) = 12.42$, $p = 0.001$, partial $\eta^2 = 0.301$). The clinically referred, non-diagnosed group demonstrated lower error percentages compared to participants with ADHD, ADHD with comorbid anxiety, and ADHD with other psychiatric diagnoses ($p = 0.001$, $p = 0.022$, and $p = 0.001$, respectively; $p < 0.05$). Conversely, individuals diagnosed with ADHD exhibited higher error percentages relative to those with ADHD + anxiety, ADHD + other psychiatric diagnoses, anxiety disorders, and other psychiatric disorders ($p = 0.019$, $p = 0.006$, $p = 0.001$, and $p = 0.001$, respectively; $p < 0.01$). The distribution of d2 Test of Attention error percentages across diagnostic groups is illustrated in Figure 2.

Comparisons of Stroop Test Card 4 scores across diagnostic groups are presented in Table 4. After adjusting for age, sex, and grade level, Stroop Test Card 4 completion times differed significantly across diagnostic groups ($F(5, 153) = 3.49$, $p = 0.005$, partial $\eta^2 = 0.108$). The clinically referred, non-diagnosed group demonstrated shorter Stroop 4 times compared with the ADHD +anxiety and ADHD +other groups ($p = 0.004$; $p = 0.012$; $p < 0.05$). Similarly, individuals in the "other psychiatric disorders" group had shorter Stroop 4 times than those in the ADHD +anxiety and ADHD +other groups ($p = 0.007$; $p = 0.021$; $p < 0.05$). The effect size was calculated as 0.160.

When age, sex, and grade level were controlled as covariates, Stroop 4 correction scores did not differ significantly across diagnostic groups ($p > 0.05$).

Comparisons of Stroop Test Card 5 scores across diagnostic groups are presented in Table 5. Stroop Test Card 5 completion times showed significant differences across diagnostic groups after covariate adjustment ($F(5, 153) = 3.22$, $p = 0.009$, partial $\eta^2 = 0.100$). Participants in the clinically referred, non-diagnosed group had shorter Stroop 5 times compared with those in the ADHD and ADHD +other groups ($p = 0.002$ and $p = 0.001$, respectively; $p < 0.01$). The effect size was calculated as 0.130. When age, sex, and grade level were controlled as covariates, Stroop 5 correction scores showed statistically significant differences across diagnostic groups ($p=0.001$; $p< 0.01$). Participants

Figure 2. Distribution of d2 Test of Attention error percentages across diagnostic groups



Note. CR, ND= Clinically referred, non-diagnosed group, AD=anxiety disorder group, ADHD=attention deficit hyperactivity disorder group, OD=Other Psychiatric Disorder group

Table 3. Comparison of psychometric test scores across diagnostic groups

	F	Df	p	Partial Eta Squared	Model F	Model p	R^2
The porteus maze test							
Gender	208,930	1	*0,303*	0,007			
Age	39,746	1	*0,653*	0,001			
Education Level	49,125	1	*0,617*	0,002	1,814	*0,052*	0,150
Diagnosis	153,463	5	*0,563*	0,027			
		Mean ± SD	*p*	Partial eta squared			
[1]Clinically referred, non-diagnosed group (n=16)		98,35±3,55					
[2]ADHD (n=62)		93,53±1,86					
[3]ADHD+anxiety (n=18)		91,62±3,84					
[4]ADHD+other psychiatric disorders (n=35)		93,76±2,40	*0,367*	0,037			
[5]Anxiety disorders (n=17)		91,20±4,50					
[6] Other psychiatric disorders (n=11)		102,11±4,53					
Digit Span	F	Df	p	Partial Eta squared			
Gender	0,034	1	*0,853*	0,000			
Age	1,585	1	*0,210*	0,011	22,441	*0,001***	0,686
Education Level	0,001	1	*0,982*	0,000			
Diagnosis	32,948	5	*0,001***	0,534			
		Mean±Sd	*p*	Partial Eta Squared			
[1]Clinically referred, non-diagnosed group (n=16)		8,45±0,32					
[2]ADHD (n=62)		2,51±0,17					
[3]ADHD+anxiety (n=18)		3,33±0,35					
[4]ADHD+other psychiatric disorders (n=35)		3,02±0,22	*0,001***	0,663			
[5]Anxiety disorders (n=17)		3,54±0,41					
[6] Other psychiatric disorders (n=11)		4,05±0,41					
d2 Test of Attention (error percentage)	F	Df	p	Partial Eta Squared			
Gender	0,021	1	*0,884*	0,000			
Age	0,846	1	*0,359*	0,006	6,546	*0,001***	0,389
Education Level	1,132	1	*0,289*	0,008			
Diagnosis	12,422	5	*0,001***	0,301			
		Mean ± SD	*p*	Partial Eta Squared			
[1]Clinically referred, non-diagnosed group (n=16)		3,74±1,50					
[2]ADHD (n=62)		15,70±0,79					
[3]ADHD+anxiety (n=18)		11,14±1,62					
[4]ADHD+other psychiatric disorders (n=35)		10,72±1,02	*0,001***	0,343			
[5]Anxiety disorders (n=17)		6,84±1,90					
[6] Other psychiatric disorders (n=11)		4,84±1,92					

Note. Analyses were conducted using ANCOVA adjusted for age, sex, and grade level. Post hoc comparisons were performed using Bonferroni correction. The clinically referred, non-diagnosed group does not represent a healthy control sample ***p<0.01*

in the clinically referred, non-diagnosed group had lower Stroop 5 correction scores compared with those in the ADHD group ($p = 0.004$; $p < 0.01$). The effect size was calculated as 0.102.

Comparisons of total Stroop test completion times across diagnostic groups are presented in Table 6. Total Stroop test completion times differed significantly across diagnostic groups after adjusting for age, sex, and grade level ($F(5, 153) = 2.42$, $p = 0.039$, partial $\eta^2 = 0.078$). Participants in the clinically referred, non-diagnosed group had shorter total Stroop completion times compared with those in the ADHD, ADHD +anxiety, and ADHD +other groups ($p = 0.001$; $p = 0.043$; $p = 0.007$; $p < 0.05$). The effect size was calculated as 0.115.

DISCUSSION

In the present study, we retrospectively evaluated the results of routinely administered neuropsychological tests (Stroop, d2, Digit Span, and Porteus

Maze) in children and adolescents presenting with complaints of inattention, with the aim of comparing executive function and attentional profiles across different diagnostic groups. Before interpreting the group differences observed in this study, an important methodological consideration should be emphasized. The clinically referred, non-diagnosed group did not constitute a healthy control sample drawn from the general population, but rather a clinically referred group evaluated for attentional complaints who did not meet criteria for a psychiatric diagnosis. As such, group comparisons should be interpreted within the context of a realworld clinical referral setting rather than as contrasts between psychopathology and normative development. This distinction is critical for understanding both the magnitude and the clinical meaning of the observed executive function differences. In interpreting these findings, it is important to consider that effect size estimates particularly for Digit Span may be influenced by the unequal distribution of participants across diagnostic groups. The clinically referred, non-diagnosed group was relatively small, and this imbalance may have contributed to inflated partial eta squared values. Accordingly, these large effect sizes should be interpreted conservatively, as reflecting potentially meaningful patterns within a realworld clinical referral sample rather than precise estimates of population level effects. In addition to group size imbalance, several methodological factors may have contributed to the relatively large partial eta squared values observed in the present study, particularly for Digit Span performance. Restricted variance within certain diagnostic groups may have accentuated between-group differences, thereby inflating effect size estimates. Moreover, the use of age-adjusted scaled scores within a clinically referred sample may introduce a degree of metric compression, which can further amplify apparent group effects. Finally, although ceiling or floor effects were not formally tested, the possibility that some measures exhibited limited score dispersion in specific groups cannot be excluded. Accordingly, the reported effect sizes should be interpreted with appropriate caution and within the methodological

Table 4. Comparison of Stroop Test Card 4 Scores Across Diagnostic Groups

	F	df	p	Partial Eta Squared	Model F	Model p	R^2
Stroop 4 time							
Gender	0,237	1	*0,627*	0,002			
Age	0,768	1	*0,382*	0,005	4,059	*0,001***	0,238
Education Level	3,402	1	*0,067*	0,023			
Diagnosis	3,487	5	*0,005***	0,108			
		Mean ± SD	*p*	Partial eta squared			
[1]Clinically referred, non-diagnosed group (n=16)		15,94±1,28					
[2]ADHD (n=62)		19,81±0,67					
[3]ADHD+anxiety (n=18)		22,90±1,38					
[4]ADHD+other psychiatric disorders (n=35)		21,20±0,86	*0,001***	0,160			
[5]Anxiety disorders (n=17)		17,02±1,62					
[6] Other psychiatric disorders (n=11)		15,20±1,63					
Stroop 4 corrections	F	df	p	Partial Eta Squared			
Gender	1,280	1	*0,260*	0,009			
Age	1,095	1	*0,297*	0,008	0,594	*0,867*	0,055
Education Level	1,076	1	*0,301*	0,007			
Diagnosis	0,733	5	*0,600*	0,025			
		Mean – SD	*p*	Partial Eta Squared			
[1]Clinically referred, non-diagnosed group (n=16)		0,28±0,20					
[2]ADHD (n=62)		0,48±0,10					
[3]ADHD+anxiety (n=18)		0,25±0,21					
[4]ADHD+other psychiatric disorders (n=35)		0,48±0,13	*0,570*	0,026			
[5]Anxiety disorders (n=17)		0,07±0,25					
[6] Other psychiatric disorders (n=11)		0,56±0,25					

Note. Analyses were conducted using ANCOVA adjusted for age, sex, and grade level. Post hoc comparisons were performed using Bonferroni correction. ***p<0.01*

context of a heterogeneous, real-world clinical referral sample rather than as precise estimates of population-level effects. Such methodological factors have been previously noted in the statistical literature as potential influences on effect size estimation (32, 34).

Our findings can be tentatively summarized along three main axes. First, short-term memory and working memory performance, as measured by the Digit Span task, was significantly higher in the clinically referred, non-diagnosed group. Second, in the domain of selective attention and processing speed, indexed by d2 error percentages, the most pronounced impairments were observed in the ADHD group. Marked deficits were also evident in the ADHD + anxiety and ADHD + other diagnosis groups. Third, indices of inhibitory control, interference suppression, and processing speed, reflected by Stroop 4, Stroop 5, and total completion times, were significantly longer in the ADHD, ADHD + anxiety, and ADHD + other groups. By contrast, scores on the Porteus Maze Test did not differ significantly among diagnostic groups.

The literature consistently emphasizes that individuals with ADHD exhibit core deficits in executive functions, particularly in working memory and attentional processes, which are considered hallmark features of the disorder. Our findings are broadly consistent with this evidence (3, 35, 36). The significantly lower Digit Span scores observed in the ADHD group compared with the clinically referred, non-diagnosed group provide additional support for the presence of deficits in verbal working memory and short-term memory among individuals with ADHD (37, 38). Similarly, our observation that d2 Test of Attention error percentages were highest in the ADHD group and lowest in the clinically referred, non-diagnosed group mirrors prior findings in the literature, highlighting substantial impairments in selective attention and error sensitivity in ADHD (39,40).

The findings of our study regarding comorbid anxiety disorder revealed a pattern that diverges

Table 5. Comparison of Stroop Test Card 5 scores Across Diagnostic Groups

	F	df	p	Partial Eta Squared	Model F	Model p	R^2
Stroop 5 time							
Gender	0,532	1	*0,467*	0,004			
Age	2,003	1	*0,159*	0,014	2,682	*0,002***	0,207
Education Level	3,847	1	*0,052*	0,026			
Diagnosis	3,215	5	*0,009***	0,100			
		Mean – SD	*p*	Partial eta squared			
[1]Clinically referred, non-diagnosed group (n=16)		20,74–2,42					
[2]ADHD (n=62)		31,34–1,27					
[3]ADHD+anxiety (n=18)		31,01–2,62					
[4]ADHD+other psychiatric disorders (n=35)		32,47–1,64	*0,001***	0,130			
[5]Anxiety disorders (n=17)		28,70–3,07					
[6] Other psychiatric disorders (n=11)		24,69–3,09					
Stroop 5 corrections	F	df	p	Partial Eta Squared			
Gender	0,077		*0,782*	0,001			
Age	0,012		*0,914*	0,000	1,433	*0,145*	0,122
Education Level	0,038		*0,846*	0,000			
Diagnosis	2,225		*0,055*	0,072			
		Mean – SD	*p*	Partial Eta Squared			
[1]Clinically referred, non-diagnosed group (n=16)		0,27–0,37					
[2]ADHD (n=62)		1,84–0,20					
[3]ADHD+anxiety (n=18)		1,71–0,40					
[4]ADHD+other psychiatric disorders (n=35)		1,57–0,25	*0,001***	0,102			
[5]Anxiety disorders (n=17)		0,83–0,47					
[6] Other psychiatric disorders (n=11)		1,39–0,48					

Note. Analyses were conducted using ANCOVA adjusted for age, sex, and grade level. Post hoc comparisons were performed using Bonferroni correction. ***p<0.01*

Table 6. Comparison of Total Stroop Test Completion Times Across Diagnostic Groups

	F	df	p	Partial Eta Squared	Model F	Model p	R^2
Stroop Total Time							
Gender	0,573		*0,450*	0,004			
Age	0,274		*0,602*	0,002			
Education Level	1,721		*0,192*	0,012	2,698	*0,002***	0,208
Diagnosis	2,420		*0,039**	0,078			
		Mean – SD	*p*	Partial eta squared			
[1]Clinically referred, non-diagnosed group (n=16)		68,60–5,18					
[2]ADHD (n=62)		87,79–2,72					
[3]ADHD+anxiety (n=18)		82,71–5,61					
[4]ADHD+other psychiatric disorders (n=35)		90,77–3,51	*0,003***	0,115			
[5]Anxiety disorders (n=17)		79,26–6,58					
[6]Other psychiatric disorders (n=11)		71,66–6,62					

Note. Analyses were conducted using ANCOVA adjusted for age, sex, and grade level. Post hoc comparisons were performed using Bonferroni correction. ***p<0.01*

somewhat from previous literature. On measures of inhibitory control and processing speed (Stroop completion times), the ADHD + anxiety group did not demonstrate superior performance compared with the ADHD-only group; instead, they exhibited similar or, in certain comparisons, even slower response times. This observation does not fully correspond with prior meta-analytic and observational findings suggesting that anxiety may attenuate inhibitory control deficits in ADHD, with relatively improved inhibitory performance reported in ADHD with comorbid anxiety.

Although the six-group structure was retained to preserve ecological validity and reflect real world clinical presentations, the relatively small size of some diagnostic subgroups and the multiple comparisons performed necessitate a cautious interpretive framework. Accordingly, the present findings should be viewed as exploratory and hypothesis generating rather than confirmatory, highlighting patterns that warrant replication in larger and more balanced samples. These findings can be interpreted within several complementary theoretical frameworks. First, executive function heterogeneity models emphasize that ADHD is not a unitary executive dysfunction but rather encompasses distinct cognitive domains, such as working memory, attention, and inhibition that follow partially dissociable patterns and developmental trajectories (35). Our results are broadly consistent with this framework, showing large effect sizes for Digit Span and d2 performance, moderate effects for Stroop completion times, and no discriminative effect for the Porteus Maze Test. This pattern suggests that comorbid anxiety may interact with certain executive domains while exerting minimal influence on others, imposing additional cognitive load rather than systematically improving inhibitory control.

From the perspective of the RDoC Cognitive Systems domain, the tasks employed in this study map onto core constructs including cognitive control and inhibition (Stroop), selective attention and processing speed (d2), and working memory (Digit Span). The observed performance patterns across ADHD, ADHD with comorbid anxiety, and anxiety-only groups support a dimensional and transdiagnostic interpretation within this clinically referred sample executive dysfunction. Rather than reflecting discrete diagnostic categories, these differences appear to index variability in underlying cognitive systems that cut across traditional diagnostic boundaries (41,42).

Attentional Control Theory (ACT) provides a coherent account of why comorbid anxiety did not confer enhanced inhibitory performance in the ADHD + anxiety group. According to ACT, anxiety disrupts processing efficiency by weakening goal-directed attentional control and increasing reliance on stimulus-driven or internally focused processes, such as worry (15, 43). Under neutral, non-emotional testing conditions, such as those characterizing the Stroop task in the present study, anxiety is unlikely to produce the heightened caution or performance-enhancing effects sometimes observed in evaluative or threat-related contexts. Instead, central executive resources may become increasingly taxed, resulting in prolonged response times despite preserved accuracy. This mechanism

plausibly explains why the ADHD + anxiety group exhibited longer Stroop completion times without corresponding increases in error rates (44).

Importantly, this pattern may also be attributable to the nature of the outcome measures employed. Executive functioning in the present study was predominantly indexed by time- and speed-based parameters. Although participants demonstrated comparable accuracy and correction scores across groups, time-dependent measures appeared to be more sensitive to the cognitive slowing and increased mental effort associated with anxiety (13,14,15). Moreover, the comorbid anxiety group was clinically heterogeneous, encompassing different anxiety disorder subtypes and varying levels of state anxiety. Such heterogeneity may further obscure any consistent masking or compensatory effects of anxiety on executive performance in clinically referred samples (45).

Finally, developmental considerations are essential for interpreting these findings. Inhibitory control tends to reach near adult levels earlier in development, whereas working memory and cognitive flexibility continue to mature throughout adolescence (46, 47). Age related convergence in inhibitory processes may therefore have reduced detectable differences between ADHD and ADHD + anxiety groups, while the more protracted developmental trajectories of working memory and attentional control remained sensitive to diagnostic variation. This interpretation aligns with developmental delay models of ADHD, which posit disrupted yet not necessarily deviant executive function maturation (48).

Together, these complementary theoretical frameworks underscore that comorbid anxiety does not exert a uniform or straightforward influence on executive functioning in ADHD. Rather, its effects appear to be domain-specific, developmentally contingent, and shaped by task characteristics, anxiety subtype, and underlying cognitive demands (36,47). This nuanced interaction carries important clinical implications, as understanding whether anxiety imposes additional burden, or alters the expression, of executive function deficits may refine both diagnostic interpretation and individualized intervention planning.

Consistent with this view, working memory impairments were evident in both the ADHD and ADHD + anxiety groups, with significantly lower Digit Span performance compared to the non-diagnosed group. This pattern aligns with theoretical and empirical models suggesting that anxiety imposes a sustained cognitive load that competes for limited executive resources, particularly within working memory systems (10, 49). Anxiety related cognitive activity may strain processing capacity, disrupt attentional focus, and complicate mental manipulation, thereby impairing short-term memory performance (15, 50).

Importantly, anxiety in the present study was assessed categorically through structured clinical interviews rather than via dimensional symptom measures. Accordingly, the “anxiety” captured here likely reflects trait-like, chronic anxiety rather than transient, state-dependent fluctuations. Tasks such as Digit Span, administered under neutral and non-evaluative conditions, are known to be more sensitive to enduring cognitive interference than to acute state anxiety. This may explain why the ADHD + anxiety group did not exhibit disproportionately greater working memory impairment relative to the ADHD-only group. This interpretation is consistent with Attentional Control Theory, which posits that state anxiety exerts stronger disruptive effects under conditions of evaluative threat, a context not present in the current clinical assessment setting (15, 43).

At the same time, prior studies have reported mixed findings, with some suggesting that anxiety may exaggerate estimates of working memory impairment in ADHD (20, 51), highlighting the complexity of this interaction. This heterogeneity was also reflected in the attentional findings of the present study. On the d2 Test of Attention, individuals with ADHD and comorbid anxiety demonstrated lower error rates compared with those with ADHD alone. This result mirrors inconsistencies in the literature and underscores the importance of considering anxiety subtypes and symptom dimensions, as different anxiety profiles may differentially influence attentional vigilance, error monitoring,

and cautious responding (14).

In contrast, inhibitory control and processing speed measures revealed a more consistent pattern across ADHD-based groups. Prolonged Stroop completion times were observed in the ADHD, ADHD + anxiety, and ADHD + other diagnosis groups, whereas error and correction rates did not differ significantly. This dissociation suggests that time-based indices may be more sensitive than accuracy metrics in capturing the cognitive slowing and increased executive load associated with anxiety. In line with Attentional Control Theory, anxiety may preserve performance effectiveness while reducing processing efficiency, leading to slower response times despite intact error control (44).

The absence of significant group differences on the Porteus Maze Test warrants specific consideration. Several methodological and conceptual factors may account for this finding. First, the task may have been insufficiently demanding across the wide developmental range of 6–18 years, resulting in restricted variability and potential ceiling effects. Second, contemporary executive function heterogeneity models emphasize that ADHD is most robustly associated with deficits in working memory, sustained attention, and interference control, while planning measures often show weaker and more inconsistent associations (3). Consistent with this framework, the present study demonstrated large effect sizes for Digit Span and d2 error percentage, moderate effects for Stroop latencies, but no discriminative effect for the Porteus Maze.

Finally, given the clinically heterogeneous and ecologically representative nature of the sample (52), it is plausible that the broad planning abilities assessed by the Porteus Maze were relatively preserved across diagnostic groups. In contrast, more narrowly defined executive processes, such as verbal working memory, selective attention, and interference control, yielded clearer diagnostic differentiation. Together, these findings suggest that the Porteus Maze Test may be less sensitive than Digit Span, d2, and Stroop measures for distinguishing ADHD and comorbid presentations within this developmental period.

From a clinical perspective, the present results suggest the practical utility of brief, routinely administered neuropsychological tools in real-world assessment settings. Digit Span and the d2 Test of Attention emerged as particularly sensitive measures for differentiating ADHD and comorbid diagnostic subgroups among patients presenting with attentional complaints. Stroop completion times, rather than error indices, provided additional insight into inhibitory control and processing speed inefficiencies, especially in the presence of comorbid anxiety. These findings further emphasize the importance of incorporating dimensional assessment of anxiety when interpreting executive function test performance, as comorbid anxiety may either obscure or exaggerate cognitive deficits depending on the domain assessed and the metrics employed.

Several limitations of this study should be acknowledged. Although children with an IQ below 70 were excluded, standardized IQ scores were not available for all participants, limiting control over more subtle differences in intellectual functioning. The Digit Span test was analyzed as a composite score due to the wide age range of the sample and reliance on age-adjusted WISC-IV norms; however, this approach may have reduced the specificity of inferences regarding distinct working memory subcomponents. Diagnostic groups were unbalanced in terms of sample size, which may have reduced statistical power for some comparisons, despite the use of covariate-adjusted ANCOVA models, conservative post-hoc corrections, and effect size reporting. The retrospective design of the study restricted the standardization of assessment conditions and precluded systematic evaluation of contextual factors such as sleep patterns or psychosocial stress. In addition, the absence of symptom severity measures prevented dimensional analyses of executive function in relation to symptom burden. Anxiety disorders were treated categorically without differentiation by subtype or severity, which may have reduced interpretive precision. Stroop 4 and 5 error scores showed extremely restricted variability, with near-ceiling performance across participants, leading to their exclusion from inferential analyses and suggesting that error-based Stroop indices may be less sensitive for differentiating diagnostic groups in this develop-

mental range. Finally, the restricted performance range observed on the Porteus Maze Test suggests limited sensitivity of this measure within the studied age group. Future prospective studies employing more balanced samples, dimensional symptom measures, and broader executive function batteries are warranted to extend and refine the present findings.

In conclusion, the present study suggests that brief and routinely administered neuropsychological measures, particularly Digit Span and the d2 Test of Attention, provide clinically meaningful and practical indicators for differentiating ADHD and comorbid diagnostic presentations in children and adolescents referred for attentional complaints. These tools may be useful for identifying impairments in working memory and selective attention within real world, time limited clinical settings. Across diagnostic groups, ADHD was characterized by robust deficits in working memory, selective attention, and processing efficiency, while prolonged response times on Stroop tasks indicated impairments in inhibitory control and cognitive speed in both ADHD and ADHD with anxiety. In contrast, the absence of group differences on the Porteus Maze Test suggests limited sensitivity of planning-based measures for diagnostic differentiation in this developmental range, highlighting the importance of task selection when evaluating executive functioning in clinical practice. At the same time, these findings should be interpreted within the context of a clinically referred and ecologically valid sample. The present results are best viewed as exploratory and hypothesis generating rather than confirmatory, particularly given the heterogeneity of diagnostic groups and the imbalance in subgroup sizes. Accordingly, replication in larger and more balanced samples is warranted to further establish the robustness and generalizability of these observations.

Importantly, our findings emphasize that comorbid anxiety does not uniformly enhance or attenuate executive functioning in ADHD. Rather, anxiety appears to exert domain-specific and sometimes counterbalancing effects, contributing to cognitive slowing and increased working memory load without conferring consistent benefits in inhibitory control. This underscores the necessity of considering comorbid anxiety, preferably through dimensional assessment, when interpreting executive function test performance in ADHD populations.

Overall, the results support the clinical utility of multi-indicator executive function assessment approaches and reinforce the value of ecologically valid data derived from routine clinical referrals. Future prospective studies incorporating standardized symptom severity measures, balanced diagnostic samples, and developmentally sensitive executive function tasks will be essential for refining diagnostic interpretation and informing individualized intervention strategies.

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REFERENCES

1. Association AP. Diagnostic and statistical manual of mental disorders (DSM-5®). American Psychiatric Pub; 2013.

2. Polanczyk GV, Willcutt EG, Salum GA, Kieling C, Rohde LA. ADHD prevalence estimates across three decades: an updated systematic review and meta-regression analysis. Int J Epidemiol 2014; 43(2):434-442.

3. Willcutt EG, Doyle AE, Nigg JT, Faraone SV, Pennington BF. Validity of the executive function theory of ADHD: A meta-analytic review. Biol Psychiatry 2005; 57(11):1336–1346.

4. Kofler MJ, Sarver DE, Harmon SL, Moltisanti A, Aduen PA, Soto EF, Ferretti N. Working memory and organizational skills problems in ADHD. J Abnorm Child Psychol 2020; 48(5):703–717.

5. Centers for Disease Control and Prevention. Data and statistics on ADHD — co-occurring conditions. U.S. Department of Health and Human Services. Retrieved from https://www.cdc.gov/adhd/data/index.html 2024.

6. Mutluer T, Doğangün B, Çalkoğlu C. Psychiatric comorbidities in children with attention-deficit/hyperactivity disorder: A clinical sample from Turkey. Clinical Psychopharmacology and Neuroscience 2022; 20(1),132–140.

7. Gümüş V, Aktepe E, Mutlu C. Psychiatric comorbidity in children and adolescents with attention-deficit/hyperactivity disorder. Anatolian Journal of Psychiatry 2015; 16(4), 255–263.

8. Riahi F, Tehrani-Doost M, Shahrivar Z, Pakbaz B. Psychiatric comorbidity in a clinical sample of children and adolescents with ADHD. Iranian Journal of Psychiatry 2014; 9(2), 71–78.

9. Alfonso SV, Lonigan CJ. Trait anxiety and adolescent's academic achievement: The role of executive function. Learning and Individual Differences 2021; 85,101941.

10. Moran TP. Anxiety and executive functioning: Insights from attentional control theory. Wiley Interdisciplinary Reviews: Cognitive Science 2016;7(4), 264–279.

11. Ursache A, Raver CC. The impact of executive function processes on emotional and social development. Developmental Psychology 2014; 50(9), 2355–2366.

12. Marsh CL, Harmon SL, Cho S, Chan ESM, Gaye F, DeGeorge L, Black KE, Irwin Harper L N, Kofler MJ. Does anxiety systematically bias estimates of executive functioning deficits in pediatric ADHD? Res child adolesc psy 2024;52(5):773-787.

13. Jarrett MA, Ollendick TH. A conceptual review of comorbidity in children and adolescents with attention-deficit/hyperactivity disorder and anxiety. Clin Psychol Rev 2008; 28(7):1266–1286.

14. Maric M, Heyne DA, van Widenfelt BM, Westenberg PM, Scholte RHJ. Anxiety and executive functioning in children with ADHD. Eur Child Adolesc Psychiatry 2018; 27(6):701–710.

15. Eysenck MW, Derakshan N, Santos R, Calvo MG. Anxiety and cognitive performance: Attentional control theory. Emotion 2007; 7(2):336–353.

16. Moran TP. Anxiety and working memory capacity: A meta-analysis and narrative review. Psychological Bulletin 2016; 142(8):831–864.

17. Tannock R. ADHD with anxiety disorders. In T. E. Brown (Ed.), ADHD comorbidities: Handbook for ADHD complications in children and adults. American Psychiatric Publishing, 2009, p.131-155.

18. Jarrett MA, Rapport HF, Rondon AT, Becker SP. ADHD and anxiety: Clinical and cognitive considerations. Curr Psychiat Rep 2016; 18(12):109.

19. Lipszyc J, Schachar R. Inhibitory control and psychopathology: a meta-analysis of studies using the stop signal task. J Int Neuropsychol Soc 2010; 16(6):1064-76.

20. Read KL, Sulik MJ, Montroy JJ, Hughes C. Anxiety symptoms and working memory in children with and without ADHD. J Atten Disord 2020; 24(6):825–835.

21. Scarpina, F, Tagini S. The stroop color and word test. Front psychol 2017; 8:557.

22. Stroop JR. Studies of interference in serial verbal reactions. J exp psychol 1935;18(6):643.

23. Karakaş S, Erdoğan E, Sak L, Soysal AŞ, Ulusoy T, Ulusoy İY, Alkan S. Stroop Testi TBAG Formu: Türk kültürüne standardizasyon çalışmaları, güvenirlik ve geçerlik. Klin Psikiyatr 1999; 2(2):75-88.

24. Egeland J, Kovalik-Gran I. Measuring several aspects of attention in one test: the factor structure of conners's continuous performance test. J Atten Disord. 2010 Jan;13(4):339-46.

25. Brickenkamp R, Zilmer E. d2 test of attention 1998.

26. Wechsler D. The Wechsler Intelligence Scale for children (4. baskı). London: Pearson Assessment, 2004.

27. Uluç S, Öktem F, Erden G, Gençöz T, Sezgin N. Wechsler Çocuklar İçin Zekâ Ölçeği-IV: Klinik bağlamda zekânın değerlendirilmesinde Türkiye için yeni bir dönem. Türk Psikoloji Yazıları 2011;14(28):49-57.

28. Wechsler D. WISC-IV technical and interpretive manual. San Antonio, TX: Psychological Corporation, 2003.

29. Sattler JM. Assessment of Children: Cognitive Foundations (5th ed.) San Diego, CA: Jerome M. Sattler Publisher.

30. Togřol B. Rb Cattell zeka testinin 2a ve 2b formları ile Porteus labirenti zeka testinin 1300 Türk çocuğuna uygulanması.Tecrübi Psikoloji Çalışmaları 1974;11:1-34.

31. Porteus SD. Porteus Maze Tests: Fifty Years Application. Palo Alto, CA: Pacific Books; 1965.

32. Cohen J. Statistical Power Analysis for the Behavioral Sciences (2nd ed.), 1988.

33. Richardson JTE. Eta squared and partial eta squared as measures of effect size in educational research. Educational Research Review 2011; 6(2), 135–147.

34. Field AP. Discovering statistics using IBM SPSS Statistics (5th ed.). SAGE Publications, London, UK, 2018

35. Kofler MJ, Irwin LN, Soto EF, Groves NB, Harmon SL, Sarver DE. Executive functioning heterogeneity in pediatric ADHD. J abnorm child psychol 2019; 47(2): 273-286.

36. Alderson RM, Kasper LJ, Hudec KL, Patros CH. Attention-deficit/hyperactivity disorder (ADHD) and working memory in

adults: a meta-analytic review. Neuropsychology 2013; 27(3):287.

37. Martinussen R, Hayden J, Hogg-Johnson S, Tannock R. A meta-analysis of working memory impairments in children with attention-deficit/hyperactivity disorder. J Am acad child adolesc psychiatry 2005; 44(4):377-384.

38. Kasper LJ, Alderson RM, Hudec KL. Moderators of working memory deficits in children with ADHD: A meta-analytic review. Clin Psychol Rev 2012;32(7):605–617.

39. Barkley RA. Behavioral inhibition, sustained attention, and executive functions: Constructing a unifying theory of ADHD. Psychol Bull 1997; 121(1): 65–94.

40. Homack S, Riccio CA. A meta-analysis of the sensitivity and specificity of the Stroop Color and Word Test with children. Arch Clin Neuropsychol 2004;19(6): 725–743.

41. Pallanti S, Salerno L. ADHD Circuitries in the R-Do-C Perspective. In: The Burden of Adult ADHD in Comorbid Psychiatric and Neurological Disorders. Springer 2020.

42. Musser ED, Raiker Jr JS. Attention-deficit/hyperactivity disorder: An integrated developmental psychopathology and Research Domain Criteria (RDoC) approach. Comprehensive Psychiatry 2019; 90, 65-72.

43. Derakshan N, Eysenck MW. Anxiety, processing efficiency, and cognitive performance: New developments from attentional control theory. European psychologist 2009; 14(2), 168-176.

44. Eysenck MW, Derakshan N. New perspectives in attentional control theory. Personality and Individual Differences 2011; 50(7), 955-960.

45. Bloemsma JM, Boer F, Arnold R, Banaschewski T, Faraone SV, Buitelaar JK, Sergeant JA, Rommelse N, Oosterlaan J. Comorbid anxiety and neurocognitive dysfunctions in children with ADHD. Eur Child Adolesc Psychiatry 2013;22(4):225–234.

46. Huizinga M, Dolan CV, Van der Molen MW. Age-related change in executive function: Developmental trends and a latent variable analysis. Neuropsychologia 2006, 44(11), 2017-2036.

47. Luna B. Developmental changes in cognitive control through adolescence. Advances in child development and behavior 2009; 37, 233-278.

48. Shaw P, Eckstrand K, Sharp W, Blumenthal J, Lerch JP, Greenstein D, Clasen L, Evans A, Giedd J, Rapoport, JL. Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. Proceedings of the national academy of sciences 2007;104(49), 19649-19654.

49. Joormann J, Gotlib IH. Selective attention to emotional faces following recovery from depression. Journal of abnormal psychology 2007; 116(1), 80.

50. Fosco WD, Hawk LW, Colder CR, Meisel SN. Executive function and developmental psychopathology. J Child Psychol Psychiatry 2020; 61(2):203–219.

51. Schatz DB, Rostain AL. ADHD with comorbid anxiety: A review of the current literature. J Atten Disord 2006; 10(2):141–149.

52. Castellanos FX, Tannock R. Neuroscience of attention-deficit/hyperactivity disorder: the search for endophenotypes. Nature Reviews Neuroscience 2002; 3(8), 617-628.

Meta-analytic evidence on esketamine in major depressive disorder: An umbrella review

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SUMMARY

Esketamine is a glutamatergic treatment option for major depressive disorder, particularly treatment-resistant depression, because of its rapid antidepressant effects. However, the expanding meta-analytic literature is characterized by methodological heterogeneity and partial overlap of primary trials, which complicates the clinical interpretation of efficacy and safety findings. A higher-level synthesis is therefore needed to contextualize the existing evidence.

We conducted an umbrella review of published meta-analyses evaluating the efficacy and/or safety of esketamine in adults with MDD. PubMed/MEDLINE and Scopus were searched for meta-analyses published between December 2020 and December 2025. Given overlap of primary trials and heterogeneity in outcome definitions, findings were synthesized qualitatively. Outcomes included depressive symptom severity, response and remission rates, suicidality-related outcomes, relapse and maintenance effects, and safety and tolerability.

Twenty-nine meta-analyses were included. Esketamine was associated with reductions in depressive symptom severity compared with placebo, with effects most pronounced at very early post-administration time points (hours to days). Reported effect sizes were generally small to moderate. Response and remission rates were higher in the acute phase, particularly at early assessments. Outcomes related to suicidal ideation were examined in a limited number of meta-analyses and were largely confined to acute post-dose evaluations. Relapse prevention and maintenance effects were reported in few meta-analyses and were mainly based on similar continuation-phase trials. Esketamine was associated with higher rates of non-serious adverse events, most commonly dissociation, dizziness, sedation, and gastrointestinal symptoms, while serious adverse events and all-cause discontinuation were not consistently increased.

At the meta-analytic level, intranasal esketamine is associated with a rapid-onset antidepressant effect of modest magnitude that appears time-sensitive. Current evidence suggests that esketamine may be considered as an adjunctive option for early symptomatic relief in selected patients. However, evidence regarding long-term effectiveness, relapse prevention, and effects on suicidal ideation remains limited. Further independently funded studies with long-term outcomes are needed to better define its clinical role.

Key Words: Esketamine, Intranasal Administration, Major Depressive Disorder, Meta-Analysis, Suicidal Ideation, Treatment-Resistant Depression

INTRODUCTION

Treatment-resistant depression (TRD) refers to patients with major depressive disorder (MDD) who remain symptomatic after two or more antidepressant trials administered at adequate doses and for sufficient durations. The clinical relevance of this population is substantial, as TRD has been linked to a an increased risk of suicide, a recurrent course, marked functional impairment, and greater utilization of healthcare services. Population-based studies indicate that approximately 20–30% of individuals with depression meet criteria for treatment resistance (1,2). Accordingly, TRD represents a major area of unmet need in clinical psychiatry.

Pharmacological treatments for depression have historically been grounded in the modulation of monoaminergic systems, including serotonin, noradrenaline, and dopamine. However, persistently

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low rates of full remission and high risks of relapse suggest that the biological underpinnings of depression extend beyond monoaminergic dysfunction alone (3, 4). In recent years, a broader neurobiological framework has been proposed, incorporating mechanisms related to synaptic plasticity, glutamatergic dysregulation, neuroinflammation, and alterations in stress-response systems (2,4). These developments have stimulated increasing interest in novel, non-monoaminergic therapeutic targets for depression.

Within this context, treatments targeting glutamatergic modulation have emerged as particularly promising options in the management of TRD. Esketamine, the S-enantiomer of ketamine that acts as an N-methyl-D-aspartate (NMDA) receptor antagonist, has gained clinical and scientific attention because of its rapid antidepressant effects and its role in modulating synaptic plasticity. Randomized controlled trials (RCTs) and subsequent meta-analytic evaluations have demonstrated that esketamine can produce relatively early-onset antidepressant effects in patients with depression (5-7). Despite accumulating meta-analytic evidence, uncertainty persists regarding the magnitude, temporal persistence, and clinical significance of esketamine's effects, supporting the need for a higher-level synthesis. Moreover, safety and tolerability outcomes related to esketamine treatment have been reported inconsistently across meta-analyses, reflecting heterogeneity in adverse event reporting across the meta-analytic literature. Uncertainty therefore remains regarding the consistency and clinical interpretation of safety findings.

Given the rapidly expanding and partially overlapping meta-analytic literature on esketamine, a higher-level synthesis is needed to clarify the consistency, magnitude, and clinical relevance of its reported effects.

The aim of this umbrella review is therefore to synthesize and critically appraise evidence reported in published meta-analyses evaluating the clinical effectiveness and safety profile of esketamine for depressive disorders. Specifically, meta-analytic findings relating to depressive symptom severity, response and remission rates, acute effects on suicidal ideation, relapse and maintenance outcomes, and safety and tolerability profiles are comparatively examined within a unified analytical framework.

METHOD

This study uses an umbrella review approach and follows PRISMA reporting principles for systematic reviews and meta-analyses. The objective of this umbrella review was to synthesize evidence from published quantitative meta-analyses examining the therapeutic effectiveness and safety outcomes of esketamine in major depressive disorder (MDD), including treatment-resistant depression (TRD) and depressive episodes accompanied by acute suicidal ideation. A PRISMA flow diagram was used to illustrate the study selection process.

Search Strategy

Eligible meta-analyses published between December 2020 and December 2025 were identified through structured searches of the PubMed/MEDLINE and Scopus databases. Searches were restricted to English-language publications. Keyword combinations addressing esketamine and depressive disorders were applied in the database searches, as outlined below:

(esketamine OR "S-ketamine" OR "Spravato" OR "intranasal esketamine") AND ("major depressive disorder" OR depression OR "treatment-resistant depression" OR TRD) AND (meta-analysis).

Reference lists of relevant publications were also reviewed, and additional focused searches were undertaken to capture any further eligible studies.

Eligibility Criteria

Meta-analyses were included if they:

- Involved adult populations with MDD or TRD,
- Evaluated esketamine treatment for efficacy

and/or safety outcomes, and

• Reported quantitative pooled estimates comparing esketamine with placebo and/or standard antidepressant treatments.

Studies were excluded if they met any of the following criteria:

• Conducted in pediatric populations

• Reported pharmacokinetic data exclusively

• Assessed racemic ketamine without providing esketamine-specific analyses

Study Selection and Data Extraction

An initial screening of titles and abstracts was performed independently by two investigators to identify potentially relevant records. Full texts were then examined for eligibility, with any unresolved differences adjudicated by a third reviewer.

Relevant data were collected using a predefined extraction framework and included publication characteristics, number of included trials and participants, treatment and comparator arms, outcome domains (depressive symptom severity, response and remission, relapse/maintenance outcomes, suicidal ideation, and safety/tolerability), effect size metrics (SMD, MD, OR, RR, or HR), heterogeneity estimates (I^2), subgroup analyses, and reported funding sources or conflicts of interest. For heterogeneity estimates, a uniform classification was applied to enhance interpretability across meta-analyses and does not imply re-analysis of original pooled estimates. Effect estimates were extracted and presented according to the original coding and directionality used in each meta-analysis and were not re-coded for standardization.

Evaluation of Methodological Quality and Evidence Synthesis

Two reviewers independently evaluated the methodological rigor of the included meta-analyses with the AMSTAR-2 tool. Given the methodological heterogeneity, overlap of primary trials, and variability in outcome definitions across meta-analyses, no additional quantitative pooling was performed. Instead, findings were synthesized qualitatively and thematically, drawing on the results reported across the selected meta-analyses.

To ensure comparability across meta-analyses, heterogeneity was interpreted using a predefined, uniform classification based on Cochrane guidance, irrespective of the thresholds applied in individual studies. I^2 values $<40\%$ were considered low, 40–60% moderate, and $>60\%$ high heterogeneity. The synthesis focused on a comparative evaluation of evidence across meta-analyses to characterize the efficacy, temporal profile, relapse/maintenance outcomes, and safety–tolerability of esketamine in depression.

Overlap Assessment

To quantify the degree of overlap among the included meta-analyses and to address the potential risk of double counting of primary studies, we constructed a citation matrix and calculated the Corrected Covered Area (CCA). The citation matrix mapped the occurrence of each primary randomized controlled trial across the included meta-analyses. The CCA was calculated using the formula $CCA=(N-r)/(rc-r)CCA=(N-r)/(rc-r)$, where N represents the total number of occurrences of primary studies across reviews, r the number of unique primary studies, and c the number of reviews included in the umbrella review.

Certainty of evidence assessment

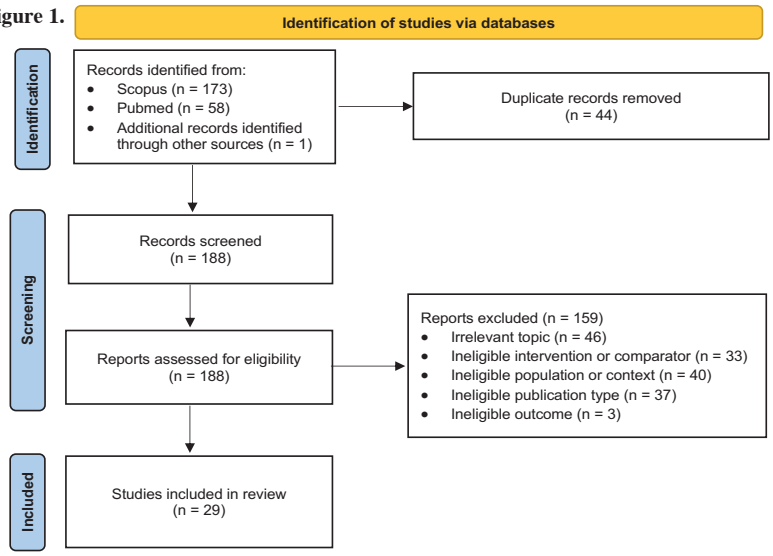
Certainty of evidence for the main outcome domains was evaluated using the GRADE approach, considering risk of bias, inconsistency, indirectness, imprecision, and publication bias.

RESULTS

Overview of included meta-analyses

A total of 29 meta-analyses were identified through

Figure 1.



the literature search and included in the final synthesis (Figure 1). All included meta-analyses synthesized data from randomized controlled trials and primarily involved samples diagnosed with major depressive disorder (MDD), with several analyses focusing specifically on treatment-resistant depression (TRD) or mixed MDD populations (Table 1).

Across meta-analyses, primary efficacy outcomes most commonly reflected changes in depressive symptom severity, assessed using validated rating scales. The Montgomery–Åsberg Depression Rating Scale (MADRS) was the most frequently employed outcome measure, while some meta-analyses also reported outcomes based on the Hamilton Depression Rating Scale (HAM-D/HDRS) or standardized derivatives of these instruments. Effect sizes were reported using standardized mean differences (SMD), mean differences (MD), Hedges' g, or Cohen's d.

Response and remission rates were frequently evaluated as secondary or co-primary endpoints, typically expressed using odds ratios (OR), risk ratios (RR), or risk differences (RD). A smaller subset of meta-analyses, particularly those incorporating continuation or longitudinal follow-up data, assessed relapse or recurrence risk, most often reported using hazard ratios (HR).

Suicidality-related outcomes were reported heterogeneously across meta-analyses. Some studies assessed acute changes in suicidal ideation using specific instruments (e.g., MADRS-SI, C-SSRS, or comparable scales), whereas others did not report suicidality-related outcomes or addressed them only as secondary or exploratory analyses. Safety and tolerability outcomes commonly included adverse events (AEs), serious adverse events (SAEs), and treatment discontinuation. In several studies, discontinuation due to adverse events and all-cause dropout rates were evaluated alongside efficacy outcomes, although the scope, selected safety endpoints, reporting formats, and duration of follow-up varied across meta-analyses.

With respect to route of administration, the majority of included meta-analyses focused on intranasal esketamine, while a limited number incorporated studies evaluating intravenous esketamine. Esketamine was evaluated as adjunctive therapy in some meta-analyses, while others examined monotherapy or both treatment approaches. Several meta-analyses also included direct, indirect, or network-based comparisons of esketamine with active treatments such as intravenous ketamine or second-generation antipsychotic augmentation.

Sample sizes varied considerably across meta-analyses, and because of substantial overlap of primary trials, calculation of a unique pooled patient population was not feasible. A substantial proportion of meta-analyses included industry-sponsored trials or reported limited information on conflicts of interest.

Table 1. Meta-Analyses of Esketamine on Efficacy, Safety, and Suicidality

#	Author (Year)	Included Studies	Total Sample Size	Treatment	Comparator	Primary Outcome Measures	Effect Size	Heterogeneity[a]	Conflict Of Interest[b]
1	Fountoulakis et al. (2025) (8)	11 RCTs (10 acute, 1 maintenance)	1,774 (acute: 959 IN ESK, 785 placebo; 20 IV ESK, 10 placebo; maintenance: 297 ESK)	IN/IV ESK + AD	Placebo + AD	MADRS; CGI-SS-r; BSSI; C-SSRS	SMD (MADRS): 24 h: -0.33 (-0.43 to -0.24) 1 week: 0.25 (-0.34 to -0.16) 2 weeks: -0.15 (-0.27 to -0.04) 4 weeks: -0.23 (-0.32 to -0.13) Suicidality: No significant effect demonstrated	Low□moderate (I†: 0□53%)	NR
2	Wang et al. (2023) (20)	12 RCTs (overall network; 2 ESK RCTs)	4,276 (343 ESK, 22 placebo)	IN ESK + AD	Placebo + AD	MADRS; response rate	MADRS: MD = -4.24 (-7.12 to -1.37; p = 0.0038) Response rate difference: 25%, p < 0.0001	NR (ESK-specific)	Industry-funded
3	Naudet et al. (2025) (15)	7 RCTs (6 acute, 1 maintenance)	1,505 (873 ESK, 692 placebo)	IN ESK + AD	Placebo + AD	MADRS; relapse risk (HR)	MADRS (acute): MD = -2.94 (95% CI -5.39 to -0.48) Relapse risk (maintenance): HR = 0.38 (0.26□0.57)	MADRS: Low□ moderate (I† = 28%) Relapse risk: NR	NR
4	Dold et al. (2020) (21)	25 RCTs (3 ESK RCTs)	9,004 (373 ESK, 268 placebo)	IN ESK + AD	Placebo + AD	MADRS	MADRS: MD = 4.09 (95% CI 2.01□6.17)	Moderate (I† = 43.9%)	No external funding; conflicts of interest declared (industry relationships)
5	VÆzquez et al. (2021) (17)	49 RCTs (7 ESK RCTs)	10,031 (711 ESK, 576 placebo)	IN ESK + AD	Placebo + AD	Response rate (MADRS/HDRS)	Response: OR = 1.96 (95% CI 1.55□2.50)	Low (I† < 1%)	No conflicts of interest declared
6	Seshadri et al. (2024) (26)	12 RCTs (7 IN ESK, 1 IV ESK RCTs)	1,549 (730 IN ESK, 557 placebo; 20 IV ESK, 10 placebo)	IN/IV ESK + AD	Placebo + AD	MADRS	IN esketamine: Hedges□ g = 0.31 (95% CI 0.180.44; p < 0.001)	Low (I† = 22%)	No conflicts of interest declared
7	Gowthami et al. (2025) (19)	17 RCTs	10,073 (5,707 ESK, 4,622 placebo)	IN ESK + AD	Placebo + AD	MADRS; response; remission	MADRS: MD = -1.47 (-3.01 to 0.07; p = 0.06) Response: OR = 0.51 (0.30□0.73; p < 0.001)[c] Remission: OR = 0.35 (0.11□0.58; p < 0.001)[c]	MADRS: high (I† = 99.2%) Response: high (I† = 79.7%) Remission: high (I† = 75.5%)	Industry-sponsored trials included
8	Nikolin et al. (2023) (24)	49 RCTs (9 IN ESK, 1 IV ESK RCTs)	3,299 (959 IN ESK, 783 placebo; 20 IV ESK, 10 placebo)	IN/IV ESK + AD	Placebo + AD	MADRS/HDRS; response; remission; all-cause drop-out	MADRS/HDRS □Acute (single dose): Low dose: SMD = -0.55 (-0.87 to -0.24; p = 0.0006) High dose: SMD = -0.48 (-0.75 to -0.20; p = 0.0007) Repeated dosing: Low dose: SMD = -0.15 (-0.49 to 0.19; p = 0.40) High dose: SMD = -0.22 (-0.54 to 0.10; p = 0.18) Follow-up: SMD = -0.33 (-0.96 to 0.31; p = 0.31) Response: OR = 1.76 (95% CI 0.89□3.49; p = 0.10) Remission: OR = 1.80 (95% CI 1.14□2.82; p = 0.011) All-cause drop-outs:Low dose: OR = 1.06 (0.48□2.34; p = 0.88) High dose: OR = 1.20 (0.83□1.74; p = 0.33)	MADRS: Acute: high (I† = 60.5%) Repeated dosing: very high (I† = 84.2%) Follow-up: high (I† = 87.6%) Response / Remission / All-cause drop-outs: NR (ESK-specific)	Industry-sponsored trials included
9	Floriano et al. (2023) (14)	3 RCTs	703 (415 ESK, 288 placebo)	IN ESK + AD	Placebo + AD	MADRS; response; remission; serious adverse events	MADRS: MD = -4.09 (95% CI -5.73 to -2.45; p=0.00001) Response: RD = 0.11 (0.05□0.16; p=0.0001) Remission: RD = 0.10 (0.03□0.17; p=0.004) SAEs: RD = 0.01 (-0.01 to 0.03; p=0.36)	MADRS: low (I† = 0%) Response: Low (I† = 8%) Remission: Low (I† = 8%) SAEs: low (I† = 8%)	No conflicts of interest declared
10	Ouyang & Li (2025) (25)	5 RCTs	1,315 (464 ESK, 465 placebo)	IN ESK + AD	Placebo + AD	MADRS; response; remission	MADRS: SMD = -3.88 (95% CI -5.71 to -2.05; p < 0.0001) (very large effect size) Response: RR = 1.99 (95% CI 1.28□3.10; p = 0.002) Remission: RR = 1.50 (95% CI 0.91□2.49; p = 0.11)	MADRS: low (I† = 0%) Response: low (I† = 0%) Remission: low (I† = 29%)	No conflicts of interest declared
11	CALDER ET AL. (2024) (12)	19 RCTS (4 IN ESK, 1 IV ESK RCTS)	2,042	IN/IV ESK + AD; 1 IN ESK (MONOTHERAPHY)	PLACEBO + AD	RESPONSE; DROPOUTS (ALL-CAUSE)	RESPONSE:1□3 DAYS: NNT = 2 (K = 1)WEEK 4: NNT = 11 (K = 4) DROP-OUTS:1□3 DAYS: NNH = -47 WEEK 4: NNH = 3 (K = 4)	NR	No external funding; conflicts of interest declared
12	Wang et al. (2021) (10)	8 RCTs	1,488 (719 ESK, 719 placebo)	IN ESK + AD	Placebo + AD	MADRS; remission; suicidality	MADRS □MDD: 2□4 h: SMD = -0.41 (95% CI -0.58 to -0.25; p < 0.00001) 24 h: SMD = -0.36 (95% CI -0.47 to -0.24; p < 0.00001) 1 week: SMD = -0.25 (95% CI -0.36 to -0.13; p < 0.0001) 3□4 weeks: SMD = -0.25 (95% CI -0.35 to -0.14; p < 0.00001) MADRS □TRD: 2□4 h: SMD = -0.67 (95% CI -1.16 to -0.17; p = 0.008) 24 h: SMD = -0.48 (95% CI -0.82 to -0.13; p = 0.007) 1 week: SMD = -0.27 (95% CI -0.42 to -0.12; p = 0.0003) 3 □4 weeks: SMD = -0.23 (95% CI -0.37 to -0.10; p = 0.0007) MADRS □MDSI: 2□4 h: SMD = -0.38 (95% CI -0.56 to -0.21; p < 0.0001) 24 h: SMD = -0.34 (95% CI -0.52 to -0.17; p = 0.0001) 1 week: SMD = -0.21 (95% CI -0.39 to -0.02; p = 0.03) 3 □4 weeks: SMD = -0.27 (95% CI -0.44 to -0.10; p = 0.002) Remission: 2□4 h: OR = 2.43 (95% CI 1.27□4.67; p = 0.007) Day 8: OR = 1.46 (95% CI 0.96□2.23; p = 0.08) Weeks 3□4: OR = 1.64 (95% CI 1.30□2.07; p < 0.0001) Suicidality: 2□4 h: OR = 2.04 (95% CI 1.37□3.05; p = 0.0005) 24 h: OR = 1.15 (95% CI 0.80□1.65; p = 0.46) Weeks 3□4: OR = 1.32 (95% CI 0.91□1.90; p = 0.44)	MADRS □MDD: low-moderate (I† = 0-42%) MADRS □TRD: high at 24 h (I† = 73%); no significant heterogeneity for other time points MADRS □MDSI: low (I† = 0) for all time poins Remission: low-moderate (I† = 0-41%) Suicidality: low (I† = 0%)	No conflicts of interest declared
13	Jawad et al. (2022) (13)	7 RCTs	1,427 (798 IN ESK, 623 placebo)	IN ESK + AD	IN placebo + AD	MADRS; response; remission; relapse prevention	MADRS: d = -0.239 (95% CI -0.335 to -0.142; p < 0.0001) Response: RR = 1.221 (95% CI 1.055□1.428; p = 0.017) Remission: RR = 1.366 (95% CI 1.182□1.578; p < 0.0001) Relapse prevention: Remitters: HR = 0.49 (95% CI 0.29□0.84) Responders: HR = 0.30 (95% CI 0.16□0.55)	MADRS: moderate (I† = 57%) Response / Remission / Relapse: NR (ESK-specific)	No external funding; conflicts of interest declared
14	Liu et al. (2022) (18)	7 RCTs	1,252 (701 ESK, 551 placebo)	IN ESK + AD	Placebo + AD	MADRS; response; remission; SDS	MADRS: MD = -2.68 (95% CI -3.98 to -1.37; p < 0.0001) SDS: MD = -2.90 (95% CI -4.01 to -1.79; p < 0.00001) Response: RR = 1.28 (95% CI 1.12□1.46; p = 0.0002) Remission: RR = 1.39 (95% CI 1.18□1.63; p < 0.0001) 24 h remission: RR = 1.96 (95% CI 1.29□2.99; p = 0.002) Sustained effective response: RR = 1.76 (95% CI 0.88□3.53; p = 0.11 AEs: Vertigo (RR = 9.21, 95% CI 4.82□17.57; p < 0.00001); dissociation (RR = 5.57, 95% CI 3.92□7.91; p < 0.00001); hypoesthesia (RR = 5.32, 95% CI 2.86□9.91; p < 0.00001); sedation (RR = 5.07, 95% CI 2.45□10.49; p < 0.0001); euphoric mood (RR = 4.56, 95% CI 1.90□10.91; p = 0.0007); paresthesia (RR = 4.25, 95% CI 2.42□7.46; p < 0.00001); blood pressure increased (RR = 3.36, 95% CI 2.23□5.06; p < 0.00001); vomiting (RR = 3.35, 95% CI 2.02□5.54; p < 0.00001); dizziness (RR = 3.20, 95% CI 2.46□4.16; p < 0.00001); nausea (RR = 2.63, 95% CI 2.01□3.44; p < 0.00001); somnolence (RR = 1.82, 95% CI 1.37□2.41; p < 0.0001); headache and anxiety not significant.	MADRS: low (I† = 0) SDS: low (I† = 0) Response: low (I† = 0) Remission: low (I† = 0) 24 h remission: low (I† = 0%) Sustained effective response: low (I† = 31%) AEs: anxiety moderate (I† = 49%), others low (I† = 0-21%)	No conflicts of interest declared

Continued Table 1. Meta-Analyses of Esketamine on Efficacy, Safety, and Suicidality

15	BAHJI ET AL. (2021A) (7)	36 RCTS (7 IN ESK, 2 IV ESK RCTS)	2,903	IN/IV ESK – AD	PLACEBO/KETAMINE – AD	MADRS/HAM-D; RESPONSE; REMISSION	MADRS/HAM-D: D = -0.38 RESPONSE: RR = 1.20 (95% CI 0.96□1.49) REMISSION: RR = 1.28 (95% CI 1.11□1.47)	NR (ESK-SPECIFIC)	INDUSTRY-SPONSORED TRIALS INCLUDED; CONFLICTS OF INTEREST DECLARED
16	Hieronymus et al. (2025) (23)	17 RCTs (2 ESK RCTs)	4,960 (349 ESK, 224 placebo)	ESK + AD	Placebo + AD	MADRS; response; drop-out	MADRS: SMD = 0.30 (SEM 0.12; p < 0.05) Response: 52% (181/349) (descriptive) Drop-out: 12% (43/349) (descriptive)	NR	No external funding; conflicts of interest declared
17	Huang et al. (2025) (16)	67 RCTs (13 IN ESK, 5 IV ESK, 1 oral ESK in MDD RCTs)	11,553 (1,785 IN ESK, 1,281 placebo; 321 IV ESK, 374 placebo; 57 oral ESK, 54 placebo)	IN/IV/oral ESK + AD	Placebo + AD / ECT	MADRS/HAMD, remission; response	Overall: SMD = -0.36 (95% CI -0.49 to -0.24) Remission rate: RR = 1.41 (95% CI 1.27□1.57) Response rate: RR = 1.28 (95% CI 1.18□1.39)	NR	NR
18	Wang et al. (2025) (27)	9 RCTs	2,394	IN ESK + AD	Placebo + AD/quetiapine	MADRS; remission; response; relapse; MADRS-SI/C-SSRS	MDD with suicidal ideation □Day 2: MADRS: SMD = -0.30 (95% CI -0.47 to -0.12; p = 0.0008) Remission rate: RR = 1.87, 95%CI: 1.11□3.15, *P* = 0.0179) TRD without suicidal ideation □Day 28: MADRS: SMD = -0.24 (95% CI -0.38 to -0.09; p = 0.001) All population: Remission (Day 28): RR = 1.36 (95% CI 1.18□1.57; p < 0.0001) Response (Day 28): RR = 1.20 (95% CI 0.99□1.46; p = 0.0630) Relapse: RR = 0.60 (95% CI 0.45□0.80, p < 0.05) Suicidal ideation: RR = 0.83 (95% CI 0.55□1.24; p = 0.3593) Drop-out (side effects): RR = 2.20 (95% CI 1.27□3.80; p = 0.0047) AEs: Sedation (RR = 4.55, 95% CI 2.20□9.38; p < 0.0001); somnolence (RR = 1.81, 95% CI 1.36□2.39; p < 0.0001); dissociation (RR = 4.54, 95% CI 2.36□8.73; p < 0.00001); dizziness (RR = 3.00, 95% CI 1.80□5.00; p < 0.0001); mental impairment and blood pressure increase not significant.	MDD with suicidal ideation □Day 2: MADRS: low (I† = 0) Remission rate: low (I† = 0) TRD without suicidal ideation □Day 28: MADRS: low (I† = 24) All population: Remission (Day 28): low (I† = 0%) Response (Day 28): moderate (I† = 51%) Relapse: low (I† = 0%) Suicidal ideation: low (I† = 0%) Drop-out (side effects): low (I† = 0%) AEs: BP: high (I† = 72%), others low (I† = 0%)	No conflicts of interest declared
19	Orace et al. (2024)[d] (11)	9 RCTs	1,752 (966 ESK, 786 placebo)	IN ESK + AD	Placebo + AD	Response; remission (MADRS)	Response: RR = 1.27 (95% CI 1.11□1.47, p = 0.001) Remission: RR = 1.37 (95% CI 1.19□1.57, p < 0.0001)	Response: low-moderate (I† = 0□58) Remission: low (I† = 0□12)	Industry-sponsored trials included
20	Papakostas et al. (2020) (6)	5 RCTs	774 (442 ESK, 332 placebo)	IN ESK + AD	Placebo + AD	MADRS; response; remission	MADRS: SMD = 0.36 (0.24□0.49; p < 0.0001) Response: RR = 1.40 (1.22□1.61; p < 0.0001) Remission: RR = 1.45 (1.20□1.75; p < 0.0001)	NR	No external funding; conflicts of interest declared
21	Hock et al. (2022) (9)	8 RCTs	1,437 (802 ESK, 635 placebo)	IN ESK + AD	Placebo + AD	MADRS; remission	MADRS:24 h: SMD = 0.34 (0.11□0.46; p < 0.0001) Endpoint: SMD = 0.26 (0.16□0.37; p = 0.004) Remission: 24 h: RR = 2.31 Endpoint: RR = 1.37	NR	No external funding; conflicts of interest declared
22	Terao et al. (2024) (32)	22 RCTs (5 ESK RCTs)	2,031 (626 ESK, 461 placebo)	IN ESK + AD	Placebo + AD	Response (MADRS/HAMD); drop-outs (due to side effects and all reasons)	Response: OR = 1.67 (1.19□2.33) Drop-out (side effects): OR = 3.03 (1.41□6.53) Drop-out (all reasons): OR = 1.25 (0.82□1.90)	NR (ESK-specific)	No conflicts of interest declared
23	Bahji et al. (2021b) (28)	24 RCTs (7 IN ESK, 1 IV ESK RCTs)	1,877 (1,097 IN ESK+placebo; 40 IV ESK+placebo)	IN/IV ESK + AD	Placebo + AD; ketamine	MADRS/HDRS; response; remission; adverse events; discontinuation; suicidality	MADRS/HDRS: SMD = -1.19 (-1.75 to -0.63) Response: RR = 1.38 (1.06□1.79) Remission: RR = 1.47 (1.12□1.94) Adverse events: RR = 3.02 (1.34□6.79) Discontinuation: RR = 1.36 (0.91□2.03) Suicidality: SMD = 0.05 (-0.44 to 0.53)	MADRS/HDRS: high (I† = 94%) Response: moderate-high (I† = 58%) Remission: low (I† = 38%) AEs / Discontinuation / Suicidality: NR (ESK-specific)	Industry-sponsored trials included; conflicts of interest declared
24	Guo et al. (2024) (29)	72 RCTs (11 IN ESK, 1 IV ESK RCTs)	12,105 (1770 IN ESK, 1396 placebo/ketiapin; 34 IV ESK, 29 ketamin)	IN/IV ESK + AD	Placebo/ketamin/ketiapin + *AD*	Response and remission (MADRS); tolerability; safety	Response rate: OR = 2.90 (1.81□4.64) Remission rate: OR = 2.00 (1.44□2.78) Tolerability: OR = 3.10 (1.89□5.08) Safety: OR = 1.30 (0.71□2.37)	NR (ESK-specific)	NR
25	Wang et al. (2024) (35)	5 RCTs (1 ESK RCT)	391 (111 ESK, 72 placebo)	IN ESK + AD	Placebo + AD	MADRS; MADRS-SI	Esketamine-specific pooled estimate not available	NA	No external funding; industry-sponsored trials included
26	Li et al. (2025) (36)	13 RCTs (3 IN ESK, 1 IV ESK RCTs)	1,109 (521 IN ESK + placebo; 59 IV ESK + placebo)	IN/IV ESK	Placebo	CGI-SS; remission rate of SI; MADRS-SI	Not pooled (different SI assessment tools)	NA	No external funding; industry-sponsored trials included
27	Chen et al. (2023) (22)	17 RCTs (3 ESK RCTs)	1,224 (517 ESK)	IN ESK	Placebo	BSS; BHS; MADRS	Suicidality: 4□6 h: SMD = 0.26 (95% CI 0.09□0.44) 24 h: SMD = 0.30 (95% CI 0.13□0.47)	NR (ESK-specific)	NR
28	Guo et al. (2025) (31)	47 RCTs (14 ESK RCTs)	5,046 (number of ESK participants not specified)	IN/IV ESK +/- AD	Placebo +/- AD	Dropout (due to AEs); incidence of AEs and SAEs	Dropout: RR = 1.85 (95% CI 1.01□3.40); p = 0.05 Any AEs: RR = 1.35 (95% CI 1.22□1.49); p < 0.00001 SAEs: RR = 1.14 (95% CI 0.74□1.73); p = 0.56	Dropout: moderate (I† = 53%) Any AEs: high (I† = 78%) SAEs: low (I† = 0%)	Industry-sponsored trials included
29	Yang et al. (2022) (30)	4 RCTs (3 IN ESK, 1 IV ESK RCTs)	551	IN/IV ESK	Placebo	AEs	Dissociation (RR = 4.54, 95% CI 2.36□8.73; p < 0.00001); dizziness (RR = 3.00, 95% CI 1.80□5.00; p < 0.0001); vertigo (RR = 7.47, 95% CI 2.55□21.86; p = 0.0002); somnolence (RR = 1.73, 95% CI 1.02□2.95; p = 0.04); nausea (RR = 2.34, 95% CI 1.04□5.25; p = 0.04); headache and dysgeusia not significant.	Low (I† = 0%)	NR

AD, antidepressant; AE, adverse event; CGI-SS, Clinical Global Impression□Severity of Suicidality; C-SSRS, Columbia□Suicide Severity Rating Scale; ESK, esketamine; HAM-D/HDRS, Hamilton Depression Rating Scale; HR, hazard ratio; IN, intranasal; IV, intravenous; MADRS, Montgomery□sberg Depression Rating Scale; MADRS -SI, Montgomery□sberg Depression Rating Scale □Suicidal Ideation item; MD, mean difference; NNH, number needed to harm; NNT, number needed to treat; NR, not reported; OR, odds ratio; RCT, randomized controlled trial; RD, risk difference; RR, risk ratio; SAE, serious adverse event; SDS, Sheehan Disability Scale; SMD, standardized mean difference.
[a]Heterogeneity interpretation followed Cochrane thresholds: low (I† <40%), moderate (40□60%), high (>60%).
[b]Conflict of interest categories were standardized based on authors□ declarations and funding statements; no reclassification of original disclosures was performed.
[c]Effect estimates <1 reflect reverse coding (non-response/non-remission as outcome); direction favors esketamine.
[d]Dose-specific subgroup analyses were reported in this meta-analysis but are not shown here; only overall pooled estimates are presented for consistency.

Methodological quality of included meta-analyses

The methodological quality of the included meta-analyses, assessed with AMSTAR-2, was generally limited. Of the 29 included studies, 20 were rated as critically low, 7 as low, and 2 as high confidence. Item-level assessment showed that several key methodological weaknesses were recurrent across reviews, particularly the lack of justification for included study designs, failure to provide a list of excluded studies, limited reporting of funding sources for included primary studies, and inadequate consideration of risk of bias when interpreting pooled findings. The full AMSTAR-2 item-level assessment is presented in Supplementary Table 1.

Overlap of primary studies across meta-analyses

The citation matrix included 29 meta-analyses (c = 29) and 41 unique primary randomized controlled trials (r = 41), with 212 total occurrences of primary studies across reviews (N = 212). The calculated CCA was 0.149 (14.9%), indicating a high degree of overlap among the included meta-analyses. The citation matrix used for the CCA calculation is provided in Supplementary Table 2.

Efficacy on depressive symptom severity

The included meta-analyses indicated reductions in depressive symptom severity following esketamine administration, with some demonstrating early-onset effects within hours to days (8-10) and others, including analyses reporting both early and later acute outcomes, demonstrating short-term efficacy over acute treatment periods (6, 9, 11-18), generally with small-to-moderate effect sizes compared with placebo (Table 1).

Table 2. Certainty of evidence for main outcome domains according to the GRADE approach

Outcome Domain	Certainty of Evidence (GRADE)
Short-Term Depressive Symptom Reduction	Moderate
Response	Moderate
Remission	Low
Suicidality / Suicidal Ideation	Low
Relapse Prevention / Maintenance	Low
Non-Serious Adverse Events	Moderate
Serious Adverse Events	Low

Meta-analyses reporting absolute changes in symptom severity indicated that adjunctive intranasal esketamine was associated with mean improvements of approximately 1.5 to 4 MADRS points compared with placebo (14,15,18-21). Consistent with these findings, the majority of meta-analyses using standardized effect size metrics (SMD, Hedges' g, or Cohen's d) reported small-to-moderate effect sizes favoring esketamine (6-10, 13, 16, 22-27). A notably larger effect size was reported in a single subgroup meta-analysis by Bahji et al., however this estimate was accompanied by wide confidence intervals and substantial heterogeneity (28).

Meta-analyses examining the temporal profile of treatment effects generally indicated that antidepressant effects of intranasal esketamine may emerge within the first few hours following admin-

Supplementary Table 1. AMSTAR-2 assessment of the methodological quality of the included meta-analyses

AMSTAR	PICO	Protocol	Study Design Justified	Search Strategy	Selection Duplicate	Extraction Duplicate	Excluded Studies	Study Description	Risk of Bias	Meta-analysis Method	RoB in Interpretation	Hetero geneity	Publication Bias	Heterogeneity Discussion	Funding Reported	Conflict of Interest	Overall Confidence
Fountoulakis et al., 2025	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	No	Yes	No	No	No	No	Yes	Critically Low
Wang et al., 2023	Yes	No	No	No	Yes	No	No	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Critically Low
Naudet et al., 2025	Yes	Yes	No	Partial yes	Yes	Yes	No	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Critically Low
Dold et al., 2020	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Critically Low
VÆzquez et al., 2021	Yes	No	No	Partial yes	Yes	No	No	Yes	No	No	Yes	No	No	Yes	No	Yes	Critically Low
Seshadri et al., 2024	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Low
Gowthami et al., 2025	Yes	Yes	No	Yes	Yes	No	No	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	Critically Low
Nikolin et al., 2023	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Low
Floriano et al., 2023	Yes	Yes	No	Partial yes	No	No	Yes	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	Low
Ouyang & Li, 2025	Yes	No	No	Partial yes	Yes	Yes	No	Yes	No	No	Yes	No	Yes	Yes	No	Yes	Critically Low
Calder et al., 2024	Yes	No	No	Partial yes	Yes	Yes	No	Yes	Yes	No	Yes	No	Yes	No	No	Yes	Critically Low
Wang et al., 2021	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	No	Yes	No	Yes	Critically Low
Jawad et al., 2022	Yes	Yes	Yes	Partial yes	Yes	Yes	No	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Critically Low
Liu et al., 2022	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically Low
Bahji et al., 2021a	Yes	Yes	No	Partial yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Low
Hieronymus et al., 2025	Yes	No	No	No	Yes	Yes	No	Yes	No	No	Yes	No	No	No	No	Yes	Critically Low
Huang et al., 2025	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Critically Low
Wang et al., 2025	Yes	Yes	No	Partial yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	High
Oraee et al., 2024	Yes	Yes	No	Partial yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Low
Papakostas et al., 2020	Yes	No	No	Partial yes	No	Yes	No	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Critically Low
Hock et al., 2022	Yes	No	No	Partial yes	No	Yes	No	Yes	No	No	Yes	No	No	Yes	No	Yes	Critically Low
Terao et al., 2024	Yes	Yes	No	Yes	Yes	Partial yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	High
Bahji et al., 2021b	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Low
Guo et al., 2024	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Critically Low
Wang et al., 2024	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Critically Low
Li et al., 2025	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Critically Low
Chen et al., 2023	Yes	Yes	No	Partial yes	Yes	No	No	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Critically Low
Guo et al., 2025	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Low
Yang et al., 2022	Yes	No	No	Partial yes	No	No	No	Yes	Yes	No	Yes	No	No	Yes	No	Yes	Critically Low

PICO: Population, Intervention, Comparator, Outcome; RoB: Risk of Bias

istration. Early symptom reductions were observed as early as 2–6 hours post-dose, with small-to-moderate standardized effect sizes reported across multiple syntheses (8-10,22). At 24 hours post-dose, antidepressant effects were still detectable but were generally modest, with small-to-moderate effect sizes reported across meta-analyses (9,10, 22). Effect sizes were generally larger at very early assessments and smaller at later acute time points (8,10,24).

In separate subgroup analyses, larger early antidepressant effects were reported in treatment-resistant depression populations at very early assessment windows (10). Independently, analyses examining administration patterns (single vs. repeated dosing) suggested that repeated dosing and later follow-up periods were associated with more modest or non-significant effects compared with early post-dose assessments (24).

Dose-related effects were examined in only one meta-analysis, in which antidepressant effects of intranasal esketamine did not demonstrate a clear dose–response pattern, with similar effect sizes observed across lower and higher dose ranges (24).

Across meta-analyses reporting heterogeneity for MADRS outcomes, I^2 values ranged from low to high (Table 1), with higher heterogeneity reported in several analyses (19,24,28).

Response and remission rates

Across the included meta-analyses, intranasal esketamine was associated with higher response and remission rates compared with placebo at acute assessment points (Table 1). Early response and remission benefits were most consistently observed at very early assessment time points across analyses, particularly within hours to days following administration. Only a small number of meta-analyses directly examined response and remission across multiple acute time points. In these analyses, later assessments tended to show smaller effect estimates compared with very early post-administration outcomes (10, 12). One meta-analysis reported significant improvements in response, remission, and 24-hour remission outcomes, whereas no significant difference was observed for sustained effective response assessed during follow-up (18).

Across meta-analyses, response and remission effect estimates were generally modest in magnitude, with variability across studies according to assessment timing and analytic methodology (6,10, 11,13,18).

Across meta-analyses reporting heterogeneity, I^2 values for response and remission outcomes were mostly low, although several analyses reported moderate or high heterogeneity (10,11,19,28).

Supplementary Table 2. Citation matrix of primary esketamine randomized controlled trials across the included meta-analyses used for the Corrected Covered Area (CCA) calculation.

Primary RCT	Fountoulakis et al., 2025	Wang et al., 2023	Naudet et al., 2025	Dold et al., 2020	VÆzquez et al., 2021	Seshadri et al., 2024	Gowthami et al., 2025	Nikolin et al., 2023	Floriano et al., 2023	Ouyang & Li, 2025	Calder et al., 2024	Wang et al., 2021	Jawad et al., 2022	Liu et al., 2022
Canuso et al., 2018	1	0	0	0	1	1	0	1	0	0	0	1	1	1
Singh et al., 2016	1	0	0	0	0	1	0	1	0	0	1	0	0	0
Fu et al., 2020	1	0	0	0	1	0	0	1	0	0	0	1	1	1
Ionescu et al., 2021	1	0	0	0	1	0	0	1	0	0	0	1	1	1
Daly et al., 2018	1	0	1	0	1	1	0	1	0	1	0	1	0	0
Fedgchin et al., 2019	1	1	1	1	1	1	0	1	1	1	1	1	1	1
Ochs-Ross et al., 2020	1	0	1	1	1	1	0	1	1	1	1	1	1	1
Popova et al., 2019	1	1	1	1	1	1	0	1	1	1	1	1	1	1
Takahashi et al., 2021	1	0	1	0	0	1	1	1	0	0	1	1	1	1
Chen et al., 2023	1	0	1	0	0	1	0	1	0	0	0	0	0	0
Jha et al., 2023	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Jones et al., 2022	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Daly et al., 2021	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Sliwa et al., 2024	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Morrison et al., 2024	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Reif et al., 2023	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Daly et al., 2019	1	0	1	0	0	0	1	0	0	1	0	0	0	0
Young et al., 2025	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Hough et al., 2021	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Citrome et al., 2020	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Jamieson et al., 2023	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Turkoz et al., 2021	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Vieta et al., 2025	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Correia-Melo et al., 2020	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Smith-Apeldooen et al., 2024	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Dijkstra et al., 2022	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Janik et al., 2025	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Jarventausta et al., 2013	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Kosik-Gonzales et al., 2025	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Ren et al., 2024	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Zeng et al., 2025	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Zhou et al., 2023	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Lapidus et al., 2014	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Ohnishi et al., 2022	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Vieira et al., 2021	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Hong et al., 2025	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Doty et al., 2021	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Katz et al., 2021	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Kern et al., 2024	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Clemens et al., 2025	0	0	0	0	0	0	1	0	0	0	0	0	0	0
McIntyre et al., 2025	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Total primary studies per meta-analysis	11	2	7	3	7	8	17	10	3	5	5	8	7	7

Supplementary Table 2 (continued). Citation matrix of primary esketamine randomized controlled trials across the included meta-analyses used for the Corrected Covered Area (CCA) calculation.

Primary RCT	Bahji et al., 2021a	Hieronymus et al., 2025	Huang et al., 2025	Wang et al., 2025	Oraee et al., 2024	Papakostas et al., 2020	Hock et al., 2022	Terao et al., 2024	Bahji et al., 2021b	Guo et al., 2024	Wang et al., 2024	Li et al., 2025	Chen et al., 2023	Guo et al., 2025	Yang et al., 2022
Canuso et al., 2018	1	0	1	1	1	1	1	0	1	1	0	1	1	1	1
Singh et al., 2016	1	0	1	0	0	0	0	0	1	0	0	0	0	1	1
Fu et al., 2020	1	0	1	1	1	0	1	0	0	1	0	1	1	1	0
Ionescu et al., 2021	1	0	1	1	1	0	1	0	0	1	0	1	1	1	0
Daly et al., 2018	1	0	1	0	1	1	1	1	1	1	0	0	0	1	1
Fedgchin et al., 2019	1	1	1	1	1	1	1	1	1	1	0	0	0	1	1
Ochs-Ross et al., 2020	1	0	1	1	1	1	1	0	1	1	0	0	0	1	0
Popova et al., 2019	1	1	1	1	1	1	1	1	1	1	0	0	0	1	0
Takahashi et al., 2021	0	0	1	1	1	0	1	1	0	1	0	0	0	1	0
Chen et al., 2023	0	0	1	0	1	0	0	1	0	0	0	0	0	1	0
Jha et al., 2023	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Jones et al., 2022	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Daly et al., 2021	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Sliwa et al., 2024	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
Morrison et al., 2024	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Reif et al., 2023	0	0	1	1	0	0	0	0	0	1	0	0	0	1	0
Daly et al., 2019	0	0	0	1	0	0	0	0	0	1	0	0	0	1	0
Young et al., 2025	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Hough et al., 2021	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Citrome et al., 2020	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Jamieson et al., 2023	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Turkoz et al., 2021	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Vieta et al., 2025	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Correia-Melo et al., 2020	1	0	0	0	0	0	0	0	1	1	0	0	0	0	0
Smith-Apeldooen et al., 2024	0	0	1	0	0	0	0	0	0	0	0	0	0	1	0
Dijkstra et al., 2022	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
Janik et al., 2025	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
Jarventausta et al., 2013	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
Kosik-Gonzales et al., 2025	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
Ren et al., 2024	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
Zeng et al., 2025	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
Zhou et al., 2023	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
Lapidus et al., 2014	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
Ohnishi et al., 2022	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0
Vieira et al., 2021	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
Hong et al., 2025	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Doty et al., 2021	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Katz et al., 2021	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Kern et al., 2024	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Clemens et al., 2025	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
McIntyre et al., 2025	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total primary studies per meta-analysis	9	2	19	9	9	5	8	5	8	12	1	4	3	14	4

Suicidality and suicidal ideation

Outcomes related to suicidality and suicidal ideation were evaluated in only a subset of the included meta-analyses, with substantial variation in assessment instruments and outcome definitions (Table 1) (8,10,22,27). Some syntheses reported suicidality as a secondary outcome or provided limited poolable evidence due to heterogeneity across assessment tools (8,22).

Meta-analyses focusing on the acute treatment phase reported early reductions in suicidal ideation within the first hours to 24 hours following administration in some analyses (2,18). Evidence beyond the acute window was sparse: Wang et al. (2021) reported statistically significant reductions in suicidal ideation at early time points, with differing statistical significance at the one-week assessment (10). By contrast, Wang et al. (2025), examining suicidal ideation as part of broader efficacy outcomes, found no statistically significant difference compared with placebo (27).

Heterogeneity reporting for suicidality-related outcomes was limited across the included meta-analyses; where reported, heterogeneity was low (10, 27), but most syntheses did not provide I^2 estimates, restricting cross-study comparisons. Importantly, suicidality was not examined as a primary, adequately powered endpoint in the included meta-analyses, and longer-term suicidal outcomes beyond the acute phase were typically assessed as secondary or exploratory measures.

Relapse and maintenance outcomes

Relapse and maintenance outcomes were examined in only a limited subset of the included meta-analyses and were reported using heterogeneous outcome measures (8,13,15,27). Naudet et al. assessed relapse risk during the maintenance phase using hazard ratios (HR) and reported a lower risk of relapse favoring esketamine (15). Jawad et al. evaluated relapse prevention separately in remitter and responder subgroups, reporting hazard ratios favoring esketamine in both populations (13). Wang et al. reported relapse outcomes using risk ratios (RR) and similarly found lower relapse rates in the esketamine groups compared with control conditions (27). Fountoulakis et al. examined maintenance and relapse-related outcomes across acute and continuation phases but reported these endpoints using heterogeneous definitions and a limited number of maintenance trials, precluding pooled estimates for relapse prevention (8).

Overall, evidence regarding relapse prevention and maintenance effects is derived from a limited number of meta-analyses and is characterized by heterogeneity in outcome definitions (e.g., hazard

ratios vs. risk ratios), follow-up duration, and patient subgroups examined (8,13,15,27). Across the included meta-analyses, relapse-related outcomes were generally reported in favor of esketamine during continuation or maintenance treatment, but these findings were largely based on overlapping data from a small number of maintenance-phase trials.

Safety and tolerability

Safety and tolerability outcomes were reported inconsistently across meta-analyses and included adverse events, serious adverse events, and discontinuation outcomes (Table 1).

Across meta-analyses, intranasal esketamine was generally associated with a higher frequency of adverse events, particularly non-serious adverse events, compared with placebo (18, 28-30). In three meta-analyses providing detailed adverse event profiles, esketamine was consistently associated with increased risks of dissociation or perceptual disturbances, dizziness or vertigo, somnolence or sedation, and nausea or vomiting. In contrast, headache and anxiety were not consistently increased across meta-analyses that reported these outcomes (18, 27, 30).

Findings related to serious adverse events were limited. Two meta-analyses reported pooled estimates for serious adverse events using different effect measures, and neither found a statistically significant difference in SAE rates between intranasal esketamine and placebo (14,31). These estimates were based on a small number of contributing trials and a low frequency of events.

Treatment discontinuation outcomes varied across meta-analyses depending on how dropout was defined. Evidence on all-cause discontinuation was limited and heterogeneous, with several meta-analyses reporting no statistically significant differences between intranasal esketamine and placebo (24, 32), while others provided only descriptive or time-dependent estimates without pooled comparisons (12, 23). In contrast, meta-analyses focusing on discontinuation due to adverse events generally reported higher discontinuation rates in the esketamine group, including a significant increase in dropout due to side effects (27,32) and a borderline increase in AE-related dropout risk (31), with directionally higher but non-significant estimates also reported elsewhere (28).

Where reported, heterogeneity for safety and tolerability outcomes ranged from negligible to high. Several analyses reported low or absent heterogeneity for serious adverse events and most non-specific adverse events, whereas higher heterogeneity was observed for outcomes such as overall adverse events, blood pressure–related adverse events, and anxiety-related measures (18,27,31).

Evidence certainty across outcome domains

Certainty of evidence was evaluated using the GRADE approach and is summarized in Table 2. Certainty was moderate for short-term depressive symptom reduction, response/remission, and non-serious adverse events, low for relapse prevention and serious adverse events, and very low for suicidality-related outcomes.

DISCUSSION

This umbrella review synthesizes meta-analytic evidence on the efficacy, safety, and tolerability of intranasal esketamine in major depressive disorder (MDD), including meta-analyses that examined treatment-resistant depression and MDD populations with acute suicidal ideation. By integrating findings across partially overlapping meta-analyses, this review clarifies not only whether esketamine is effective, but also when, for whom, and to what extent its effects are clinically meaningful.

Interpretation of antidepressant efficacy and temporal profile

Taken together, the included meta-analyses suggest that the antidepressant effects of intranasal esketamine are largely time-sensitive, with clinical benefits concentrated in the early phase following administration. Although a favorable direction of effect is consistently observed across outcome measures, the extent and durability of symptom

improvement vary across meta-analyses, with differences attributable to assessment timing, patient populations, and analytic approaches (8-10).

Rather than clearly indicating sustained antidepressant efficacy across the full acute treatment period, the overall evidence points to a pattern in which initial symptom reductions diminish over time, particularly in analyses incorporating later acute follow-up assessments (8, 10, 22, 24). This temporal attenuation suggests that the observed benefits may be driven primarily by early pharmacodynamic effects, rather than by cumulative or maintenance-related mechanisms.

Subgroup findings further indicate that larger early effects are not uniformly observed across populations, but appear more prominent in selected contexts, such as treatment-resistant depression or very early assessment windows (10). The observation of more pronounced early effects in TRD warrants cautious interpretation. Clinically, individuals with TRD may present with greater baseline severity and longer illness duration, potentially allowing for larger absolute symptom reductions during rapid-acting interventions. From a mechanistic perspective, it has been proposed that glutamatergic mechanisms may be particularly relevant in TRD, potentially rendering this subgroup more responsive to NMDA-modulating agents in the acute phase (33). Methodologically, greater baseline severity increases the measurable change on continuous scales, regression-to-the-mean effects cannot be excluded, and enriched or selective trial designs may amplify early treatment–placebo contrasts. These factors may collectively contribute to the observed subgroup pattern and should be considered when interpreting early efficacy signals in TRD populations. A similar caution applies to findings derived from very early assessment windows. Acute psychoactive effects, expectancy-related influences, and transient state changes immediately following administration may contribute to larger apparent treatment effects within the first hours (34). Such early signals may not necessarily predict sustained clinical benefit over subsequent follow-up periods.

Evidence regarding administration patterns and dosing remains limited, and available analyses do not support a consistent dose–response relationship, underscoring the need for cautious interpretation of subgroup and dose-related findings (24). In this context, dose- and time-stratified analyses reported by Nikolin et al. demonstrated that both low and high doses were associated with comparable and statistically significant symptom reductions following single-dose administration, whereas repeated dosing and later follow-up assessments were not associated with sustained antidepressant effects (24). Similarly, dose-specific subgroup analyses reported by Oraee et al. suggested that higher fixed or flexible dosing strategies may be associated with more robust early efficacy estimates. However, these findings were not supported by dose–response meta-regression analyses and were accompanied by variable heterogeneity (11). Collectively, these findings indicate that esketamine efficacy is more likely related to early pharmacodynamic effects and the achievement of an adequate, individually tolerated dose rather than reflecting a linear or cumulative dose–response relationship.

From a clinical perspective, the temporal pattern observed across meta-analyses—characterized by rapid onset of effect followed by attenuation over subsequent weeks—has important implications for treatment positioning. Rather than supporting intranasal esketamine as a definitive maintenance strategy, this pattern is more consistent with a short-term “bridge” intervention aimed at rapid symptom stabilization during periods of acute severity or crisis. In this framework, esketamine may serve to accelerate early improvement while longer-term pharmacological or psychosocial treatments take effect. Such positioning aligns more closely with the available evidence than conceptualizing esketamine as a sustained antidepressant maintenance therapy.

Beyond temporal dynamics, the magnitude of observed effects also warrants careful clinical interpretation. A key issue in interpreting these findings is the distinction between statistical and clinical significance. Across meta-analyses reporting absolute changes, adjunctive intranasal esketamine was associated with mean MADRS differences of approximately 1.5 to 4 points compared with place-

bo. Although statistically significant in several analyses, the relationship of these differences to the Minimal Clinically Important Difference (MCID) remains uncertain. MCID estimates for the MADRS vary across methodological approaches, and no universally accepted threshold exists. Differences in the range observed here are likely to represent modest effects at the group level and may not necessarily translate into a clearly perceptible or clinically substantial advantage for the average patient. This distinction is particularly relevant when positioning esketamine within treatment algorithms, where considerations of cost, tolerability, and comparative effectiveness influence clinical decision-making.

Response and remission: temporal patterns and clinical interpretation

Taken together, the available meta-analytic evidence suggests that intranasal esketamine is associated with higher response and remission rates compared with placebo during the acute phase of treatment, with benefits most consistently observed at very early assessment time points (9,10,12).

Only a limited number of meta-analyses examined response and remission across multiple acute time points. In these analyses, later assessments yielded smaller effect estimates compared with very early post-administration outcomes, suggesting a tendency toward attenuation over time (10,12,18). This temporal pattern parallels findings reported for continuous symptom severity measures and supports the interpretation that response and remission outcomes may be particularly sensitive to the timing of assessment, with early benefits not consistently maintained at later acute and follow-up evaluations.

Across meta-analyses, response and remission effect estimates were generally modest in magnitude, although considerable variability was observed across studies. Meta-analyses reporting pooled estimates using relative risks or odds ratios typically indicated favorable but non-uniform effects, with differences attributable to outcome definitions, assessment schedules, background antidepressant treatments, and analytic strategies (6,11,13,18). Where reported, heterogeneity for response and remission outcomes was frequently moderate to high, underscoring the methodological diversity of the included evidence (19,28).

From a clinical perspective, these findings suggest that intranasal esketamine may facilitate early categorical treatment responses, including response and remission, in a subset of patients during the acute phase of treatment. However, the durability of these categorical outcomes across subsequent acute follow-up assessments appears less consistent. Accordingly, response and remission outcomes should be interpreted with careful attention to the timing of assessment and in relation to continuous symptom measures, rather than being viewed as standalone indicators of sustained antidepressant efficacy.

Suicidality and suicidal ideation: interpretation and clinical implications

Evidence on suicidality and suicidal ideation remains more limited and methodologically heterogeneous than the evidence on depressive symptom severity. Across the included meta-analyses, suicidality was assessed using different definitions and instruments, including any available suicidality measure, resolution of suicidality, treatment-period suicidal ideation, and suicide scale scores derived from instruments such as SSI, BSS, BDI, and MSSI (8,10,22,27,28).

Within this heterogeneous evidence base, statistically significant findings were observed mainly at very early assessment time points. Wang et al. (2021) found that, in patients with major depression and suicidal ideation, resolution of suicidality was greater with esketamine than with placebo at 2–4 hours, but not at 24 hours or day 28 (10). Bahji et al. also reported significant reductions in suicidality in the acute phase and at 1 week, whereas the effect at 2 weeks was no longer statistically significant; in their subgroup analysis, the pooled suicidality effect for esketamine remained significant (28). Similarly, Chen et al. (2023) reported significant reductions in suicidal ideation scores for intranasal esketamine at 4–6 hours and 24 hours, while also noting heterogeneity related to diffe-

rences in the included populations and scales (22). In contrast, more recent esketamine-focused syntheses did not support a sustained or overall anti-suicidal effect. Fountoulakis et al. (2025) reported that the effect size concerning suicidality was not significant at any time point and concluded that esketamine showed virtually no beneficial effect over placebo on suicidality (8). Likewise, Wang et al. (2025) found no significant difference between esketamine and placebo in treatment-period suicidal ideation overall, and this outcome remained non-significant across subgroups defined by baseline suicidal ideation status (27).

Taken together, these findings suggest that studies with significant results differed systematically from others primarily in timing of assessment and outcome definition, and to some extent in population. Significant effects were generally confined to the first hours or first week after administration, whereas later assessments were usually non-significant. In addition, some meta-analyses focused specifically on patients with major depression and suicidal ideation, whereas others pooled broader MDD/TRD samples with or without suicidal ideation. Overall, the available meta-analytic evidence supports, at most, a possible early and short-lived reduction in suicidal ideation in some acute-phase analyses, but does not support firm conclusions regarding a sustained anti-suicidal effect of intranasal esketamine.

Relapse prevention and maintenance: limited and heterogeneous evidence

Compared with acute efficacy outcomes, evidence regarding relapse prevention and maintenance effects of intranasal esketamine is derived from a small subset of meta-analyses and remains methodologically heterogeneous. Across the included syntheses, relapse-related outcomes were assessed using differing definitions and statistical approaches, including hazard ratios and risk ratios, with follow-up durations and patient subgroups varying substantially (8,13,15,27).

Within these limitations, available meta-analytic findings generally indicate a directional advantage favoring esketamine in reducing relapse risk during continuation or maintenance treatment. Reduced relapse risk was reported in analyses using hazard ratios among remitter and responder subgroups (13), as well as in analyses reporting hazard ratios or risk ratios for relapse outcomes during continuation or maintenance treatment (15,27). Fountoulakis et al. also discussed relapse and maintenance outcomes based on continuation-phase trials, but were unable to generate pooled relapse estimates due to heterogeneous definitions and the limited number of available maintenance studies (8). However, these findings primarily reflect repeated analyses of data from a small number of randomized withdrawal maintenance trials, most notably SUSTAIN-1. As such, they do not represent independent pooled evidence derived from multiple maintenance-phase randomized trials.

From a clinical perspective, these findings suggest a possible role for intranasal esketamine in short-term relapse prevention during continuation treatment among patients who have achieved response or remission. However, the reliance on a small number of randomized withdrawal trials and the absence of robust, pooled long-term maintenance data preclude firm conclusions regarding sustained relapse prevention. Consequently, current evidence supports cautious interpretation of maintenance effects and highlights the need for longer-term, methodologically consistent studies specifically designed to evaluate relapse prevention efficacy.

Safety and tolerability: Adverse event profiles and treatment discontinuation

Across the included meta-analyses, safety outcomes were most commonly reported in aggregated forms, such as overall adverse event rates, treatment discontinuation, or tolerability indices, rather than as individual symptom categories. Across these syntheses, intranasal esketamine was consistently associated with a higher overall frequency of adverse events compared with placebo, supporting a general signal of increased treatment-related side effects (28,31).

Only three meta-analyses provided detailed, symp-

tom-level adverse event data. Across these analyses, a convergent pattern of non-serious adverse events emerged. The most frequently and consistently reported adverse events were dissociation, dizziness/vertigo, sedative effects, and gastrointestinal symptoms. These adverse events were significantly more common in the esketamine group across all three meta-analyses, despite differences in study populations and analytic approaches. In contrast, headache was not significantly increased and blood pressure–related adverse events were inconsistently reported and did not show a uniform increase across studies (18, 27, 30).

Evidence regarding serious adverse events remains limited and inconclusive. Across the small number of meta-analyses that provided pooled estimates, including analyses reporting risk differences or risk ratios, no statistically significant increase in SAE risk was observed with intranasal esketamine compared with placebo (14, 31). However, interpretation of these findings is constrained by low event rates, short follow-up durations, and reliance on a limited number of contributing trials. As a result, the current meta-analytic evidence does not allow firm conclusions regarding rare or longer-term serious safety outcomes.

Treatment discontinuation outcomes highlight an important distinction between overall treatment acceptability and tolerability driven by adverse events. Across meta-analyses, all-cause discontinuation rates did not differ significantly between intranasal esketamine and placebo, suggesting comparable overall acceptability (24, 32). In contrast, meta-analyses specifically examining discontinuation due to adverse events generally reported higher dropout rates in esketamine-treated groups, including a statistically significant increase in two analyses and a marginally significant increase in another (27, 31, 32), with directionally higher but non-significant estimates also reported elsewhere (28). This pattern suggests that discontinuation may be more closely related to specific non-serious adverse effects, particularly dissociative symptoms, somnolence, and vestibular–perceptual adverse effects, rather than to global treatment acceptability.

From a risk–benefit perspective, the magnitude of symptomatic improvement should be interpreted alongside the substantially elevated risk ratios observed for certain adverse events, particularly vertigo and dissociation. While remission rates show statistically significant advantages over placebo in some analyses, these benefits appear modest in absolute terms. In contrast, relative risks for dissociation and vertigo were markedly increased, implying that the Number Needed to Harm (NNH) for certain non-serious adverse events may approach or even fall below the conceptual Number Needed to Treat (NNT) for remission in some contexts. Although formal NNT and NNH calculations were beyond the scope of this umbrella synthesis, this imbalance underscores the importance of individualized risk–benefit assessment and shared decision-making.

This pattern, together with the finding of similar all-cause discontinuation but higher adverse event–related dropout, points to symptom-specific tolerability concerns rather than reduced overall acceptability. To facilitate clearer interpretation and cross-study comparability, future meta-analyses would benefit from more standardized, symptom-level adverse event reporting.

Interpretation of the umbrella findings should be informed by the methodological quality of the included meta-analyses. Although most included reviews were rated as low or critically low confidence on AMSTAR-2, the two high-quality meta-analyses did not materially contradict the overall direction of the findings. Rather, they supported the evidence for short-term antidepressant efficacy of intranasal esketamine, while providing less consistent or less favorable support for suicidality-related outcomes and tolerability/acceptability. This pattern suggests that the overall conclusions are not solely driven by low-quality evidence; however, confidence should differ across outcome domains, with the strongest support seen for short-term depressive symptom reduction.

The overall certainty of evidence varied across outcomes. While evidence for short-term depressive symptom reduction and non-serious adverse events was relatively more robust, the certainty for suici-

dality-related outcomes and relapse prevention was limited due to heterogeneity across studies and imprecision of available estimates. These findings highlight that, although intranasal esketamine demonstrates consistent short-term antidepressant effects, the strength of evidence supporting other clinically relevant outcomes remains more uncertain.

Clinical implications and contribution of this umbrella review

This umbrella review clarifies the clinical role of intranasal esketamine by emphasizing the timing and durability of its antidepressant effects across meta-analyses. Clinically, this pattern supports positioning esketamine as an adjunctive option for rapid symptom stabilization rather than sustained maintenance treatment. Tolerability concerns, particularly dissociative and vestibular symptoms, should be weighed against modest efficacy gains. By integrating efficacy, temporal profiles, and safety outcomes at an umbrella level, this review delineates the strengths and limits of the current evidence base and underscores the need for standardized outcome reporting and longer-term data in future research.

Limitations

Several limitations should be acknowledged. The calculated CCA indicated a high degree of overlap among the included meta-analyses, reflecting substantial reliance on a limited set of pivotal esketamine randomized controlled trials, many of which were industry-sponsored. This overlap suggests that the apparent breadth of the meta-analytic literature largely represents repeated syntheses of a shared evidence base rather than fully independent bodies of evidence, and therefore the consistency observed across meta-analyses should be interpreted with caution. The literature search was restricted to PubMed/MEDLINE and Scopus databases. Although these databases cover a large proportion of psychiatric research, the exclusion of Embase and the Cochrane Library may have limited retrieval of additional eligible meta-analyses. Methodological heterogeneity across meta-analyses, including differences in patient populations, dosing regimens, outcome definitions, and follow-up durations, and, in some cases, pooling of intranasal and intravenous ketamine administration routes, further constrains direct comparability. A further methodological limitation is the potential for functional unblinding. The acute psychoactive effects of intranasal esketamine, particularly dissociation and vertigo, may have enabled participants and investigators to infer treatment allocation despite formal blinding. This could have influenced subjective outcome reporting and potentially inflated efficacy estimates. Evidence for longer-term efficacy, relapse prevention, and sustained safety remains limited, as most meta-analyses focus on acute treatment phases with relatively short follow-up. Finally, the predominance of industry-sponsored primary trials warrants cautious interpretation, as potential funding-related influences cannot be fully excluded.

This umbrella review synthesizes the available meta-analytic evidence on intranasal esketamine in major depressive disorder and indicates that intranasal esketamine is associated with a rapid-onset antidepressant effect of modest magnitude, with the most pronounced benefits observed in the early post-administration period. Overall, the evidence supports the use of intranasal esketamine as an adjunctive treatment option rather than a standalone or first-line antidepressant, particularly for carefully selected patients in whom rapid symptom reduction is clinically prioritized, rather than for sustained symptom control.

Meta-analytic findings suggest that intranasal esketamine may be associated with transient reductions in suicidal ideation during the very early post-administration period; however, evidence for sustained anti-suicidal, relapse-preventive, or maintenance effects remains limited and methodologically heterogeneous. From a safety perspective, esketamine is consistently associated with increased rates of non-serious adverse events, while serious adverse events and all-cause discontinuation do not appear to be consistently elevated relative to placebo.

Future research should focus on longer-term, independently funded randomized studies with stan-

dardized outcome definitions, clearly specified maintenance endpoints, and comprehensive safety reporting to establish a more precise, evidence-informed clinical positioning of intranasal esketamine across depressive disorders.

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REFERENCES

1. Gaynes BN, Lux L, Gartlehner G, Asher G, Forman-Hoffman V, Green J, Boland E, Weber RP, Randolph C, Bann C. Defining treatment-resistant depression. Depress Anxiety 2020; 37:134-145. doi: 10.1002/da.22968.

2. McIntyre RS, Alsuwaidan M, Baune BT, Berk M, Demyttenaere K, Goldberg JF, Gorwood P, Ho R, Kasper S, Kennedy SH. Treatment-resistant depression: definition, prevalence, detection, management, and investigational interventions. World Psychiatry 2023; 22:394-412. doi: 10.1002/wps.21120.

3. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, Niederehe G, Thase ME, Lavori PW, Lebowitz BD. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry 2006; 163:1905-1917. doi: 10.1176/ajp.2006.163.11.1905.

4. Hillhouse TM, Porter JH. A brief history of the development of antidepressant drugs: from monoamines to glutamate. Exp Clin Psychopharmacol 2015; 23:1-21. doi: 10.1037/a0038550.

5. Daly EJ, Trivedi MH, Janik A, Li H, Zhang Y, Li X, Lane R, Lim P, Duca AR, Hough D. Efficacy of esketamine nasal spray plus oral antidepressant treatment for relapse prevention in patients with treatment-resistant depression: a randomized clinical trial. JAMA Psychiatry 2019; 76:893-903. doi: 10.1001/jamapsychiatry.2019.1189.

6. Papakostas GI, Salloum NC, Hock RS, Jha MK, Murrough JW, Mathew SJ, Iosifescu DV, Fava M. Efficacy of esketamine augmentation in major depressive disorder: a meta-analysis. J Clin Psychiatry 2020; 81:19r12889. doi: 10.4088/JCP.19r12889.

7. Bahji A, Zarate CA, Vazquez GH. Efficacy and safety of racemic ketamine and esketamine for depression: a systematic review and meta-analysis. Expert Opin Drug Saf 2022; 21:853-866. doi: 10.1080/14740338.2022.2047928.

8. Fountoulakis KN, Saitis A, Schatzberg AF. Esketamine treatment for depression in adults: a PRISMA systematic review and meta-analysis. Am J Psychiatry 2025; 182:259-275. doi: 10.1176/appi.ajp.20240515.

9. Hock RS, Feeney A, Iovieno N, Murrough JW, Mathew SJ, Iosifescu DV, Fava M, Jha MK, Papakostas GI. Rapidity of symptom improvement with intranasal esketamine for major depressive disorder: a systematic review and meta-analysis. J Clin Psychiatry 2022; 84:44591. doi: 10.4088/JCP.21r14086.

10. Wang SM, Kim NY, Na HR, Lim HK, Woo YS, Pae CU, Bahk WM. Rapid onset of intranasal esketamine in patients with treatment-resistant depression and major depression with suicidal ideation: a meta-analysis. Clin Psychopharmacol Neurosci 2021; 19:341-354. doi: 10.9758/cpn.2021.19.2.341.

11. Oraee S, Alinejadfard M, Golsorkh H, Sadeghian M, Fanaei M, Centis R, D'Ambrosio L, Sotgiu G, Goudarzi H, Migliori GB. Intranasal esketamine for patients with major depressive disorder: a systematic review and meta-analysis. J Psychiatr Res 2024; 180:371-379. doi: 10.1016/j.jpsychires.2024.11.010.

12. Calder CN, Kwan AT, Teopiz KM, Wong S, Rosenblat JD, Mansur RB, Rhee TG, Ho R, Cao B, McIntyre RS. Number needed to treat for ketamine and esketamine in adults with treatment-resistant depression: a systematic review and meta-analysis. J Affect Disord 2024; 356:753-762. doi: 10.1016/j.jad.2024.04.039.

13. Jawad MY, Di Vincenzo JD, Ceban F, Jaberi S, Lui LM, Gillissie ES, Alnafeesi Y, Rosenblat JD, McIntyre RS. The efficacy and safety of adjunctive intranasal esketamine treatment in major depressive disorder: a systematic review and meta-analysis. Expert Opin Drug Saf 2022; 21:841-852. doi: 10.1080/14740338.2022.2058488.

14. Floriano I, Silvinato A, Bernardo WM. The use of esketamine in the treatment of patients with oral antidepressant-resistant depression: systematic review and meta-analysis. Rev Assoc Med Bras 2023; 69:e2023D696. doi: 10.1590/1806-9282.2023D696.

15. Naudet F, Pellen C, Fodor LA, Gastaldon C, Barbui C, Turner EH, Le Pabic E, Cristea IA. Efficacy and safety of esketamine for treatment-resistant depression: registered report for a systematic review with an individual patient data meta-analysis of randomized, double-blind, placebo-controlled trials. BMC Med 2025;23(1):677. doi: 10.1186/s12916-025-04435-x.

16. Huang C, Hu L, Liu W, Geng F, Wong GTC, Zhang Y, Reif A, Bao Y, Xue Q, Lu L. Efficacy and safety of esketamine on major depression, postpartum depression and perioperative depression: a systematic review and meta-analysis. Mol Psychiatry 2026; 31:545-558. doi: 10.1038/s41380-025-03320-6.

17. Vázquez GH, Bahji A, Undurraga J, Tondo L, Baldessarini RJ. Efficacy and tolerability of combination treatments for major depression: antidepressants plus second-generation antipsychotics vs esketamine vs lithium. J Psychopharmacol 2021; 35:890-900. doi: 10.1177/02698811211013579.

18. Liu P, Zhang SS, Liang Y, Gao ZJ, Gao W, Dong BH. Efficacy and safety of esketamine combined with antidepres-

sants for treatment-resistant depression: a meta-analysis. Neuropsychiatr Dis Treat 2022; 18:2855-2865. doi: 10.2147/NDT.S388764.

19. Gowthami B, Mehta I, Baiju S, Appani A, Suvarna T, Randhawa KS, Kakkad AM, Syed AB, Kumar V, Ramteke HD. Efficacy and safety of esketamine nasal spray in treatment-resistant depression: a systematic review and meta-analysis of randomized controlled trials. medRxiv [Preprint]. 2025. doi: 10.1101/2025.09.22.25336317.

20. Wang L, Chen X, Gu X, De Smedt H, Popova V, Fu DJ, Canuso CM, Drevets WC, Chen G. A meta-analysis of the antidepressant responses in pivotal trials on esketamine nasal spray and atypical antipsychotics. Neuropsychiatr Dis Treat 2023; 19:2857-2870. doi: 10.2147/NDT.S417027.

21. Dold M, Bartova L, Kasper S. Treatment response of add-on esketamine nasal spray in resistant major depression in relation to add-on second-generation antipsychotic treatment. Int J Neuropsychopharmacol 2020; 23:440-445. doi: 10.1093/ijnp/pyaa034.

22. Chen CC, Zhou N, Hu N, Feng JG, Wang XB. Acute effects of intravenous sub-anesthetic doses of ketamine and intranasal inhaled esketamine on suicidal ideation: a systematic review and meta-analysis. Neuropsychiatr Dis Treat 2023; 19:587-599. doi: 10.2147/NDT.S401032.

23. Hieronymus F, López E, Sjögren HW, Lundberg J. Control group outcomes in trials of psilocybin, SSRIs, or esketamine for depression: a meta-analysis. JAMA Netw Open 2025; 8:e2524119. doi: 10.1001/jamanetworkopen.2025.24119.

24. Nikolin S, Rodgers A, Schwaab A, Bahji A, Zarate C, Vazquez G, Loo C. Ketamine for the treatment of major depression: a systematic review and meta-analysis. EClinicalMedicine 2023; 62:102127. doi: 10.1016/j.eclinm.2023.102127.

25. Ouyang Y, Li J. Efficacy of esketamine nasal spray for treatment-resistant depression: a meta-analysis of randomized controlled studies. Medicine (Baltimore) 2025; 104:e41495. doi: 10.1097/MD.0000000000041495.

26. Seshadri A, Prokop LJ, Singh B. Efficacy of intravenous ketamine and intranasal esketamine with dose escalation for major depression: a systematic review and meta-analysis. J Affect Disord 2024; 356:379-384. doi: 10.1016/j.jad.2024.03.137.

27. Wang Z, Jiang L, Ma W, Li X, Gao Q, Lian S, Yu W. Esketamine nasal spray in major depressive disorder: a meta-analysis of randomized controlled trials. Clin Pharmacol Ther 2025; 117:1637-1649. doi: 10.1002/cpt.3555.

28. Bahji A, Vazquez GH, Zarate CA Jr. Comparative efficacy of racemic ketamine and esketamine for depression: a systematic review and meta-analysis. J Affect Disord 2021; 278:542-555. doi: 10.1016/j.jad.2020.09.071.

29. Guo Q, Guo L, Wang Y, Shang S. Efficacy and safety of eight enhanced therapies for treatment-resistant depression: a systematic review and network meta-analysis of randomized controlled trials. Psychiatry Res 2024; 339:116018. doi: 10.1016/j.psychres.2024.116018.

30. Yang S, Wang J, Li X, Wang T, Xu Z, Xu X, Zhou X, Chen G. Adverse effects of esketamine for the treatment of major depressive disorder: findings from randomized controlled trials. Psychiatr Q 2022; 93:81-95. doi: 10.1007/s11126-020-09871-x.

31. Guo H, Tang L, He M, Tang W, Liu J, Wu S, Yuan S, Wang J, Tang X. Comparative safety and tolerability of ketamine and esketamine for major depressive disorder: a systematic review and meta-analysis. Front Pharmacol 2025; 16:1681060. doi: 10.3389/fphar.2025.1681060.

32. Terao I, Tsuge T, Endo K, Kodama W. Comparative efficacy, tolerability and acceptability of intravenous racemic ketamine with intranasal esketamine, aripiprazole and lithium as augmentative treatments for treatment-resistant unipolar depression: a systematic review and network meta-analysis. J Affect Disord 2024; 346:49-56. doi: 10.1016/j.jad.2023.11.023.

33. Zarate CA, Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA, Charney DS, Manji HK. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch Gen Psychiatry 2006; 63:856-864. doi: 10.1001/archpsyc.63.8.856.

34. Kryst J, Kawalec P, Mitoraj AM, Pilc A, Lasoń W, Brzostek T. Efficacy of single and repeated administration of ketamine in unipolar and bipolar depression: a meta-analysis of randomized clinical trials. Pharmacol Rep 2020; 72:543-562. doi: 10.1007/s43440-020-00097-z.

35. Wang YT, Wang XL, Lei L, Guo ZY, Kan FF, Hu D, Gai C, Zhang Y. A systematic review and meta-analysis of the efficacy of ketamine and esketamine on suicidal ideation in treatment-resistant depression. Eur J Clin Pharmacol 2024; 80:287-296. doi: 10.1007/s00228-023-03605-1.

36. Li J, Ma L, Sun H, Li M, Cao Y, Peng Y, Xu J. Efficacy of racemic ketamine or esketamine monotherapy for reducing suicidal ideation in uni- or bipolar depression: a systematic review and meta-analysis. Eur Arch Psychiatry Clin Neurosci 2025; 275:1359-1371. doi: 10.1007/s00406-024-01920-x.

Methylphenidate induced acute orofacial and limb dyskinesia in a patient with autism spectrum disorder

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SUMMARY

Methylphenidate is the first-line pharmacological agent used in the treatment of children with Autism Spectrum Disorder (ASD) and comorbid Attention-Deficit Hyperactivity Disorder (ADHD); however, it may rarely cause movement disorders. This case report presents a 9-year-old male patient who developed acute orofacial and limb dyskinesia following the initiation of high-dose modified-release methylphenidate, four weeks after the abrupt discontinuation of aripiprazole treatment. The dyskinesia completely regressed upon cessation of the stimulant therapy and did not recur during subsequent gradual dose titration. The case is discussed in the context of the hypothesis that dopaminergic hypersensitivity resulting from antipsychotic withdrawal may lower the threshold for stimulant-induced dyskinesia. Furthermore, the importance of careful dose titration and close clinical monitoring when re-initiating stimulant therapy is emphasized, particularly in patients with neurodevelopmental disorders who have a history of recent antipsychotic discontinuation.

Key words: Autism Spectrum Disorder, methylphenidate, dyskinesia, aripiprazole, side effect.

INTRODUCTION

Attention-Deficit Hyperactivity Disorder (ADHD) is commonly seen in children with Autism Spectrum Disorder (ASD) (1), with reported comorbidity rates ranging from 50% to 70% (2). The co-occurrence of ASD and ADHD is associated with greater impairment in adaptive functioning and poorer quality of life (3). Psychiatric medication prescription rates are increasing in ASD (4), and ADHD is the most common psychiatric disorder contributing to this trend (5).

The current literature suggests that methylphenidate (MPH) is the first-line treatment in children and adolescents with ASD and ADHD (6,7). The side effects associated with methylphenidate include reduced appetite, insomnia, headaches, anxiety, weight loss, abdominal pain, irritability, and increases in heart rate and blood pressure (8). Most side effects are mild, often transient, and can be alleviated through dose adjustment (9). However, the neurobiological structure of ASD can present unique challenges. Unlike typically developing children, individuals with ASD often exhibit dysfunctions in dopaminergic signaling (10) and abnormal basal ganglia functioning (11). These neurodevelopmental characteristics may lead to a 'neurobiological vulnerability', lowering the threshold for adverse motor events such as dyskinesias when central dopaminergic pathways are stimulated. Therefore, understanding this biological susceptibility is crucial for clinical management.

Dyskinesia is characterized by involuntary, repetitive, abnormal muscle movements that often affect the face, limbs, and trunk. It is often caused by medications, neurological disorders like Parkinson's and Huntington's diseases, metabolic imbalances, and genetic predispositions. Medications associated with this condition include antipsychotics, antidepressants, mood stabilizers, anticonvulsants, antiemetics, and many other drugs (12). Several case reports indicate that MPH can lead to involuntary movement disorders such as

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tics, chorea, and dyskinesia in a wide range of children, from healthy children to those with multiple developmental disabilities (13-16). However, while reports describing these adverse motor events specifically in the ASD population are limited, they are particularly clinically relevant given the unique neurobiological susceptibility of these patients. To date, only a few cases of stimulant-induced orofacial dyskinesia have been described in children and adolescents with ASD (17, 18).

This case report describes acute orofacial and limb dyskinesia developing in a boy treated with methylphenidate for ADHD. To our knowledge, this is one of the rare reports in the literature with methylphenidate induced both orofacial and limb dyskinesia in children and adolescents with ASD, highlighting the importance of careful titration and monitoring in this vulnerable group.

Case Presentation

A 9-year-old male with ASD was referred to our child and adolescent psychiatry clinic by the pediatric emergency department due to abnormal and involuntary movements. His birth history indicated that he was born following an uneventful pregnancy and delivery, and there were no known medical conditions or psychiatric disorders in the family. There was no family history of any movement disorder. His developmental milestones were delayed: he spoke his first words at 18 months, began using two-word phrases at four years, and walked independently at 20 months. He achieved toilet training at the age of five. At two years old, he received a diagnosis of ASD due to limited social communication and interaction, including poor eye contact, failure to respond to his name, and sensory sensitivities. Two years ago, he was diagnosed with ADHD and mild intellectual disability according to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria at another child and adolescent psychiatry clinic. Although standardized psychometric tests were not available at presentation, the diagnosis was confirmed based on clinical assessment of adaptive functioning and developmental history according to DSM-5 criteria.

His treatment regimen had included modified-release methylphenidate (MPH) at 30 mg/day and aripiprazole at 7.5 mg/day for approximately one year. Four weeks prior to admission, his mother had abruptly discontinued all medications, due to perceived improvement. At the end of a 4 week drug-free period, his mother restarted treatment (MPH 30 mg/day, Modified-Release formulation) because of a significant increase in inattention and hyperactivity symptoms without medical consultation. On the morning of admission, he received the first dose of MPH after the four-week discontinuation and developed involuntary movements approximately 2 hours after taking the medication. Four hours after taking the medication, he presented to the pediatric emergency department due to persistent symptoms.

Physical examination revealed a generally well-developed child with stable vital signs. His cooperation was limited. He used single purposeful words in verbal communication occasionally. Notably, he exhibited abnormal involuntary movements affecting the orofacial region and limbs, including facial grimacing, lip licking, tongue rolling, and involuntary shaking of the bilateral arms and legs. These involuntary movements were characterized as non-rhythmic, rapid, and uncontrollable, clearly distinguishing them from the patient's usual stereotypies associated with ASD.

A detailed neurological examination was performed to exclude other underlying pathologies. There was no rigidity or spasticity in muscle tone. Deep tendon reflexes were bilaterally normoactive, and no pathological reflexes were observed. Cerebellar function tests were intact. Extrapyramidal system examination revealed no resting tremor, bradykinesia, or dystonic posturing. Sensory and cranial nerve examinations were normal. Consequently, the clinical presentation primarily suggested isolated dyskinesia. His mother stated that they used MPH only and did not use any other drug, herbal product or substance. There was no recent history of infection. The clinical presentation was assessed as dyskinesia. Total Abnormal Involuntary Movement Scale (AIMS) score was 22 points, indicating moderate-to-severe dyskinesia. This severity was accompanied by functional impairment, particularly limiting the patient's abil-

ity to cooperate and communicate verbally.

The patient was monitored in the 24-hour observation unit without any intervention. Approximately 10 hours after medication ingestion, a decrease in involuntary movements was observed, and the AIMS score decreased to 6 points, reflecting a marked clinical improvement to mild severity. Dyskinetic symptoms resolved completely by the following day. MPH was discontinued, and the patient was discharged. During the pediatric neurology follow-up, cranial magnetic resonance imaging (MRI) and electroencephalogram (EEG) results were normal. No dyskinetic movements were observed during the one-month follow-up at the child and adolescent psychiatry clinic. During the subsequent visit, it was reported that the patient had some problems due to attention and hyperactivity problems. The family requested the re-initiation of MPH treatment. After discussing the possible risks, the family expressed their preference for reinitiating treatment, given the patient's previous positive response to MPH. His body weight was 28 kg. MPH was re-initiated at 10 mg/day and was gradually titrated up to 30 mg/day over a period of 3 months. According to the Clinical Global Impression-Improvement (CGI-I) rating scale, his attention and hyperactivity symptoms showed moderate to much improvement during the three months of treatment. During the subsequent six-month follow-up, the patient underwent systematic evaluation using the AIMS. The AIMS score was 0, indicating a complete absence of dyskinetic movements. Although video documentation was not obtained during follow-up, the consistency between clinician assessments and caregiver reports supports the conclusion of non-recurrence. Written informed consent was obtained from his parents for the publication of this case report.

DISCUSSION

In our case report, a 9-year-old male with ADHD and ASD developed orofacial and limb dyskinesia immediately after the first dose of MPH 30 mg/day. Subsequently, MPH was discontinued, and dyskinetic symptoms resolved completely after the cessation of the medication. One month later, MPH was reinitiated with the dose titration regimen, and dyskinesia did not recur. Assessment using the Naranjo Adverse Drug Reaction Probability Scale yielded a score of 8 that shows probable adverse drug reaction (19). However, due to the recent complexity of the patient's recent psychotropic regimens, causality attribution based on solely on the scale should be interpreted with caution. A high score primarily reflects a significant temporal relationship between drug intake and dyskinesia, rather than potential confounding factors, such as the possible contributing role of dopaminergic hypersensitivity following aripiprazole discontinuation.

Establishing an accurate diagnosis required a systematic differential diagnostic approach to exclude other movement disorders. First, acute dystonia was ruled out due to the absence of sustained muscle contractions, and the presence of normal muscle tone on neurological examination. Second, stereotypies were excluded as the observed movements were acute in onset, non-rhythmic, and distinguishable from the patient's baseline repetitive behaviors. Third, epileptic phenomena and structural lesions were excluded based on normal findings in both the EEG and cranial MRI. Fourth, a tic disorder was not considered a primary diagnosis due to the absence of a past history of tics, the continuous and involuntary nature of the movements, and the clear temporal relationship with drug intake.

Another critical issue in this case is the potential neuroadaptive changes that may occur during the 4-week period following the abrupt discontinuation of aripiprazole. Aripiprazole is an atypical antipsychotic with partial agonist effects on D2 receptors (20). It has a mean elimination half-life of 75 hours, whereas its active metabolite, dehydroaripiprazole, has a half-life of approximately 94 hours (21). Although pharmacokinetic studies in children and adolescents indicate that psychotropic drugs reach peak concentrations more rapidly, accumulation and elimination processes are comparable to those in adults and maintain prolonged D2 receptor occupancy (22). Consequently, the physiological washout period, during which the drug and its active metabolites are cleared and receptor occupancy decreases, can extend up to 2-3 weeks.

Furthermore, chronic antipsychotic use may lead to the upregulation of postsynaptic dopamine receptors, resulting in receptor supersensitivity manifesting as hypersensitivity to dopaminergic stimulation (23). We hypothesize that the patient's dopaminergic system was in a state of supersensitivity due to the discontinuation of aripiprazole four weeks prior. The re-administration of methylphenidate at a relatively high dose (30 mg/day; 1.07 mg/kg for a 28 kg child) likely resulted in a sudden and substantial increase in synaptic dopamine levels. This dopamine surge, acting upon the already hypersensitive D2 receptors, likely precipitated the acute dyskinetic movements.

Dyskinesias can be categorized into two groups based on the time between the initiation of stimulant therapy and the onset of dyskinetic symptoms. The first group is characterized by cases in which dyskinesia develops immediately after the initiation of stimulant therapy, and involuntary movements resolve completely on the same day (13, 16, 24). The second group describes patients who develop dyskinesia a few weeks after initiation of stimulant therapy, which may persist for months after discontinuation (25). The underlying mechanisms of these two groups of dyskinesias differ: The first group is associated with overstimulation of dopamine receptors due to higher serum levels of the stimulant, while the second group is associated with hypersensitivity of dopamine receptors (13). A review of the literature on methylphenidate-induced dyskinesia in patients with ASD highlights heterogeneity regarding the potential underlying mechanisms across reported cases. For instance, Baweja et al. (17) described late-onset dyskinesia occurring after prolonged use, whereas Lee et al. (18) reported a case report of acute-onset dyskinesia. Our case also underscores the specific contribution of antipsychotic withdrawal within this heterogeneity. In contrast to previous reports, the presence of a pronounced aripiprazole washout period leads to a hypersensitivity model, suggesting that dyskinesia may also be the result of a sensitized dopaminergic system. It is crucial for clinicians to recognize that stimulant-induced movements in ASD can often be multifactorial in nature.

In the literature, it has been reported that, depending on the severity of dyskinetic symptoms, management may involve conservative observation or pharmacological intervention with biperiden (26) or diphenhydramine (15). In our case, no pharmacological treatment was initiated because the dyskinetic symptoms were not severe and showed a tendency to subside spontaneously. Previous case reports of dyskinesia in patients with ASD have indicated that dyskinesia spontaneously resolved after discontinuation of methylphenidate (17, 18). Methylphenidate treatment in patients with ASD has been reported to be associated with lower efficacy and more adverse side effects compared to individuals with typically developing ADHD (27). Therefore, cautious dose titration in small increments with frequent reassessment has been recommended to improve tolerability in the treatment with methylphenidate in this group (28). In our case, dyskinesia did not recur when we restarted methylphenidate with gradual dose titration.

Finally, the findings cannot be generalized to the entire ASD population, primarily because this is a single case report with a complex pharmacological history where medication changes were caregiver-driven rather than clinician-controlled, introducing uncertainty regarding exact dosing intervals. However, this case report underscores an important clinical implication that the "safety margin" for pharmacological manipulations in neurodevelopmental disorders is narrow. Clinicians should consider that adverse motor movements may not be solely the side effects of a single agent but rather result of complex neuroadaptive interactions, particularly the interaction between antipsychotic withdrawal and stimulant re-introduction.

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REFERENCES

1. Roselló R, Martinez-Raga J, Mira A, Pastor JC, Solmi M, Cortese S. Cognitive, social, and behavioral manifestations of the co-occurrence of autism spectrum disorder and attention-deficit/hyperactivity disorder: a systematic review. Autism. 2022;26(4):743-60.

2. Rong Y, Yang CJ, Jin Y, Wang Y. Prevalence of attention-deficit/hyperactivity disorder in individuals with autism spectrum disorder: a meta-analysis. Res Autism Spectr Disord. 2021;83:101759.

3. Sikora DM, Vora P, Coury DL, Rosenberg D. Attention-deficit/hyperactivity disorder symptoms, adaptive functioning, and quality of life in children with autism spectrum disorder. Pediatrics. 2012;130(Suppl 2):S91-7.

4. Kamimura-Nishimura K, Froehlich T, Chirdkiatgumchai V, Adams R, Fredstrom B, Manning P. Autism spectrum disorders and their treatment with psychotropic medications in a nationally representative outpatient sample: 1994–2009. Ann Epidemiol. 2017;27(7):448-53.e1.

5. Jobski K, Höfer J, Hoffmann F, Bachmann C. Use of psychotropic drugs in patients with autism spectrum disorders: a systematic review. Acta Psychiatr Scand. 2017;135(1):8-28.

6. National Institute for Health and Care Excellence (NICE). Attention deficit hyperactivity disorder: diagnosis and management [NG87]. London: NICE; 2018. Available from: https://www.nice.org.uk/guidance/ng87

7. Cortese S, Adamo N, Del Giovane C, Mohr-Jensen C, Hayes AJ, Carucci S, Atkinson LZ, Tessari L, Banaschewski T, Coghill D, Hollis C, Simonoff E, Zuddas A, Barbui C, Purgato M, Steinhausen HC, Shokraneh F, Xia J, Cipriani A. Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis. Lancet Psychiatry. 2018;5(9):727-38.

8. Graham J, Coghill D. Adverse effects of pharmacotherapies for attention-deficit hyperactivity disorder: epidemiology, prevention and management. CNS Drugs. 2008;22(3):213-37.

9. Santosh PJ, Taylor E. Stimulant drugs. Eur Child Adolesc Psychiatry. 2000;9(Suppl 1):I27-43.

10. Pavăl D. A dopamine hypothesis of autism spectrum disorder. Dev Neurosci. 2017;39(5):355-60.

11. Prat CS, Stocco A, Neuhaus E, Kleinhans NM. Basal ganglia impairments in autism spectrum disorder are related to abnormal signal gating to prefrontal cortex. Neuropsychologia. 2016;91:268-81.

12. Correll CU, Kane JM, Citrome LL. Epidemiology, prevention, and assessment of tardive dyskinesia and advances in treatment. J Clin Psychiatry. 2017;78(8):1136-47.

13. Balázs J, Besnyő M, Gádoros J. Methylphenidate-induced orofacial and extremity dyskinesia. J Child Adolesc Psychopharmacol. 2007;17(3):378-82.

14. Yilmaz AE, Donmez A, Orun E, Tas T, Isik B, Sonmez FM. Methylphenidate-induced acute orofacial and extremity dyskinesia. J Child Neurol. 2013;28(6):781-3.

15. Waugh JL. Acute dyskinetic reaction in a healthy toddler following methylphenidate ingestion. Pediatr Neurol. 2013;49(1):58-60.

16. Senecky Y, Lobel D, Diamond GW, Weitz R, Inbar D. Isolated orofacial dyskinesia: a methylphenidate-induced movement disorder. Pediatr Neurol. 2002;27(3):224-6.

17. Baweja R, Mills S, Waxmonsky J. Dexmethylphenidate extended release-associated orofacial dyskinesia in an adolescent with autism spectrum disorder after prolonged use. J Child Adolesc Psychopharmacol. 2018;28(6):423.

18. Lee M, Wang L. Methylphenidate-induced orofacial dyskinesia: report of two school-age boys in Taiwan. HK J Paediatr (New Series). 2017;22(2):107-9.

19. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, Janecek E, Domecq C, Greenblatt DJ. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30(2):239-45.

20. Tuplin EW, Holahan MR. Aripiprazole, a drug that displays partial agonism and functional selectivity. Curr Neuropharmacol. 2017;15(8):1192-207.

21. Caccia S. Pharmacokinetics and metabolism update for some recent antipsychotics. Expert Opin Drug Metab Toxicol. 2011;7(7):829-46.

22. Findling RL, Kauffman RE, Sallee FR, Carson WH, Nyilas M, Mallikaarjun S, Pikalov A. Tolerability and pharmacokinetics of aripiprazole in children and adolescents with psychiatric disorders: an open-label, dose-escalation study. J Clin Psychopharmacol. 2008;28(4):441-6.

23. Chouinard G, Samaha AN, Chouinard VA, Peretti CS, Kanahara N, Takase M, Iyo M. Antipsychotic-induced dopamine supersensitivity psychosis: pharmacology, criteria, and therapy. Psychother Psychosom. 2017;86(4):189-219.

24. Hollis CP, Thompson A. Acute dyskinesia on starting methylphenidate after risperidone withdrawal. Pediatr Neurol. 2007;37(4):287-8.

25. Lipkin PH, Goldstein IJ, Adesman AR. Tics and dyskinesias associated with stimulant treatment in attention-deficit hyperactivity disorder. Arch Pediatr Adolesc Med. 1994;148(8):859-61.

26. Arslan EA, Arslan E, Kilinç A, Göksu Ö. Effect of biperiden treatment in acute orofacial and extremity dyskinesia with methylphenidate therapy. Pediatr Emerg Care. 2018;34(11):e217-e8.

27. Stigler KA, Desmond LA, Posey DJ, Wiegand RE, McDougle CJ. A naturalistic retrospective analysis of psychostimulants in pervasive developmental disorders. J Child Adolesc Psychopharmacol. 2004;14(1):49-56.

28. Mahajan R, Bernal MP, Panzer R, Whitaker A, Roberts W, Handen B, Hardan A. Clinical practice pathways for evaluation and medication choice for attention-deficit/hyperactivity disorder symptoms in autism spectrum disorders. Pediatrics. 2012;130(Suppl 2):S125-38.

A suicide attempt with long-acting methylphenidate in an adolescent with attention deficit hyperactivity disorder: Clinical management and a biopsychosocial approach

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SUMMARY

Attention deficit hyperactivity disorder (ADHD) is a well-established risk factor for suicidal ideation, suicide attempts, and completed suicide. Methylphenidate, a first-line pharmacological treatment for ADHD, is being increasingly prescribed. Given the rising rates of methylphenidate use and the high prevalence of suicide among individuals with ADHD, it is anticipated that clinicians will increasingly encounter suicide attempts involving this easily accessible medication. However, there are limited case reports of suicide attempts involving methylphenidate in individuals with ADHD. In this case report, we present a comprehensive biopsychosocial evaluation of a 14-year-old adolescent girl with ADHD who attempted suicide by taking 900 mg of long-acting methylphenidate, while discussing potential underlying mechanisms and risk factors for suicidality. We also addressed the clinical management of high-dose methylphenidate ingestion in children and adolescents, a topic for which the literature provides limited guidance. This case highlights several risk factors for suicidal behavior in adolescents, including untreated ADHD, comorbid psychiatric disorder, dysfunctional family dynamics, emotional dysregulation, impulsivity, social stressors, academic difficulties, family history of suicide and inadequate coping mechanisms. Our findings emphasize the importance of sustained ADHD treatment, routine suicidality screening in adolescents with ADHD and providing psychoeducation for families. Suicidal behavior is a complex and multifactorial process shaped by the interaction of biological, psychological, and environmental factors. A multidisciplinary approach grounded in the biopsychosocial model is essential for effective assessment and intervention.

Key words: Attention deficit hyperactivity disorder, methylphenidate, suicide attempt, biopsychosocial model

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder in childhood, characterized by inattention, impulsivity, and hyperactivity (1). ADHD is rarely standalone and often comorbid with other psychiatric disorders (2). It has been linked to increased suicidal thoughts, attempts, and completed suicides, and is considered an independent risk factor for suicide (3-5).

Methylphenidate, the first-line pharmacological treatment for ADHD, is increasingly prescribed worldwide (6,7). In the United States, among individuals aged 0–19 years, methylphenidate is the most commonly reported agent in poison control exposures related to ADHD medications (8). However, no comparable national data exist for Turkey, representing a limitation, as patterns of medication use and overdose may vary across countries. Given the increasing use of methylphenidate and the high prevalence of suicide in ADHD, it is anticipated that clinicians will increasingly encounter suicide attempts involving this easily accessible medication. Although case reports of suicide attempts involving methylphenidate in individuals with ADHD exist, these are often discussed predominantly from a biological perspective (9-14). In this context, we present an adolescent with ADHD who attempted suicide with high-dose methylphenidate, discussed comprehensively from a biopsychosocial perspective, highlighting under-

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lying mechanisms and risk factors for suicidal behavior in ADHD.

CASE

A 14-year-old girl was brought to the emergency department approximately an hour after ingestion of 25 tablets of 36 mg (900 mg) long-acting methylphenidate which works with an osmotic controlled release system (OROS). No nausea or vomiting occurred following the ingestion. Upon admission, she was conscious with stable vital signs, and physical examination, toxicology screening, and blood ethanol levels were unremarkable. She received activated charcoal (1 g/kg) and was discharged after 24 hours of observation, remaining asymptomatic with normal vital signs and laboratory results.

She reported ingesting a high dose of her prescribed medication following an argument with her boyfriend. Similarly, three months earlier, she had ingested 10 tablets of 36 mg (360 mg) OROS methylphenidate after an argument with her boyfriend. The patient, who had not been under regular ADHD treatment, used leftover prescribed methylphenidate stored at home. She stated that her aim in these suicide attempts was not to end her life but to upset her boyfriend, and expressed regret afterward. Both episodes were unplanned, emotionally driven, and consistent with impulsive behavior. No other suicide attempts or self-injurious behaviors were reported.

The patient's mother and father were primary school graduates, employed as cleaning staff and at a gas station, respectively. She had a 21-year-old sister who had attempted suicide by medication overdose following an argument with her boyfriend five years earlier. Although the patient did not witness the incident, her sister had shared the experience with her afterward. The sister had no psychiatric diagnosis or treatment at that time or afterward. There was no other family history of psychiatric illness or suicide. Family relationships were described as emotionally distant yet stable. Both sisters exhibited limited problem-solving skills and maladaptive coping with interpersonal stress, particularly in romantic relationships.

Pregnancy, labor, and postpartum were uneventful, and neuromotor milestones were achieved on time. There was no history of illness, accident or surgery. Her academic performance was poor. The patient had been involved in two school altercations resulting in legal cases. She reported occasional smoking and alcohol use with peers but denied substance abuse. Her first psychiatric evaluation occurred at age five following physically aggression toward a peer. At that time, she was diagnosed with ADHD. Although she did not attend regular follow-up, she occasionally used different methylphenidate formulations throughout her treatment.

In the psychiatric interview conducted in the emergency department, the patient presented as a female adolescent appearing her stated age, dressed appropriately for her socioeconomic status. She was conscious and fully oriented. No perceptual or memory defect was detected. Mood was euthymic, and affect was congruent with thought content. Speech rate and quantity were normal. Thought process was coherent and goal-directed, focusing on recent arguments with her boyfriend and regret over her suicide attempt. No current suicidal or homicidal thoughts were reported. During clinical evaluation, her intellectual functioning was observed to be consistent with mild intellectual disability (MID). The WISC-IV test administered during outpatient follow-up showed impairments in verbal comprehension (66), working memory (59), and processing speed (59), with borderline perceptual reasoning (72) and a full-scale IQ of 53.

According to DSM-5, intellectual disability requires not only low IQ but also significant impairments in adaptive functioning. In this case, academic underachievement (conceptual domain), impulsive and poorly regulated interpersonal behavior (social domain), and difficulties in daily living and legal problems (practical domain) together indicated clinically significant impairments in adaptive functioning. It is possible that untreated ADHD symptoms adversely affected attention, working memory, and processing speed, resulting in underestimation of true cognitive abilities. Based on the clinical history, cognitive testing, and adaptive functioning assessments (Children's Global Assessment Scale score: 55, indicating moderate impairment), the patient was diagnosed with

comorbid MID. No additional psychiatric comorbidities were identified according to DSM-5 criteria and psychometric assessments (Beck Depression Inventory: 7; State-Trait Anxiety Inventory: 28/30, both below clinical cut-off). The treatment plan included ADHD management, support tailored to MID, psychoeducation, and family training, together with multidisciplinary follow-up. Written informed consent was obtained from the patient and her parents to publish this manuscript.

DISCUSSION

Psychostimulants are first-line pharmacological treatment for ADHD (6). Methylphenidate accounts for nearly half of reported ADHD medication misuse, mostly in adolescents (8). Despite increasing ADHD diagnoses and stimulant prescriptions, epidemiological data on stimulant-related toxicity remain limited. A recent adult study reported 64 deaths associated with methylphenidate or (lis)dexamfetamine; 41 involved methylphenidate, about 20% were intentional, and mostly with polysubstance use and psychiatric comorbidity (15). While deaths are rare relative to prescription volume, caution is warranted in patients with psychiatric comorbidity, substance use, cardiovascular disease, or polypharmacy. This study provides the most contemporary evidence on stimulant-related mortality, however, focuses exclusively on adults. Adolescent-specific data remain limited, representing an important gap in the literature.

High doses of psychostimulants can cause hypertension, tachycardia, arrhythmia, hyperthermia, irritability, mood changes, hallucinations, and seizures. Hospitalization is advised for methylphenidate exposures exceeding 4 mg/kg or 120 mg (16). Induction of emesis is not recommended, and while no specific antidote exists, activated charcoal is advised. Benzodiazepines are indicated for agitation, dystonia, or seizures. In cases of respiratory depression, arrhythmias, or cardiac arrest, standard advanced cardiac life support protocols should be initiated. Emergency management should prioritize cardiovascular stabilization and neurological monitoring, followed by psychiatric evaluation and suicide risk assessment. If the patient remains stable and asymptomatic for 24 hours with normal laboratory results, discharge may be considered (16).

Methylphenidate exposures reported to poison control centers showed that only 31% of the cases developed symptoms—most commonly tachycardia, agitation, and lethargy—and none were severe or life-threatening (17). Moreover, in intentional ingestions, additional symptoms—including vomiting, dizziness, mydriasis, and tremor—have been reported. Consistent with these findings and previous case reports (9-14), no serious symptoms occured in our case despite ingestion of 900 mg of OROS methylphenidate. Both our case and those in the literature involved long-acting formulations, whose pharmacokinetic properties may influence overdose presentation (6). Evidence suggests that long-acting formulations generally cause mild or no adverse effects (16). Although long-acting methylphenidate appears safer acutely, its extended-release profile may prolong toxicity, necessitating extended observation. Overall, knowledge regarding high-dose methylphenidate effects remains largely case-based, underscoring the need for further research.

Although stimulants have been used for decades, concerns about methylphenidate's safety and its potential link to suicidality persist. Reports of suicide directly related to methylphenidate are rare and mostly limited to case studies. Large-scale cohort studies and meta-analyses indicate that stimulant treatment does not increase suicidality and may even reduce the risk of suicide attempts (18-20). Moreover, consistent long-term treatment has been linked to fewer suicide attempts (21), suggesting that concerns about increased suicide risk due to ADHD medications may be unwarranted. Given ADHD's high prevalence and strong association with suicidality, effective and sustained treatment may reduce suicide risk (2). In our case, the patient lacked consistent follow-up or medication, underscoring untreated ADHD as a potential contributor to suicidal behavior and the importance of treatment adherence.

A meta-analysis reported that ADHD increases the risk of suicide planning by 2.4 times, suicidal

ideation by 4.5 times, and completed suicides by 6.7 times (4). The present case, with repeated suicide attempts, underscores ADHD as a significant risk factor for suicidality. While this association is well established, the underlying factors remain unclear and likely reflect a complex interaction of biological, psychological, and social influences. Therefore, a comprehensive understanding of suicide risk requires evaluation through the biopsychosocial model (22).

ADHD is a neurodevelopmental disorder that leads to various structural, functional, and neurochemical brain alterations. Dysregulation of neurotransmitter systems—particularly dopamine, serotonin, and noradrenaline—contributes to impulsivity, and abnormalities have been identified in brain regions responsible for impulse control and emotional regulation (2). These neurobiological factors help explain difficulties in emotion regulation and impulse control. Impulsivity and poor response inhibition, core features of ADHD, are consistently associated with increased suicide risk (23). ADHD has been identified as an independent risk factor for suicidal ideation and attempts, regardless of comorbid psychiatric disorders, and is particularly associated with repeated suicide attempts (5,23). A cohort study further reported significantly elevated rates of suicidal ideation and completed suicides among individuals with untreated ADHD (24). Early diagnosis and appropriate pharmacological treatment appear to have protective effect on suicidal behavior, mainly by reducing impulsivity (22,25). Our case, diagnosed with ADHD but not receiving regular treatment and exhibited repeated impulsive suicide attempts, highlights the importance of comprehensive ADHD management and routine suicide screening, particularly in patients with poor treatment adherence.

Evaluating psychological factors is essential for understanding the underlying causes of suicidal behavior. Increased suicide risk in individuals with ADHD is primarily associated with comorbid disorders, such as depression, bipolar disorder, anxiety disorders, substance use disorders, personality disorders, autism spectrum disorders, and intellectual disability. Suicide risk is significantly elevated when these comorbidities remain undiagnosed or untreated (23). Our case also presents with comorbid ADHD and MID, both neurodevelopmental disorders. ADHD symptoms tend to be more severe in those with intellectual disability (26). However, knowledge regarding the clinical presentation and prevalence of ADHD in this population remains limited, as individuals with lower cognitive functioning are frequently excluded from research (26). Further studies focusing on this population are warranted to improve understanding and guide clinical practice.

Children with neurodevelopmental disorders often exhibit inadequate emotion regulation and rely on limited coping strategies when faced with emotional distress (27). In ADHD, these challenges are compounded by executive functioning deficits—working memory, cognitive flexibility, and planning—which hinder effective problem-solving and adaptive responses to stress (27). Our patient impulsively ingested a high dose of methylphenidate following an interpersonal conflict, illustrating how impaired emotion regulation and executive control may converge, leading to maladaptive behaviors. Notably, both suicide attempts occurred after arguments with her boyfriend, and she later expressed that the behavior was not motivated by suicidal intent but represented a maladaptive interpersonal problem-solving response. These findings highlight emotion regulation difficulties, impulsivity, and the use of suicidal behavior as a maladaptive coping strategy in response to interpersonal stress.

The patient's recurrent impulsive behaviors raise considerations regarding non-suicidal self-injury (NSSI), defined as deliberate self-harm without suicidal intent. In adolescents, NSSI is often linked to difficulties managing emotions, impulsivity, and limited coping strategies—all present in this case. Recognizing NSSI is clinically important, as repeated NSSI can exacerbate emotional dysregulation, interpersonal difficulties, and future suicide risk (28). These observations underscore the importance of interventions targeting emotion regulation and impulse control into treatment plans for adolescents with ADHD. Evidence-based interventions —such as cognitive-behavioral therapy, family-based interventions incorporating parent training, and adjunctive pharmacological options (e.g., antipsychotics for severe agitation or mood dysreg-

ulation) —may reduce the risk of repeated NSSI and provide structured coping mechanisms in emotionally charged situations (29). Early identification and management of comorbid psychiatric disorders remain essential to reduce future suicide risk (29). In this case, due to irregular follow-up and poor adherence, close monitoring and targeted pharmacological or behavioral interventions were not feasible. Nevertheless, psychoeducation and family training were provided to enhance coping strategies and mitigate future risk.

Familial and social factors play a significant role in suicidal behavior. Children with intellectual disability often experience academic difficulties, social exclusion, and interpersonal challenges, contributing to low self-esteem—a key factor associated with increased suicide risk (23). In our case, academic underachievement and peer relationships difficulties may have contributed to diminished self-esteem and served as triggers for suicide attempts. Family history of suicide is also linked to higher suicide risk among children with ADHD (23). Notably, the patient's sister had attempted suicide following a similar interpersonal conflict, suggesting maladaptive coping strategies within the family. Internalization of such dysfunctional patterns may have influenced the patient's response to emotional distress. Additionally, medication accessibility represents a significant risk factor for overdose and suicide attempts, particularly in adolescents with impulsive behavior and untreated ADHD. In this case, both suicide attempts involved methylphenidate previously prescribed and accessible at home, highlighting the role of medication access. Furthermore, familial and environmental factors, such as low socioeconomic status, limited parental education, unstable employment, and a family psychiatric history are well-established risk factors for suicide (23). In our case, both parents had low education levels and low-income jobs, indicating potential social vulnerabilities. Therefore, parents psychoeducation is crucial to raise awareness about the suicide risk. Families should be informed about limiting access to potentially harmful objects, including medications and sharp instruments, particularly in impulsive children. Physicians should emphasize secure drug storage and encourage parental supervision. Enhancing protective factors—such as social support and academic engagement—may serve as important buffers against suicide risk in this vulnerable population.

These clinical insights underscore the multifactorial nature of suicidal behavior in adolescents with neurodevelopmental disorders, shaped by biological, psychiatric, and social factors. Clinicians should be vigilant when treating this population, given their heightened vulnerability and limited coping skills. Preventive strategies—such as sustained ADHD treatment, early family psychoeducation, structured interventions targeting emotion regulation and impulsivity, and secure medication storage—may reduce suicide risk. Strengthening school-based support and integrating routine suicide risk screening into ADHD follow-up could facilitate early identification of high-risk individuals. Given the complexity of suicidal behavior, a multidisciplinary approach incorporating the biopsychosocial model is essential for effective assessment and intervention. Future interventions should combine pharmacological management with evidence-based psychosocial approaches that enhance coping skills and emotion regulation, providing a comprehensive framework for this vulnerable population. As suicide remains a leading cause of death among adolescents and young adults, further research is needed to clarify the link between ADHD and suicidality.

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REFERENCES

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: DSM-5. Arlington, VA: American Psychiatric Publishing, 2013.

2. Biederman J, & Faraone, S.V. (2005) Attention-deficit hyperactivity disorder. The Lancet 2005; 366(9481):237-248. https://doi.org/10.1016/j.biopsych.2004.10.020

3. Balazs J, Kereszteny A. Attention-deficit/hyperactivity disorder and suicide: A systematic review. World journal of psychiatry 2017; 7(1):44. https://doi.org/10.5498/wjp.v7.i1.44

4. Septier M, Stordeur C, Zhang J, Delorme R, Cortese S. (2019). Association between suicidal spectrum behaviors and attention-deficit/hyperactivity disorder: a systematic review and meta-analysis. Neuroscience & Biobehavioral Reviews 2019; 103:109-118. https://doi.org/10.1016/j.neubiorev.2019.05.022

5. Huang KL, Wei HT, Hsu JW, Bai YM, Su TP, Li CT, Lin WC, Tsai SJ, Chang WH, Chen TJ, Chen MH. Risk of suicide attempts in adolescents and young adults with attention-deficit hyperactivity disorder: a nationwide longitudinal study. The British Journal of Psychiatry 2018; 212(4):234-238. https://doi.org/10.1192/bjp.2018.8

6. Huss M, Duhan P, Gandhi P, Chen CW, Spannhuth C, Kumar V. Methylphenidate dose optimization for ADHD treatment: review of safety, efficacy, and clinical necessity. Neuropsychiatric disease and treatment 2017; 1741-1751. https://doi.org/10.2147/NDT.S130444

7. Bachmann CJ, Wijlaars LP, Kalverdijk LJ, Burcu M, Glaeske G, Schuiling-Veninga CC, Hoffmann F, Aagaard L, Zito JM. Trends in ADHD medication use in children and adolescents in five western countries, 2005-2012. European Neuropsychopharmacology 2017; 27(5):484-493. https://doi.org/10.1016/j.euroneuro.2017.03.002

8. King SA, Casavant MJ, Spiller HA, Hodges NL, Chounthirath T, Smith GA. Pediatric ADHD medication exposures reported to US poison control centers. Pediatrics 2018; 141(6). https://doi.org/10.1542/peds.2017-3872

9. Fettahoglu EC, Satilmis A, Gokcen C, Ozatalay E. Oral megadose methylphenidate ingestion for suicide attempt. Pediatric International 2009; 51:844–845. 10.1111/j.1442-200X.2009.02929.x

10. Klampfl K, Quattländer A, Burger R, Pfuhlmann B, Warnke A, Gerlach M. Case report: intoxication with high dose of long-acting methylphenidate (Concerta(®)) in a suicidal 14-year-old girl. ADHD Attention Deficit and Hyperactivity Disorders 2010; 2:221-224. https://doi.org/10.1007/s12402-010-0032-0

11. Ozdemir E, Karaman MG, Yurteri N, Erdogan A. A case of suicide attempt with long-acting methylphenidate (Concerta). ADHD Attention Deficit and Hyperactivity Disorders 2010; 2:103-105. https://doi.org/10.1007/s12402-010-0026-y

12. Murat, D, Arman A. Suicidal attempt with high dose long-acting methylphenidate: a case report. Marmara Medical Journal 2013; 26(3):165–167. 10.5472/MMJ.2013.02663.1

13. Kilicoğlu AG, İpek H, Mutlu C, Doğan H, Avci A, Erdoğan A. 3240 mg long acting methylphenidate intake for suicide attempt. Anatolian Journal of Psychiatry 2014; 15: S1. https://doi.org/10.5455/apd.40639

14. Eryilmaz G, Gul IG, Yorbik O, Isiten N. Long-acting methylphenidate toxicity: a case report. Bulletin of Clinical Psychopharmacology 2014;24(4): 384-386. https://doi.org/10.5455/bcp.20140709015737

15. Darke S, Peacock A, Duflou JA, Farrell M, Lappin J. Methylphenidate and (lis)dexamfetamine toxicity-related deaths of adults, Australia, 2000-24: analysis of NCIS data. The Medical journal of Australia 2025; 222(5):259-261. https://doi.org/10.5694/mja2.52604

16. Scharman EJ, Erdman AR, Cobaugh DJ, Olson KR, Woolf AD, Caravati EM, Chyka PA, Booze LL, Manoguerra AS, Nelson LS, Christianson G, Troutman WG. American Association of Poison Control Centers. Methylphenidate poisoning: an evidence-based consensus guideline for out-of-hospital management, Clinical Toxicology 2007; 45(7):737-752. https://doi.org/10.1080/15563650701665175

17. White SR, Yadao CM. Characterization of methylphenidate exposures reported to a regional poison control center. Archives of pediatrics & adolescent medicine 2000; 154(12):1199-1203. 10.1001/archpedi.154.12.1199

18. Chang Z, Quinn P D, O'Reilly L, Sjölander A, Hu, K, Gibbons R, Larsson H, D'Onofrio BM. Medication for attention-deficit/hyperactivity disorder and risk for suicide attempts. Biological psychiatry 2020; 88(6):452-458. https://doi.org/10.1016/j.biopsych.2019.12.003

19. Kim JH, Park S, Lee YJ. Systematic review of suicidal behaviors related to methylphenidate and atomoxetine in patients with attention deficit hyperactivity disorder. Journal of the Korean Academy of Child and Adolescent Psychiatry 2023; 34(2):125. https://doi.org/10.5765/jkacap.220040

20. Liu WJ, Mao HJ, Hu LL, Song MF, Jiang HY, Zhang L. Attention-deficit/hyperactivity disorder medication and risk of suicide attempt: A meta-analysis of observational studies. Pharmacoepidemiology and drug safety 2020; 29(11):1364-1372. https://doi.org/10.1002/pds.5110

21. Liang SH, Yang YH, Kuo TY, Liao YT, Lin TC, Lee Y, McIntyre RS, Kelsen BA, Wang TN, Chen VC. Suicide risk reduction in youths with attention deficit/hyperactivity disorder prescribed methylphenidate: A Taiwan nationwide population-based cohort study. Research in developmental disabilities 2018; 72:96-105. https://doi.org/10.1016/j.ridd.2017.10.023

22. Arun P, Das S. Methylphenidate and Suicide. In Neuropathology of Drug Addictions and Substance Misuse. Academic Press 2016; p:692-698. https://doi.org/10.1016/B978-0-12-800634-4.00069-X

23. Austgulen A, Skram NKG, Haavik J, Lundervold AJ. Risk factors of suicidal spectrum behaviors in adults and adolescents with attention-deficit / hyperactivity disorder – a systematic review. BMC Psychiatry 2023; 23(1):612. https://doi.org/10.1186/s12888-023-05099-8

24. Hurtig T, Taanila A, Moilanen I, Nordström T, Ebeling H. Suicidal and self-harm behaviour associated with adolescent attention deficit hyperactivity disorder-a study in the Northern Finland Birth Cohort 1986. Nordic Journal of Psychiatry 2012; 66(5):320-328. https://doi.org/10.3109/08039488.2011.644806

25. Lichtenstein P, Halldner L, Zetterqvist J, Sjölander A, Serlachius E, Fazel S, Långström N, Larsson H. Medication for attention deficit-hyperactivity disorder and criminality. New England Journal of Medicine 2012; 367(21):2006-2014. 10.1056/NEJMoa1203241

26. Lindsey M. Comprehensive health care services for people with learning disabilities, Advances in psychiatric treatment 2002; 8(2):138-147. https://doi.org/10.1192/apt.8.2.138

27. Predescu E, Sipos R, Costescu CA, Ciocan A, Rus DI. Executive Functions and Emotion Regulation in Attention-Deficit/Hyperactivity Disorder and Borderline Intellectual Disability. Journal of clinical medicine 2020; 9(4):986. https://doi.org/10.3390/jcm9040986

28. Gillies D, Christou MA, Dixon AC, Featherston OJ, Rapti I, Garcia-Anguita A, Villasis-Keever M, Reebye P, Christou E, Al Kabir N, Christou PA. Prevalence and characteristics of self-harm in adolescents: meta-analyses of community-based studies 1990–2015. Journal of the American Academy of Child & Adolescent Psychiatry 2018; 57(10):733-741. https://doi.org/10.1016/j.jaac.2018.06.018

29. Glenn CR, Franklin JC, Nock MK. Evidence-based psychosocial treatments for self-injurious thoughts and behaviors in youth. Journal of Clinical Child & Adolescent Psychology 2015; 44(1):1-29. https://doi.org/10.1080/15374416.2014.945211

The clinical importance of caregiver mental health in autism outpatient care

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Dear Editor,

In autism outpatient settings, clinical attention is naturally directed toward the child's symptoms, functioning, and co-occurring behavioral difficulties. However, the psychological burden carried by caregivers is also an important, yet easily overlooked, component of the treatment process. In routine outpatient care, this may occur because visits are primarily child-centered, consultation time is limited, and structured screening protocols for caregiver well-being are not consistently integrated into autism services.

A clearer conceptual distinction between caregiver burden, caregiver mental health symptoms, and broader contextual stressors may help refine this clinical argument. Caregiver burden refers to the perceived emotional, practical, and role-related demands of caregiving; caregiver mental health symptoms may include depression, anxiety, burnout, or clinically significant distress; and contextual stressors may include financial strain, stigma, limited social support, and service-related difficulties. These domains should not be viewed merely as secondary contextual issues, but as clinically relevant factors that may influence treatment engagement, family functioning, and continuity of care (1,2). Research has shown that caregiver well-being is closely intertwined with the broader therapeutic environment in which autism care is delivered (2,3).

Caregiver mental health difficulties may interfere with appointment adherence, implementation of recommendations, participation in parent-mediated interventions, and collaboration with clinicians (3,4). Consistent with family-systems and transactional caregiving perspective, caregiver distress and child emotional-behavioral difficulties may reciprocally influence one another, shaping treatment engagement, adherence, and the family's capacity to implement recommendations. For this reason, caregiver burden should not be understood simply as an expected consequence of the child's symptoms. Recent findings suggest that the association between autism severity and parental stress or depressive symptoms may be shaped by intermediary processes such as the child's emotional-behavioral difficulties and caregivers' internalized stigma (5). Given the largely cross-sectional nature of much of the available evidence, these associations should be interpreted cautiously and should not be assumed to represent a unidirectional causal pathway. This perspective is clinically relevant because it frames caregiver mental health as a meaningful and potentially modifiable domain rather than an inevitable by-product of caregiving (1,5,6).

Although the realities of high-volume outpatient practice often preclude comprehensive family assessments, attention to caregiver well-being may still be clinically valuable. Clinicians often already refer families for appropriate mental health or social support services when a clear need becomes apparent. Even so, in treatment-resistant situations, or when families do not spontaneously express their difficulties, brief and structured inquiry may be useful. This could include questions

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regarding the distribution of caregiving responsibilities, financial or practical strain, persistent caregiver emotional distress, and the availability of social support. Although not a substitute for comprehensive psychiatric assessment, such brief inquiry may increase family awareness, help identify unmet needs, and guide clinicians toward appropriate further evaluation, support, or referral when necessary (2,6,7). This is particularly relevant because limited support and greater psychosocial burden have been associated with poorer caregiver mental health and lower resilience in parents of autistic children (2,6,7).

For these reasons, a brief and feasible caregiver-sensitive approach may be valuable in autism care. Even when comprehensive evaluation is not possible, a few minutes of structured inquiry may help clinicians recognize families at greater risk and guide more appropriate support or referral. However, implementation requires attention to practical barriers, including limited consultation time, clinician confidence in addressing caregiver distress, and the availability of mental health services for caregivers, social support, or community-based referral pathways. Such an approach may strengthen both family functioning and the sustainability of treatment. Therefore, brief caregiver-sensitive screening should be considered a routine component of autism outpatient care, not as an additional burden on clinicians, but as a practical step toward more family-centered and sustainable treatment.

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REFERENCES

1. Papadopoulos C, Lodder A, Constantinou G, Randhawa G. Systematic review of the relationship between autism stigma and informal caregiver mental health. J Autism Dev Disord. 2019;49(4):1665-1685.

2. Dimachkie Nunnally A, Factor RS, Sturm A, Valluripalli Soorya L, Wainer A, Taylor S, Ponzini M, Abbeduto L, Gulsrud AC. Examining indicators of psychosocial risk and resilience in parents of autistic children. Front Behav Neurosci. 2023 May 15;17:1102516. doi: 10.3389/fnbeh.2023.1102516. PMID: 37255619; PMCID: PMC10226532.

3. Ingersoll B, Berger NI. Parent engagement with a telehealth-based parent-mediated intervention program for children with autism spectrum disorders: predictors of program use and parent outcomes. J Med Internet Res. 2015;17(10):e227.

4. Croen LA, Shankute N, Davignon MN, Massolo ML, Yoshida CK. Demographic and clinical characteristics associated with engagement in behavioral health treatment among children with autism spectrum disorders. J Autism Dev Disord. 2017;47(11):3347-3357.

5. Seçinti DD, Diş D, Albayrak ZS, Şen E. Depression and parental distress among caregivers of autistic children: a serial mediator analysis. BMC Psychol. 2024;12(1):339.

6. Rizzo A, Sorrenti L, Commendatore M, Mautone A, Caparello C, Maggio MG, Özaslan A, Karaman H, Yıldırım M, Filippello P. Caregivers of Children with Autism Spectrum Disorders: The Role of Guilt Sensitivity and Support. J Clin Med. 2024 Jul 20;13(14):4249. doi: 10.3390/jcm13144249. PMID: 39064288; PMCID: PMC11278243.

7. Chen X, Tong J, Jiang B, Ma S, Wang X, Sun X, Liu Y, Yan D, Wang L. Courtesy stigma among primary caregivers of children with autism spectrum disorder in eastern China. Front Psychiatry. 2023 Nov 17;14:1236025. doi: 10.3389/fpsyt.2023.1236025. PMID: 38045614; PMCID: PMC10690950.

Beyond detection: The quieter risks of large language models in scientific publishing

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Dear Editor,

The recent editorial by Uzman Ozbek (1) provides a careful account of the ethical challenges that large language models (LLMs) now pose for scientific publishing, including the limited reliability of detection tools, the disproportionate flagging of non-native English authors as suspected AI users (2), and the impossibility of treating non-human systems as accountable authors (3). I would like to extend this discussion in a direction that deserves more editorial attention: the risks that remain even when authors disclose their AI use openly and avoid overt misconduct such as fabricated data or invented citations (4).

Most current debate focuses on what can, in principle, be caught. Yet a subtler problem may matter more in the long run: the gradual weakening of the fit between evidence, uncertainty, and claim that polished, model-assisted prose can produce without anyone noticing.

Several recent findings make the concern concrete. When LLMs summarise scientific work they overgeneralise systematically, nearly five times more often than human writers (5). They often sound confident when wrong, and readers mistake decisive tone for evidential strength (6). Even when AI-suggested references are real and on-topic, they may only loosely support — or contradict — the claims they accompany; a medical evaluation found 50–90% of LLM responses not fully grounded in the sources they cited (7). Lexical analyses of fifteen million PubMed abstracts already detect stylistic traces of LLM-assisted writing (8), and co-writing studies show that model assistance reduces lexical and content diversity (9). Redundant and low-yield publications have risen alongside LLM adoption (10–12). When models advise on methods they often recommend additional complexity, though current reporting guidance for clinical prediction and machine learning emphasises transparency, applicability, and decision relevance over technical sophistication (13,14). LLMs are now used at both ends of the publishing pipeline, with evidence that automated reviewers favour model-shaped prose (15,16), rewarding the same drift twice.

Considered separately, these effects look minor. Considered together, they describe a slow erosion of calibration in the scientific record. A cautious "may suggest" upgraded to "demonstrates" can travel a long way once a paper is cited, summarised, or translated into clinical recommendations, and unlike fabricated references such drift leaves no clean signature.

The editorial closes with the question of whether human and machine writing can still be distinguished (1). A companion question may be more tractable and more useful: even when disclosure is honest, are editorial and peer-review processes equipped to assess what AI has done to the argument? Asking authors not only whether AI was used but for what purpose, and prompting reviewers to test whether each claim remains proportionate to the design, sample, and uncertainty (3,17),

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would move the editorial task from a futile contest with detection tools toward the evaluative judgement that remains uniquely human. Such structured prompts would also protect authors who use AI fairly, including non-native English speakers, from being penalised for the wrong reasons (2). In an era of fluent machines, the most important safeguard for the scientific record may not be better detection, but better questions.

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REFERENCES

1. Uzman Ozbek S. Scientific publishing in the era of artificial intelligence. Turkish J Clin Psych. 2026;29(1):5–7. doi:10.5505/kpd.2026.94580.

2. Pratama AR. The accuracy-bias trade-offs in AI text detection tools and their impact on fairness in scholarly publication. PeerJ Comput Sci. 2025;11:e2953. doi:10.7717/peerj-cs.2953.

3. Zielinski C. Why artificial intelligence is not an author. Eur Sci Editing. 2025;51:e142904. doi:10.3897/ese.2025.e142904.

4. Elali FR, Rachid LN. AI-generated research paper fabrication and plagiarism in the scientific community. Patterns (N Y). 2023;4(3):100706. doi:10.1016/j.patter.2023.100706.

5. Peters UH, Chin-Yee B. Generalization bias in large language model summarization of scientific research. R Soc Open Sci. 2025;12(4):241776. doi:10.1098/rsos.241776.

6. Zhou K, Hwang JD, Ren X, Sap M. Relying on the unreliable: the impact of language models' reluctance to express uncertainty. In: Proceedings of the 62nd Annual Meeting of the Association for Computational Linguistics (Volume 1: Long Papers). Bangkok: Association for Computational Linguistics; 2024. p. 3623–43. doi:10.18653/v1/2024.acl-long.198.

7. Wu K, Wu E, Wei K, Zhang A, Casasola A, Nguyen T, Riantawan S, Shi P, Ho D, Zou J. An automated framework for assessing how well LLMs cite relevant medical references. Nat Commun. 2025 Apr 16;16(1):3615. doi: 10.1038/s41467-025-58551-6. PMID: 40240349; PMCID: PMC12003634.

8. Kobak D, González-Márquez R, Horvát EÁ, Lause J. Delving into LLM-assisted writing in biomedical publications through excess vocabulary. Sci Adv. 2025;11(27):eadt3813. doi:10.1126/sciadv.adt3813.

9. Padmakumar V, He H. Does writing with language models reduce content diversity? In: Proceedings of the 12th International Conference on Learning Representations (ICLR); 2024 May 7–11; Vienna, Austria. Available from: https://openreview.net/forum?id=Feiz5HtCD0

10. O'Grady C. Low-quality papers surge thanks to public data and AI. Science. 2025;388(6749):807–8. doi:10.1126/science.adz1715.

11. Maupin D, Suchak T, Barnett A, Spick M. Dramatic increases in redundant publications in the Generative AI era. BMC Med. 2026;24:29. doi:10.1186/s12916-025-04569-y.

12. Kusumegi K, Yang X, Ginsparg P, de Vaan M, Stuart T, Yin Y. Scientific production in the era of large language models. Science. 2025;390(6779):1240–3. doi:10.1126/science.adw3000.

13. Volovici V, Syn NL, Ercole A, Zhao JJ, Liu N. Steps to avoid overuse and misuse of machine learning in clinical research. Nat Med. 2022;28(10):1996–9. doi:10.1038/s41591-022-01961-6.

14. Collins GS, Moons KGM, Dhiman P, Riley RD, Beam AL, Van Calster B, Ghassemi M, Liu X, Reitsma JB, van Smeden M, Boulesteix AL, Camaradou JC, Celi LA, Denaxas S, Denniston AK, Glocker B, Golub RM, Harvey H, Heinze G, Hoffman MM, Kengne AP, Lam E, Lee N, Loder EW, Maier-Hein L, Mateen BA, McCradden MD, Oakden-Rayner L, Ordish J, Parnell R, Rose S, Singh K, Wynants L, Logullo P. TRIPOD+AI statement: updated guidance for reporting clinical prediction models that use regression or machine learning methods. BMJ. 2024 Apr 16;385:e078378. doi: 10.1136/bmj-2023-078378. Erratum in: BMJ. 2024 Apr 18;385:q902. doi: 10.1136/bmj.q902. PMID: 38626948; PMCID: PMC11019967.

15. Hosseini M, Horbach SPJM. Fighting reviewer fatigue or amplifying bias? Considerations and recommendations for use of ChatGPT and other large language models in scholarly peer review. Res Integr Peer Rev. 2023;8:4. doi:10.1186/s41073-023-00133-5.

16. Laurito W, Davis B, Grietzer P, Gavenčiak T, Böhm A, Kulveit J. AI–AI bias: large language models favor communications generated by large language models. Proc Natl Acad Sci U S A. 2025;122(31):e2415697122. doi:10.1073/pnas.2415697122.

17. Committee on Publication Ethics (COPE). Authorship and AI tools [Internet]. COPE; 2023 [cited 2026 May 28]. Available from: https://publicationethics.org/cope-position-statements/ai-author