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RESEARCH ARTICLE

EXTENDED-RELEASE CLONIDINE FOR CHRONIC IRRITABILITY AND TEMPER DYSCONTROL IN PEDIATRIC ADHD WITH COMORBID DMDD: A CASE REPORT

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ABSTRACT

Background: Attention-deficit/hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder of childhood and frequently co-occurs with chronic irritability and Disruptive Mood Dysregulation Disorder (DMDD), for which no pharmacotherapy is currently approved. Extended-release clonidine (clonidine-ER), an α2-adrenergic agonist approved for ADHD, may plausibly benefit the dysregulation of such comorbid presentations, though direct evidence in DMDD is lacking. **Case Presentation:** This is a case of a 12-year-old with a history of prematurity and periventricular leukomalacia (PVL) presenting with chronic irritability, recurrent episodes of severe temper outbursts across settings, inattention, anxiety, and depressive symptoms. Clonidine-ER oral suspension (0.1 mg/mL) was started at 0.5 mL (0.05 mg) and titrated to 3 mL (0.3 mg). At subsequent follow-up, there were improvements in behavior control, agitation, aggression, compliance with authorities, and sleep. **Discussion:** Central activation of α2-adrenergic receptors reduces noradrenergic hyperarousal and enhances prefrontal regulatory function, accounting for the beneficial effects observed in ADHD and the irritability/aggression seen in DMDD. This is consistent with clonidine's established efficacy in ADHD with comorbid behavioral disorders, although concurrent medication changes and reliance on maternal report limit causal attribution. **Conclusion:** Extended-release clonidine may improve chronic irritability and DMDD symptoms in comorbid ADHD and warrants controlled study; this observation is hypothesis-generating rather than confirmatory.

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INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder of childhood that frequently persists into adulthood (Cabral *et al*., 2020). The diagnosis is established using behavioral criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR), as no biological markers are available. Its core symptoms span two domains, inattention and hyperactivity-impulsivity, and are frequently accompanied by difficulties with emotional regulation and irritable mood (American Psychiatric Association, 2022).

Disruptive mood dysregulation disorder (DMDD) was introduced to minimize the overdiagnosis of pediatric bipolar disorder (Sun *et al*., 2026; Tapia & John, 2018) is defined by severe, recurrent temper outbursts (verbal and/or behavioral) inconsistent with developmental level, occurring at least three times weekly alongside a persistently irritable mood, for at least one year and across at least two settings (American Psychiatric Association, 2022). Notably, there is no pharmacotherapy approved specifically for DMDD, and medication has not shown clear benefit on its own; treatment therefore typically targets comorbid conditions (Tapia & John, 2018). Comorbid DMDD affects approximately 21.8% of

children with ADHD, presenting with lower self-control (Mulraney *et al*., 2015). Emotion-related impulsivity is a tendency towards disinhibited thoughts and actions during heightened emotional states and is seen across several dimensions of ADHD (Rosenthal *et al*., 2024). Impulsivity in patients with ADHD alone is expressed by restlessness and making quick decisions, while in DMDD, it appears as explosive and aggressive behavior (Waltereit *et al*., 2025).

Extended-release clonidine (clonidine-ER) is a part of a drug class called α2-adrenergic agonists, and has been approved for treatment of ADHD in children and adolescents aged 6-17 years (Croxtall, 2011; Ming *et al*., 2011). By stimulating α2-adrenergic receptors, it improves the core symptoms of ADHD (Croxtall, 2011; Ming *et al*., 2011). Beyond its core ADHD indication, clonidine-ER has shown efficacy in randomized trials both as monotherapy and as an adjunct to stimulants, and its regulation of hyperarousal and behavioral dysregulation suggests possible benefits for comorbid conditions marked by irritability associated with ADHD (Ming *et al*., 2011). There are no trials for DMDD, but clonidine-ER may be helpful in disorders with similar affective dysregulation, which is supported by the fact that it is pharmacologically similar to guanfacine (Waltereit *et al*., 2025). This case evaluates its clinical utility in addressing severe comorbid emotional dysregulation

CASE PRESENTATION: Ms. B, a now 12-year-old female, presented to a private outpatient psychiatric practice in September 2024 at the age of 10 years. She had been born prematurely with periventricular leukomalacia (PVL) and had to attend a center for developmentally disabled children from the age of 18 months to 5 years of age, followed by mainstream integration in a class setting along with a one-on-one aide, showing academic skills ranging from below average to average. Behavioral and psychotherapeutic interventions (parent management training (PMT) and individual therapy) were recommended, including earlier school-based supports, but none produced sustained improvement. At presentation, the primary concerns were chronic irritability and severe, recurrent temper outbursts, which were more pronounced at home but also reported in the school and camp settings by her classroom aide and staff. She demonstrated aggressive behavior including yelling, crying, pinching, and scratching whenever her expectations were not met. Additionally, she had depressive symptoms such as low mood, lack of motivation, hopelessness, and the inability to cope with being overwhelmed at school, with inattentive features. Her level of anxiety was assessed with the 7-item Generalized Anxiety Disorder Scale (GAD-7), and she had a total score of 11, suggesting moderate anxiety. Mental status examination revealed the patient to be oriented and appropriately aged, with irritable and oppositional behavior. The mood was depressed with an irritable affect. Her speech was at a normal rate and loudness. The thought process was linear with no suicidal ideation, and no psychotic symptoms were detected. Her vital signs were stable with a blood pressure (BP) of 115/78 mmHg and a heart rate (HR) of 77 bpm. In summary, her complex presentation of persistent inattention, chronic irritability, and severe temper outbursts spanning multiple settings for over a year warranted diagnoses of ADHD, comorbid DMDD, and Generalized Anxiety Disorder (GAD). The diagnostic process was complicated by symptom overlap with DMDD, Oppositional Defiant Disorder (ODD), and anxiety in a child with a complex neurodevelopmental history. Following her initial evaluation, pharmacological management was initiated with escitalopram 7.5 mg daily. Despite these changes, she continued to display behavioral dyscontrol. Thus, at a follow-up visit, clonidine-ER oral suspension was prescribed at 0.5 mL (0.05 mg) and was subsequently titrated to 1 mL (0.1 mg). Following a transient escalation in behavioral symptoms (including refusal to eat and sleep, biting, pinching, and spitting out medications), clonidine-ER was increased to 2 mL (0.2 mg) and subsequently to 3 mL (0.3 mg); escitalopram to 10 mg. In a follow-up of 4 months with her mother, Ms. B showed notable improvement following the increase in clonidine-ER to 3 mL (0.3 mg) (Table 1, Figure 1), with reported reduction in aggressiveness and agitation, with willingness to comply with authority figures, and improvements in her sleep; her appetite was unchanged. Her vitals remained stable, with her most recent BP of 112/72 mmHg and HR of 72. Throughout treatment, irritability was monitored using the parent-report Affective Reactivity Index (ARI-P), a six-item standardized measure scored from 0 to 12, with higher scores indicating greater irritability.

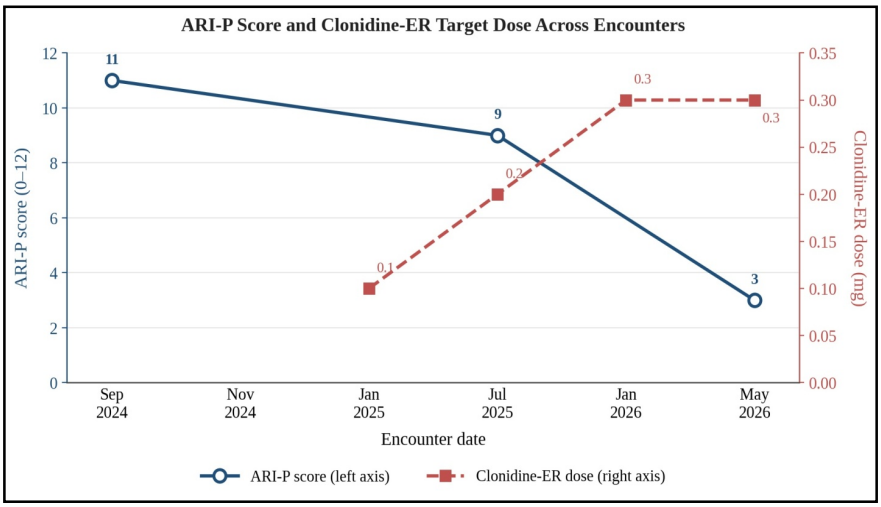
DISCUSSION

Ms. B is a 12-year-old girl with a perinatal history of prematurity and PVL, a clinical diagnosis of ADHD, GAD, and a phenotype of chronic irritability and severe, recurrent temper dyscontrol with outbursts, consistent with DMDD. As clonidine-ER is approved for ADHD but not for DMDD, this case raises the question of whether an agent chosen for its ADHD indication also benefited the emotional and behavioral dysregulation central to her presentation. PVL has been increasingly associated not only with cerebral palsy but also with ADHD, anxiety, and DMDD (Parikh *et al*., 2025). This patient was previously reported by our group with a focus on the psychiatric sequelae of PVL (Parikh *et al*., 2025); the present report extends that work by describing her response to clonidine-ER. The comorbidity of chronic irritability and ADHD is prevalent and clinically significant, with the hallmark feature of DMDD being chronic irritability. Among children from a community sample with ADHD, about 21.8% fulfilled the diagnostic criteria for DMDD compared to only 1.4% of children without ADHD (Mulraney *et al*., 2015). Among children with ADHD, DMDD shows very high overlap with ODD (89.7%) and anxiety (41%), and adds to the burden of ADHD, particularly in social functioning (Mulraney *et al*., 2015). Ms. B's presentation aligns strongly with the ADHD-irritability phenotype, characterized by severe recurrent outbursts, persistent irritability between episodes, and constant aggression towards family. Given this overlap, distinguishing DMDD from ODD was central to Ms. B's diagnosis. Per DSM-5-TR, because Ms. B met full criteria for both conditions, a diagnosis of DMDD was assigned in preference to ODD. While non-pharmacological interventions like PMT and school-based supports are considered first-line treatments for chronic irritability and DMDD, in Ms. B's case these approaches were insufficient, which helped inform the decision to pursue pharmacological management. The pharmacology of clonidine offers a plausible mechanism that makes single-agent treatment of core ADHD symptoms along with irritable-aggressive behavior of Ms. B possible. Clonidine is a centrally acting α2-adrenergic agonist of α2A, α2B, and α2C receptor subtypes, of which the first two play a crucial role in modulating attention in the prefrontal cortex (PFC) (Croxtall, 2011). It acts on the presynaptic autoreceptors in the locus coeruleus to reduce noradrenaline release in the PFC, which in

Table 1. Medication Dosing and Affective Reactivity Index (Parent-Report) Scores Across Visits

Encounter Date	Clonidine-ER Dose	Escitalopram Dose	ARI-P Score (0–12)
September 2024	NA	7.5 mg	11
November 2024	NA	7.5 mg	NA
January 2025	Initiated 0.05 → 0.1 mg	7.5 mg	NA
July 2025	0.1 → 0.2 mg	10 mg	9
January 2026	0.2 → 0.3 mg	10 mg	NA
May 2026	0.3 mg	10 mg	3

Note. ARI-P = Affective Reactivity Index, parent-reported version. Each of the six items is rated 0 (not true), 1 (somewhat true), or 2 (certainly true), for a total of 0-12; higher scores indicate greater irritability. Clonidine-ER was administered as a 0.1 mg/mL oral suspension, and escitalopram as oral tablets. NA = Not assessed at encounter.



Note. ARI-P = Affective Reactivity Index, parent-report version (score range 0–12); ER = extended-release. The left axis shows the ARI-P score, and the right axis shows the clonidine-ER dose in milligrams. Clonidine-ER values reflect the target (end-titration) dose at each encounter. Where ARI-P scores were unavailable (November 2024, January 2025, January 2026), the line was interpolated between scores to preserve a continuous trajectory.

Figure 1. Irritability Trajectory and Clonidine-ER Titration Across Treatment Encounters

turn lowers arousal while reducing hyperactivity and impulsivity. Postsynaptically, it directly stimulates the α2-adrenoreceptors to help strengthen the prefrontal working-memory networks and thus promote attentiveness (Croxtall, 2011). Modulation of noradrenergic tone along with prefrontal regulation provides a rationale for the benefits seen in states of both behavioral and emotional dyscontrol (Ming *et al*., 2011). The mechanism supporting clonidine's efficacy in ADHD is thus not only obvious in inattention but could plausibly extend to impulsiveness and reactive aggression seen in irritability/explosive-predominant presentations. Clonidine-ER is approved in the United States for ADHD in children and adolescents aged 6-17 years at doses of 0.1-0.4 mg/day, and two placebo-controlled phase III trials demonstrated significant improvement in ADHD symptoms both as monotherapy and as adjunctive therapy to stimulants (Croxtall, 2011; Ming *et al*., 2011). Clonidine has outperformed placebo in treating hyperactivity and impulsivity in children with ADHD and tic disorders, and improved ADHD, oppositional, and conduct symptoms in comorbid patients (Ming *et al*., 2011). Yet, all these trials included participants with comorbidities, making it difficult to distinguish whether the improvements were associated with specific ADHD symptoms or comorbid problems (Ming *et al*., 2011), which can also apply to this case. Clonidine, in both extended- and immediate-release forms, is well tolerated in children and adolescents. Common side effects are drowsiness, fatigue, and mild reduction in HR and BP, with electrocardiographic changes that are not clinically significant. (Croxtall, 2011; Ming *et al*., 2011). With such a side effect profile, periodic cardiac monitoring along with slow titration is advised (Ming *et al*., 2011); in Ms. B's case, her BP and HR remained relatively stable during upward titration. Her sleep improved, and her appetite remained unchanged. Given her prematurity, PVL, and concurrent medications, further observation is prudent. Certain limitations apply to this case, as it involved concurrent changes to escitalopram, so improvement cannot be definitively attributed to clonidine (Cabral *et al*., 2020), and no controlled evidence yet establishes clonidine's efficacy in DMDD. Nonetheless, the temporal correlation between clonidine-ER and improvement in Ms. B's irritability and aggressive behaviors is noteworthy and hypothesis-generating, and is in conjunction with the proposed pharmacodynamics in reducing hyperarousal of noradrenergic pathways and improving prefrontal cortical functioning, making a case for α2-agonists in affective dysregulation.

CONCLUSION

This case suggests that clonidine-ER may improve chronic irritability and temper dyscontrol in a patient with ADHD and comorbid DMDD symptoms, with medication selected for the treatment of ADHD. Though no causal relation can be established in view of the uncontrolled nature of this study design and concomitant medication changes, the temporal relationship should be noted, especially since there are no Food and Drug Administration (FDA)-approved medications for DMDD.

ETHICAL REVIEW AND CONSENT: Formal ethical approval was not required for this study under local and institutional regulations. Written informed consent was obtained from the patient's parents to publish this case. Consent for publication of this case report was obtained separately and directly from the patient's parents. They reviewed the case description and provided written informed consent for publication of her clinical details.

CONFLICT OF INTEREST STATEMENT: The authors have no conflicts of interest to disclose.

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