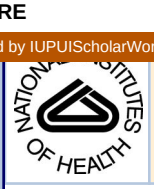

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Using Stimulants to Treat ADHD-Related Emotional Lability

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Abstract

Emotional lability, or sudden strong shifts in emotion, commonly occurs in youth with attention-deficit/hyperactivity disorder. Although these symptoms are impairing and disruptive, relatively little research has addressed their treatment, likely due to the difficulty of reliable and valid assessment. Promising signals for symptom improvement have come from recent studies using stimulants in adults, children and adolescents. Similarly, neuroimaging studies have begun to identify neurobiological mechanisms underlying stimulants' impact on emotion regulation capacities. Here, we review these recent clinical and neuroimaging findings, as well as neurocognitive models for emotional lability in ADHD, issues of relevance to prescribers and the important role of psychiatric comorbidity with treatment choices.

Keywords

Attention deficit/hyperactivity-disorder; stimulant; methylphenidate; emotional lability; mood dysregulation

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is among the most commonly diagnosed pediatric psychiatric disorders, affecting 3–10% of school age children [1]. Although the diagnostic criteria of ADHD include inattention, hyperactivity, and impulsivity, many children with ADHD also demonstrate significant levels of emotional lability [2]. The term, emotional lability, has many possible connotations, but here we are referring to sudden, strong shifts in emotions that are inappropriate to the setting or the child's developmental stage [3, 4]. Children with high levels of emotional lability have been shown to tolerate

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Compliance with Ethics Guidelines
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frustration poorly, have high levels of irritability and demonstrate frequent crying spells or tantrums [2]. Emotional lability may also be associated with an over-expression of positive emotions such as exuberance, excitability, and energy that are disproportionate to the eliciting circumstance, and can be off-putting to peers [5, 6]. These emotional reactions, both for positive and negative emotions, are typically brief in duration, lasting on the order of minutes to hours, rather than days to weeks, and thus differ from emotional lability associated with bipolar spectrum disorders, which are characterized by protracted episodes (e.g., days-weeks) of low or high emotional states. Emotional lability in ADHD may, however, overlap diagnostically with disruptive mood dysregulation (DMDD) [7] or "severe mood dysregulation," both of which are characterized by chronic temper outbursts [2, 8]. In one epidemiologic survey, 30.8% of youth with DMDD also met criteria for ADHD [9], highlighting the significant overlap between these diagnostic constructs.

The prevalence of emotional lability in children with ADHD has been examined in several clinical and population based studies. In a study of 5,326 children with ADHD, Stringaris and colleagues [10] found that parents reported impairing levels of emotional lability (termed "mood lability" in this study) in 38% of the sample. Using a clinical sample, Becker and colleagues [11] reported a slightly higher rate, with 40–49% of children with ADHD having elevated levels of parent-reported emotional symptoms (symptoms similar to emotional lability). Based on the emotional lability subscale of the Parent and Teacher Conners' ADHD rating scale, Sobanski and colleagues [2] found that in a clinical sample of 1186 children with ADHD, 25% had severe levels of emotional lability and an additional 50% had moderate levels. Differing assessment tools and study samples have likely contributed to the broad range in prevalence estimates of emotional lability in ADHD.

Impairments specifically linked to emotional lability in ADHD have been reported in several longitudinal studies [2, 12]. Barkley and colleagues [13] examined the effects of emotional lability (which the authors termed "emotional impulsiveness") on 135 children with ADHD followed into adulthood. After controlling for the influence of hyperactive/impulsive and inattentive symptoms, the study found that emotional lability independently contributed to higher rates of incarceration, poorer academic achievement, more driving accidents, and more problematic poor social and marital relations. Moreover, emotional lability was found to have a larger effect on patients' overall impairment than hyperactive/impulsive symptoms [13]. Studies have also shown that the presence of emotional lability in hyperactive children is associated with more severe ADHD symptoms, more frequent comorbid disorders, and higher rates of substance use disorders [2, 14, 15].

NEUROBIOLOGICAL MODELS OF EMOTIONAL LABILITY IN ADHD

Two competing hypotheses have been advanced to explain the neurobiological bases of emotional lability in ADHD [3, 16, 17]. (Though other hypotheses have been offered, we focus here on the two most widely cited perspectives.) The first, which we have termed the "*dyscontrol hypothesis*," attributes emotional lability in ADHD primarily to impairments in executive control [18]. With this view, emotional lability represents an impaired capacity to suppress responses triggered by emotional stimuli [19]. According to the dyscontrol hypothesis, emotional processing is largely normal in children with ADHD; however,

hyperactive children are impaired in their capacity to down-regulate, or inhibit, emotional responses and thus manifest highly emotional behaviors and reactions. This is a parsimonious hypothesis in that impairments in executive functions are well documented in ADHD [20]. The dyscontrol hypothesis can thus be folded into existing neurocognitive models of ADHD as an additional manifestation of a disorder of executive functions.

Empirical support for the dyscontrol hypothesis, however, is somewhat lacking. As Nigg and colleagues [21] have pointed out, most children with ADHD do not manifest impairment on any given executive function measure. Moreover, recent functional neuroimaging studies have examined emotional processing and lability in children with ADHD [22–24]. These studies have consisted of relatively small samples and require replication, but nonetheless, suggest that anomalies within frontolimbic circuits, which are not typically associated with executive functions, may underlie emotional lability in children with ADHD.

An opposing hypothesis, which we term the "*affectivity hypothesis*," maintains that emotional lability in children with ADHD emerges not from impaired executive functions, but rather through the more direct route of dysfunctional emotional processing itself. Emotional stimuli, according to the affectivity hypothesis, elicit inordinately strong emotional responses in children with ADHD [25]. According to the affectivity hypothesis, it is not the regulation of emotion that is impaired, but rather the production of the emotional response itself that is abnormally robust.

The affectivity hypothesis has received less research and clinical focus than the dyscontrol hypothesis perhaps because ADHD is conceptualized largely as a cognitive, or non-affective disorder. Within this paradigm, the dyscontrol hypothesis offers a more integrated explanation of emotional lability in ADHD than does the affectivity hypothesis. The dyscontrol hypothesis views emotional lability as an outgrowth of impaired executive functions, which are viewed as a component of attention, broadly defined. The dyscontrol hypothesis thus provides a heuristic model for the overt emotionality, while maintaining an emphasis on attentional impairments [18]. Conversely, the affectivity hypothesis broadens the lens into the pathophysiology of ADHD by emphasizing the importance of neurobiological systems underling emotional processing, in addition to attentional control and executive functions [22].

The central role of an attentional deficit in ADHD has been questioned by recent neuropsychological studies [21, 26] in which demonstrable, consistent impairments in sustained focus have been difficult to demonstrate, at least in the laboratory setting. This has led some authors to challenge the prevailing conceptualization of ADHD as a primarily cognitive disorder.

A parallel debate persists over how stimulants attenuate emotional lability in children with ADHD [3]. Stimulants may enhance executive control, thereby enhancing children's ability to suppress emotional responses. Conversely, stimulants may have a more direct salutary effect on emotional processing, such that emotional stimuli elicit a more modest response. Neuroimaging studies have only begun to test these competing hypotheses, but preliminary

studies suggest that stimulants may attenuate atypical emotional processing in regions associated with emotion including the amygdala and medial prefrontal cortex [3, 27] and through improvements in regions associated with inhibitory control, such as the inferior frontal gyrus [28]. Such findings are supportive of both hypotheses, suggesting that stimulants may have a direct salutary effect on emotional processing regions and regions traditionally associated with more cognitive functions, that may influence emotion regulation. However, these findings need replication with larger samples, tasks capable of probing emotional lability and placebo-controlled, longitudinal designs.

Stimulant Effects on Emotional Lability

Though debate persists over the neural mechanisms by which stimulants improve emotional lability, clinical experience has long suggested that stimulants can have positive, favorable effects on emotional lability. In Charles Bradley's historic studies of benzedrine (the first studies documenting stimulants' beneficial effects in children), he noted that the children he treated had greater "control…over the expression of their emotions" [29]. Similar anecdotal reports are well represented in literature [30, 31].

Despite anecdotal support, empirical support for stimulant effects on emotional lability is less robust. The paucity of empirical support for stimulant effects on emotional lability stands in stark contrast with the numerous, randomized clinical trials demonstrating stimulant's short term efficacy on the diagnostic symptoms of ADHD [32, 33]. This disparity in empirical support may, to some extent, reflect the lack of reliable assessment instruments for monitoring treatment related improvements in emotional lability. Whereas several well-validated, parent- and teacher-report instruments are available to assess diagnostic symptoms of ADHD, few instruments have been developed for similarly assessing emotional lability. The lack of reliable and valid instruments to assess emotional lability makes it challenging to design randomized clinical trials to test stimulant effects on emotional lability. Nonetheless, five randomized, double blind, placebo-controlled trials of stimulant treatment in children or adults with ADHD in which emotional lability (or similar constructs) was a reported outcome measure have been published (Table 1).

The largest study was a multi-center, double-blind, randomized, parallel group, placebo-controlled trial involving 363 adults with ADHD [34]. Following 24 weeks of treatment with extended release methylphenidate (MPH-ER), there was a significant reduction in emotional lability, as assessed by the emotional dysregulation items on the Wender-Reimherr Adult ADHD Scale [35]. The effect size ranged from 0.28 to 0.4, which is lower than stimulants' effect size on diagnostic ADHD symptoms (meta-analyses suggest a range of 0.6–0.8 [36, 37]), but it is still clinically significant. Other placebo-controlled trials of methylphenidate in adults with ADHD similarly report improvements in emotional lability (Table 1) with larger effect sizes of up to 0.7 [38, 39]. More recently, in a randomized, double-blind, placebo-controlled efficacy study of lisdexamfetamine (LDEX), Childress et al [40] reported a significant improvement in emotional lability in the LDEX-treated children with ADHD and high levels of emotional lability. The sample consisted of 283 children with ADHD and emotional lability, who were assessed by parent report on the Conners' ADHD rating scale [40]. Another study in children examined the

neuropsychological and clinical effects of methylphenidate in 75 boys with ADHD treated in a 12-week, placebo-controlled, double-blinded, crossover trial [41]. Significant reductions in emotional lability were noted on the emotional lability subscale of the Conners' Parent and Teacher ADHD rating scale. Effect sizes ranged from 0.42–0.46 and 0.45–0.79 for parent and teacher reports, respectively.

Stimulant-Induced Irritability

Clinical decision making in regards to emotional lability is complicated by the fact that exacerbation of irritability is a reported side effect of stimulant treatment [42, 43]. Whereas improvement in emotional lability can be expected for many patients with ADHD, in a small minority, stimulants can induce or worsen emotional lability, through increases in irritability. Prior to initiating treatment with a stimulant, careful discussion of this potential side effect is warranted. Additionally, clinicians need to consider that stimulants can have withdrawal effects as blood serum levels begin to decline. For example, some patients experience increases in irritability and poor frustration tolerance, termed "rebound irritability." These withdrawal effects need to be differentiated from stimulant-induced emotional lability. This typically can be discerned based on the timing of the symptoms – withdrawal effects occur toward the end of the stimulant's duration of action, whereas stimulant-induced emotional lability typically occurs as stimulant levels are peaking. Making this distinction has clinical importance because withdrawal effects can often be alleviated with low doses of a short-acting stimulant administered in the afternoon as the morning dose of stimulant is waning. Conversely, stimulant-induced emotional lability may require discontinuing or switching medications. Recent work suggests that the majority of parents who report that their child is unable to tolerate stimulant medications due to irritability, are misattributing rebound irritability or lack of efficacy to stimulant-induced irritability [44].

In sum, whereas stimulants' efficacy in reducing the diagnostic symptoms of ADHD has been repeatedly demonstrated, studies of stimulant effects on emotional lability, though suggestive, are far less numerous. Further replication, particularly in pediatric samples, is needed, as are long-term follow up studies to determine whether stimulant-induced reductions in emotional lability are sustained and whether the negative outcomes associated with ADHD are reduced. Of particular concern are youth whose emotional lability is refractory to stimulant treatment. Clinicians are often left treating these children with agents that have limited empirical support in this population, such as mood stabilizers and atypical antipsychotics. Developing more reliable and valid symptom scales and neuropsychological measures of emotional lability would facilitate conducting more clinical trials aimed at examining stimulant effects on emotional lability. Lastly, neurobiological studies using brain-imaging techniques can help clarify the neurobiological basis of emotional lability in ADHD with the goal of providing targets for novel treatment development. Novel interventions are particularly needed for youth struggling with emotional lability that is refractory to stimulant and other available treatments.

ADHD and Anxiety

In addition to emotional lability, many youth with ADHD also struggle with significant levels of anxiety, and between 20 – 40% have a comorbid anxiety disorder [45, 46]. A treatment concern related to emotional lability is whether children and adolescents with both ADHD and significant anxiety have a differential response to stimulants compared to individuals with ADHD alone. Furthermore, does the presence of a comorbid anxiety disorder interfere with the response of ADHD symptoms to stimulant treatment? If the presence of an anxiety disorder deters the efficacy of stimulant treatment, this would suggest that clinicians should consider a different treatment algorithm for ADHD when anxiety is present.

Anxiety associated with ADHD may emerge from an inability to function in daily life due to the social and cognitive limitations associated with ADHD. This type of anxiety may differ etiologically from the worry and phobic behaviors characteristic of a primary anxiety disorder [47]. Alternatively, emotion regulation deficits that lead to emotional lability could also predispose to anxiety disorders in a subset of youth with ADHD. If this hypothesis linking emotional lability with anxiety disorders were validated, co-occurring treatment of both disorders might be possible with stimulant treatment alone. To date, this question has not been experimentally probed. However, several studies from the late 1980s/early 1990s suggested that some children and adolescents with ADHD and comorbid anxiety disorders were less responsive to stimulant treatment than children with ADHD alone, for treatment of core AHDH symptoms [48, 49]. Children with comorbid anxiety also had higher rates of side effects, including tics, although there was no evidence that stimulants worsened symptoms of either ADHD or anxiety. Treatment of emotion-related symptoms, either anxiety or emotional lability, was not addressed in these studies.

Impairments in working memory, a subset of executive functioning, have been linked to ADHD [50]. Stimulants are believed to not only reduce hyperactivity, but also increase aspects of cognitive processing including working memory, which allows an individual to hold and manipulate information while planning and carrying out a task. Tannock and colleagues [51] demonstrated that even a single dose of MPH improved tasks of verbal–auditory working memory (digit span forward and backward) in non-anxious children with ADHD, whereas there were no beneficial effects on those with ADHD and comorbid anxiety. A more recent study showed that MPH had moderate but beneficial effects on selective aspects of verbal–auditory working memory and on a visual-spatial working memory in children with ADHD but showed no such improvements in children with ADHD and anxiety [52]. However, there was again no evidence that stimulants worsened either behavioral or cognitive responses in participants with ADHD and anxiety [52]. This is in contrast to anecdotal reports suggesting that stimulant treatment in children with both ADHD and significant anxiety may exacerbate symptoms across diagnostic domains, anxiety and ADHD.

Additional studies suggest that co-morbid anxiety neither interferes in the response to stimulants on diagnostic symptoms of ADHD, nor increases side effects. Diamond and colleagues [53] randomized 91 children with ADHD and ADHD + anxiety to an acute and clinically applicable titration trial of MPH, followed by a four-month extended trial.

Subjects with and without anxiety responded equally well to the stimulant, and there were no differences in side effects between groups. Most notably, in the Multimodal Treatment Study (MTA)[32], 579 children with ADHD were randomized to community treatment, intensive behavioral intervention, medication management, or a combination of medication management and behavioral intervention. Children with ADHD and anxiety showed an equally positive response to MPH as those children with ADHD without anxiety [32]. Children with ADHD and anxiety, however, showed a more pronounced response when treated with MPH combined with the behavioral intervention. Therefore, when treating a child with ADHD and comorbid anxiety, clinicians may consider adding a psychosocial treatment to the psychopharmacological intervention.

When treating patients with both ADHD and anxiety, a fundamental question regarding pharmacotherapy is whether the initial treatment should target ADHD or anxiety symptoms, or potentially both with a single pharmacologic agent. The American Academy of Pediatrics (AAP) Clinical Practice Guidelines for the diagnosis and treatment of ADHD[54] note that clinicians must first consider whether ADHD symptoms are the manifestation of another condition such as an anxiety disorder or if they indicate a discrete diagnosis of ADHD. A thorough clinical and development history, as well as assessment of ADHD symptoms in varied settings (e.g., home and school) is critical to making this distinction. If the diagnosis of ADHD is confirmed, the AAP guidelines note that appropriate treatment of ADHD can result in the resolution of comorbid symptoms such as anxiety [54]. Similarly, the Texas Children's Medication Algorithm Project (CMAP), a consensus conference that developed treatment algorithms for the pharmacotherapy of ADHD and comorbid conditions, suggests that if a child has ADHD and anxiety, treatment should begin with either a stimulant or atomoxetine (Strattera) [55]. The addition of a second pharmacological agent, such as an SSRI, should be considered when monotherapy does not produce adequate symptom improvement.

CONCLUSIONS

Although emotional lability is an associated feature common in ADHD, relatively little research has focused on treatments to address this impairing symptom in children and adolescents. Recent studies, some in adults, have utilized assessment tools capable of valid and reliable monitoring of emotional lability across treatment. These studies are uniformly supportive of stimulant use to treat emotional lability in ADHD, although certainly in youth, additional research to validate these findings is needed. Of note, few concerns for induction of irritability in stimulant treated youth in these studies were raised. Neurobiological models explaining how stimulant use can improve emotional lability have begun to be tested and suggest mechanisms consistent with both effects on emotion regulatory brain regions as well as general improvements in inhibitory control regions, which impact emotion as well as cognition. Future work is needed to further refine these neurobiological mechanisms, using larger samples and placebo-controlled designs. In addition, while stimulant treatments for emotional lability appear promising, there remains a need to address treatment strategies for stimulant refractory youth, to address the issue of treating emotional lability outside of the context of ADHD and to identify evidence-based practices for augmentation agents for partial responders. Finally, the mechanistic relationship with comorbidities (e.g., emotional

lability and anxiety disorders) needs further empirical exploration. If a causal link between 2 symptom clusters were to be identified, such a link would drive treatment decisions, both toward and away from stimulant use.

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TABLE 1

Double-blind Randomized Placebo-controlled Clinical Trials Measuring the Efficacy of Psychostimulants in Treating Emotional Dysregulation in ADHD

Study (Year)	Participants: (N)	Design (Duration)	Medication (dose)[a]	Outcome Measure	Treatment Response
Adults					
Reimherr et al. (2007)	(47) Adults w/ primary ADHD	Crossover, placebo-controlled trial (Each arm: 4 weeks)	OROS Methylphenidate (0.75 mg/kg)	Wender- Reimherr Adult ADHD Scale, emotional dysregulation items	OROS Methylphenidate reduced emotional dysregulation (effect size: 0.7)
Rösler et al. (2010)	(363) Adults w/ primary ADHD	Multi-center, parallel group, placebo- controlled trial (24 weeks)	Methylphenidate-ER (0.55 mg/kg)	Wender- Reimherr Adult ADHD Scale, emotional dysregulation items	Methylphenidate – ER reduced emotional lability (effect size: 0.28–0.4)
Marchant et al. (2011)	(90) ADHD alone: N=21; ADHD + ED[b]: N=28; ADHD + ODD[c]: N=9; ADHD + ED + ODD: N=32	Cross-over, placebo-controlled trial of transdermal MPH (each arm: 4 weeks)	Transdermal Methylphenidate Patch (23.8 mg ± 6.6 mg)	Wender- Reimherr Adult ADHD Scale, emotional dysregulation items	All groups showed benefit on psychostimulants; trend for those with ED to demonstrate greatest improvement
Children					
Childress et al. (2011)	(283) 6–12 years with primary ADHD; 179 with prominent emotional lability at baseline	Multi-center, parallel group, placebo- controlled trial (4 weeks total)	Lisdexamfetamine (LDX) (30, 50, or 70 mg/day)	Conners Parent Rating Scale of emotional lability (angry, loss of temper, and irritability)	Lisdexamfetamine significantly reduced emotional dysregulation in participants with *prominent* emotional lability but not in those with *low* emotional lability
Coghill et al. (2007)	(75) 7–15 boys with ADHD (76% with comorbid diagnoses; 41% with ODD & 28% with Conduct Disorder	Cross-over, placebo-controlled trial (12 weeks total)	Methylphenidate 0.3 vs. 0.6 mg/kg/dose BID vs. placebo	Conners Parent and Teacher Rating Scales of emotional lability	Low and high doses of Methylphenidate significantly reduced emotional lability in parent and teacher reports. Low dose (effect-size parent: 0.46; teacher: 0.45). High dose (effect size parent: 0.42; teacher: 0.79)

[a] Mean Dosage

[b] ED: Emotional dysregulation

[c] ODD: Oppositional Defiant Disorder