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Review

Pharmacological treatment strategies for emotional lability in adults with attention-deficit/hyperactivity disorder: focus on the Conners' Adult ADHD Rating Scales

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SUMMARY

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental condition starting in childhood and presenting with symptoms of inattention and impulsivity/hyperactivity which may severely impair an individual's functioning. Emotional lability (EL) is a symptom dimension characterized by rapidly shifting mood and affect which can be found in several mental disorders, including ADHD. EL is associated with more severe ADHD symptoms, more frequent comorbid disorders, and adverse outcomes. The present narrative review aimed to summarize the efficacy of pharmacological treatments on EL measured using the Conners' Adult ADHD Rating Scales (CAARS) - Impulsivity/Emotional Lability subscale in adults with ADHD. Evidence has shown inconsistent results. Future research should standardize outcome measures and investigate the role of non-pharmacological treatment.

Key words: attention-deficit, hyperactivity, Conners, emotional lability, methylphenidate

Introduction

Attention-deficit/hyperactivity disorder

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental condition characterized by age-inappropriate levels of inattention and/or hyperactivity-impulsivity interfering with normal development, or functioning, of a person [1]. The disorder starts during childhood and affects around 5% of children and adolescents and 2.8% of adults worldwide [2]. However, the real prevalence of adult ADHD may be underestimated because the disorder in the adult population is often underdiagnosed or misdiagnosed [3]. Rates of ADHD show prominent sex differences but change throughout development in both clinical and community settings [4,5]. Typically, in child and adolescent clinics, around 80% of ADHD cases are male, whereas in adult clinics, the proportion of males is closer to 50% [4]. One possible reason is the fact that males with ADHD typically present with greater hyperactivity-impulsivity levels than females, allowing an earlier recognition of the condition; conversely, girls predominantly display inattentive symptoms and less overt disruptive behaviours [6].

People with ADHD frequently present comorbid mental disorders, which vary in different age groups. Children with ADHD are frequently affected by oppositional defiant disorder and conduct disorder; conversely, substance use disorders (SUD), mood and anxiety disorders, antisocial personality disorder, as well as sleep disorders, are more common in adolescence and adulthood [7]. The core symptoms and the presence of comorbidities worsen the functional outcome of people with ADHD compared to the general population. For instance, people with ADHD show difficulties in relationship with peers and relatives, worse quality of life, impaired

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school performance and lower education attainment, reduced job performance, higher rates of unemployment, and increased emotional problems [8].

The most widely used medications for ADHD are two psychostimulants, namely methylphenidate and the amphetamines. Second-line medications include atomoxetine, guanfacine, and clonidine, prescribed after lack of response, intolerance, or contraindication to the psychostimulants. Meta-analytical evidence supports the short-term efficacy of pharmacological treatments for ADHD, but evidence for the long-term efficacy of medications is less clear. Behavioral therapies, such as parent training or social skills training, are considered the standard add-on to medication treatment for severe presentations at any age. Additionally, they are suggested as first-line treatment for very young children and for adult with mild to moderate symptoms. A recent meta-analysis highlighted the positive effect of psychological interventions on ADHD cognitive symptomatology [9]. Other non-pharmacological interventions such as cognitive training and neurofeedback are probably not efficacious [8].

In Europe, guidelines for the diagnosis and treatment of adult ADHD have been recently published [10,11]. European guidelines suggest a careful planning of the transition from childcare to adult services, and a re-evaluation of the clinical characteristics of the patient to assess eventual changes in therapeutic needs of the ADHD patient [10].

To date, no national guidelines for adult ADHD have been published [12,13]. As for the pharmacological treatment, methylphenidate has become a label drug only in 2007 by implementation of an Italian register. For the treatment of ADHD diagnosed in adulthood, atomoxetine is the only medication authorized and refunded, Methylphenidate is label drug only for people who have been diagnosed with ADHD before the age of 18 years and can be used as maintenance therapy until 25 years of age to the utmost. Amphetamines are not available on the Italian territory [12,13].

Emotional lability

Besides the core symptoms of inattention and hyperactivity/impulsivity, several authors have drawn attention to the presence of emotional symptoms in individuals with ADHD [14,15]. Barkley's theoretical model has underlined the importance of emotional self-regulation as a core symptom of ADHD [16]. Wender has proposed to include emotional dysregulation among the Utah diagnostic criteria for adult ADHD [17]. According to the Wender's construct, emotional dysregulation comprises three domains: temper control, emotional over-reactivity, and emotional lability (EL). The term "deficient emotional self-regulation" has been proposed to refer to being quick to get angry or become upset, easily frustrated, overreact emotionally, easily excited, lose temper, argue with others, being touchy or easily annoyed by others and angry or resentful [18]. On the other hand, Brown's model proposes the domain "affective interference" [19]. Finally, Conners' model adds EL as an emotional feature of ADHD [20]. All these concepts are widely overlapping and correlated.

In the present review, the term EL is used as a symptom dimension characterized by irritability, unpredictable moods, setting off easily, hot temper, low frustration tolerance and difficulties in anger management, in line with Conners' model [20]. Clinical and population-based studies have estimated that up to 50% of individuals with ADHD may present with symptoms of EL [21]. Indeed, people with ADHD show poor tolerance to frustration, high levels of irritability and demonstrate frequent crying spells or tantrums [21]. EL may also be associated with an over-expression of positive emotions such as exuberance, excitability, and energy that may be disproportionate to the circumstances [22].

EL is found not only in ADHD, but also in several other psychiatric conditions, such as borderline personality disorder or bipolar spectrum disorders. However, in ADHD, the duration of both positive and negative emotional reactions is typically brief, lasting on the order of minutes to hours, differently from the EL associated with bipolar spectrum disorders, which is characterized by long-lasting episodes of low or high mood states.

Clinical correlates of emotional lability in ADHD

EL is a major cause of morbidity and psychosocial impairment. Impairments specifically linked to EL in ADHD have been reported in several longitudinal studies [21,23]. Barkley and colleagues [24] found that EL independently contributed to higher rates of incarceration, poorer academic achievement, more driving accidents, and more problematic poor social and marital relations, after controlling for the influence of hyperactive/impulsive and inattentive symptoms. Moreover, EL was found to have a larger effect on patients' overall impairment than hyperactive/impulsive symptoms [24]. Studies have also shown that the presence of EL in hyperactive children is associated with more severe ADHD symptoms, more frequent comorbid disorders, and higher rates of substance use disorders [21]. Also, EL has been associated with greater ADHD functional impairment, lower quality of life, and ADHD persistence. Of note, these studies have reported that EL explains part of the functional impairment in ADHD that is not accounted by the core symptoms of inattention and hyperactivity/impulsivity [14]. EL has also been shown to predict suicidal ideation and non-suicidal self-injury and can thus represent a significant challenge for clinicians and caregivers [25].

Measuring emotional lability in ADHD

Different scales have been used in research to evaluate EL in people with ADHD, e.g. the Emotional Dysregulation Scale (EDS) derived from Wender–Reimherr Adult Attention Deficit Disorder Scale (WRAADDS) [26], the Emotional Impulsiveness Scale (EIS) [24], the Rating Scale ADHD Training Evaluation–Self Report (RATE-S) [27], the Affective Lability Scale (ALS) [28], the Behavior Rating Inventory of Executive Function (BRIEF-A) [29], or the Brown Attention-Deficit Disorder Rating Scales (ADD) [19]. Nonetheless, most of these scales include symptoms that are not specific to EL.

In the present review, we will focus on the studies which have assessed EL using the Conners' Adult ADHD Rating Scales (CAARS) [20,30]. The CAARS represent one of the major psychological tests employed to measure adult ADHD for research and clinical purposes. Designed to assess ADHD in individuals aged 18 years and older, the CAARS are composed of several scales (short, long, screener) in both self-report and observer-report forms. The self-report long version includes 66 items divided in the following subscales: inattention/memory problems, hyperactivity/restlessness, impulsivity/emotional lability, problems with self-concept, DSM-IV inattentive symptoms, DSM-IV hyperactive–impulsive symptoms, DSM-IV ADHD symptoms total and ADHD index. Individuals rate themselves on a 4-point Likert-type scale ranging from 0 (not at all or never) to 3 (very much, very frequently). In the following sections, we will analyze the domain of Impulsivity/Emotional Lability subscale (12 items) as the target outcome for pharmacological treatments.

Aim of the study

Two relevant meta-analyses have recently investigated the effectiveness of pharmacological treatments on EL and related dimensions in people with ADHD. In 2017, Moukhtarian and colleagues [31] included nine randomized, double-blind, placebo-controlled trials of stimulants and atomoxetine in adults aged 18-60 years, with any mental health diagnosis characterized by emotional or mood instability, with at least one outcome measure of EL. EL outcomes showed moderate but definite effects (SMD = -0.41, 95% CI = -0.57 to -0.25). In the included studies, EL was measured using the WRAADDS-EDS or the BRIEF-A-BRI, emotional control subscales. More recently, Lenzi et al. [32] included 21 trials in a meta-analysis on emotional dysregulation, finding small-to-moderate effects for methylphenidate (n = 13, SMD = 0.34, 95% CI = 0.23–0.45), atomoxetine (n = 5, SMD = 0.24, 95% CI = 0.15–0.34), and lisdexamfetamine (n = 3, SMD = 0.50, 95% CI = 0.21–0.8). Emotional dysregulation was measured using a variety of scales.

Given that CAARS has been under researched, while being useful in measuring EL in adult ADHD, the present narrative review will summarize the current evidence on pharmacological treatment strategies for this symptom dimension as measured using the Impulsivity/Emotional Lability subscale of the CAARS.

Efficacy of pharmacological treatment of emotional lability in adults with ADHD measured using the CAARS Impulsivity/Emotional Lability subscale

Methylphenidate (MPH)

In 2007, a double-blind placebo-controlled crossover trial [33] tested the efficacy of a new biphasic multilayer-release (MLR) methylphenidate formulation. Fifty participants were randomly assigned to MLR methylphenidate or placebo. Patients were titrated to optimal effect over 1 to 3 weeks followed by 2 weeks of treatment on a stable dose. Thirty-nine participants were included in a per-protocol analysis. No significant difference was observed with MLR methylphenidate over placebo in the CAARS Impulsivity/Emotional Lability subscale, both self-report and observer-report.

In a large trial by Medori et al. [34], 401 adults with ADHD were randomly assigned to receive prolonged-release osmotic release oral system (OROS) methylphenidate (18 mg, 36 mg, or 72 mg/day) or placebo for 5 weeks. Analyses conducted on the difference between baseline and double-blind endpoint showed significant improvement in the 18 mg/day and 72 mg/day goups, compared to placebo ($p = 0.49$ and $p < 0.001$, respectively) in the Impulsivity/Emotional Lability subscale of CAARS. No significant differences were found between OROS methylphenidate 36 mg daily and placebo.

The COMPAS [35] was the first multimodal, multicenter randomized clinical trial to examine the efficacy of nonpharmacological treatments (cognitive behavioral group psychotherapy [GPT] vs. individual clinical management [CM]) in combination with methylphenidate (sustained release; initial dosage of 10 mg/d; titration with 10 mg/week over 6 weeks up to 60 mg/d; individual dosage to a maximum daily dosage of 1.3 mg/kg of body weight) or placebo. Sessions of GPT and CM were held weekly for the first 12 weeks and monthly thereafter (9 months). Patients received either methylphenidate or placebo for 1 year. The CAARS ratings revealed comparable results in total and subscale scores, with no difference between GPT and CM [35].

Rösler and colleagues [36] have conducted a 24-week controlled trial involving 363 adults with ADHD. Participants received a treatment with extended-release methylphenidate (MPH-ER), which comprised of 50% immediate-release MPH and 50% extended-release MPH with a duration of action of about 8 h. EL decreased

significantly by week 5 in the MPH-ER group, and improvement continued through week 24 with an effect size for decrease in EL of 0.37 among the intent-to-treat population.

Wigal et al. [37] assessed the onset and duration of efficacy of multilayer-release methylphenidate (PRC-063) over 16 h compared with placebo in adults with ADHD using the simulated adult workplace environment. After dose-optimization with PRC-063, participants entered a double-blind, placebo-controlled, crossover phase. Of the 59 randomized participants, 45 participants completed the study. No significant differences were found in the CAARS Impulsivity/Emotional Lability scale between PRC-063 and placebo (p = 0.32).

Lisdexamfetamine dimesylate

DuPaul and colleagues [38] tested the efficacy of lisdexamfetamine dimesylate (LDX) in 24 college students with ADHD over five weekly phases (no-drug baseline, placebo, 30-, 50-, and 70-mg LDX per day) in a double-blind, placebo-controlled, crossover study. No significant main effect for dosage was found for CAARS Impulsivity/Emotional Lability subscale.

Atomoxetine

A recently published meta-analysis [39] included 15 published RCTs on the efficacy of atomoxetine in adult ADHD. Although 8 of them adopted the CAARS as outcome measure, none have reported the specific results for the Impulsivity/Emotional Lability subscale.

Duloxetine

In a 6-week double-blind trial [40], 30 adults with ADHD received placebo or duloxetine 60 mg daily. Scores on the subscle of CAARS Impulsivity/Emotional Lability decreased of around 48% after treatment, representing the domain of CAARS with the greatest improvement, vs an increase of 7.7% in the placebo group.

Discussion

The prevalence of EL is much higher in subjects with ADHD than the general population, regardless of age, and some authors have suggested that EL may be considered a diagnostic symptom of ADHD. Longitudinal studies have shown that EL may have a severe impact on the course and functional outcomes of people with ADHD. Therefore, it appears fundamental to investigate the effectiveness of commonly used treatment strategies on this symptom dimension.

Charles Bradley's historic studies (the first studies documenting stimulants' beneficial effects in children) reported that children treated with benzedrine had greater "control… over the expression of their emotions" [41]. Besides anecdotical evidence, research has shown that both stimulants and non-stimulants may improve EL in ADHD, although with small-to-medium effect sizes, generally lower than the effect sizes found in meta-analyses on core symptoms (i.e., inattention, hyperactivity and impulsivity) [31,32]. However, so far, meta-analytical evidence has not given a specific focus to the Conners' Adult ADHD Rating Scales (CAARS) for the outcome evaluation.

In the present review, we narratively synthesized the results of RCTs which have adopted the Impulsivity/Emotional Lability subscale of the CAARS among outcome tools. We found only a few trials on stimulants (methylphenidate and lisdexamfetamine dimesylate) and one study on duloxetine. Findings are inconsistent.

Among stimulants, only one large study [36] reported significant improvement in the selected outcome after treatment with extended-release methylphenidate. Potential reasons may rely in the formulation of the medication as well as is the long duration of the study (24 weeks) compared with the others. Stimulants may act in a double manner. On the one hand, they may enhance executive control, thereby indirectly improving children's ability to suppress emotional responses; on the other hand, they may have a more direct effect on emotional processing, such that emotional stimuli elicit a more modest response. Indeed, neuroimaging studies have preliminary suggested that stimulants may attenuate atypical emotional processing in regions associated with emotion including the amygdala and medial prefrontal cortex and through improvements in regions associated with inhibitory control, such as the inferior frontal gyrus [42,43]. 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 [44]. Interestingly, it has been recently shown that cognitive energetic processes are linked to EL in ADHD [45]. According to cognitive energetic models, the quality of information processing is dependent of the individual's energetic state, which is determined by arousal, activation, and effort[46]. Cognitive energetic processes may explain a proportion of the overlap between EL, negative emotional expressions and ADHD symptoms in children [45]. Duloxetine may also represent a promising treatment for EL in ADHD, although results are based on one trial only [40].

The present review has several limitations. First, it is circumscribed to pharmacological treatments, whereas psychosocial treatments may represent valid complementary strategies, particularly in the Italian territory where the use of stimulants is strictly regulated. Additionally, we included only studies which assessed EL using the CAARS Impulsivity/Emotional Lability subscale. Therefore, the results here presented cannot be generalized to all RCTs assessing therapies for emotional

dysregulation symptoms in ADHD. It is worth mentioning that results on the efficacy were non-significant for the large majority of the study, in contrast with meta-analytical evidence which have included RCTs reporting different outcome measures. This might be related to the psychometric properties of the tool, which have been discussed in a recent paper [47], showing a wide range of internal consistency estimates and discriminant validity estimates in the same range as convergent validity estimates. Of note, the heterogeneity of scales used in research on EL and ADHD may reflect the lack of specific and reliable assessment instruments for monitoring treatment-related improvements in EL, which makes it challenging to design RCTs to test the effects of medications on EL and draw reliable conclusions on their efficacy. Another important limitation of our review is the related to the lack of a systematic search; thus, the present paper may have potentially missed relevant studies in the field.

In conclusion, EL is an important symptom dimension which may be associated with clinical and psychosocial outcomes in ADHD. Studies adopting CAARS as an outcome tool have shown limited evidence of efficacy of pharmacological treatments. Given the inconsistent definition of EL and the heterogeneity of outcome tools, guidance on treating EL in ADHD is currently limited. Future research should focus on investigating the effectiveness on non-pharmacological treatment strategies, analyzing EL treatment outside the context of a symptom dimension of ADHD, achieving agreement on EL definition, and consequently adopting standardized measures for EL.

Conflict of interest statement

The authors declare that this research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Authors' contributions

Conceptualization, EA and LF-P; methodology, EA and LF-P; writing-original draft, LF-P; writing-review and editing, EA. All authors have read and agreed to the published version of the manuscript.

Ethical consideration

Not applicable.

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