



Psychosocial Treatments Targeting Anxiety and Depression in Adolescents and Adults on the Autism Spectrum: Review of the Latest Research and Recommended Future Directions

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Abstract

Purpose of Review This synthesis of treatment research related to anxiety and depression in adolescents and adults with autism spectrum disorder (ASD) focuses on the scientific support for various forms of psychosocial interventions, useful adaptations to standard interventions, and engagement of candidate therapeutic mechanisms.

Recent Findings There is considerable evidence for the efficacy of cognitive-behavioral therapy (CBT) to treat co-occurring problems with anxiety, but there has been relatively little research on treatment of co-occurring depression. Multiple mechanisms of treatment effect have been proposed, but there has been little demonstration of target engagement via experimental therapeutics.

Summary Comorbidity between ASD and anxiety and/or mood problems is common. Although there is evidence for the use of CBT for anxiety, little work has addressed how to effectively treat depression. There is emerging support for alternative treatment approaches, such as mindfulness-based interventions. We encourage rigorous, collaborative approaches to identify and manipulate putative mechanisms of change.

Keywords Autism · Intervention · Anxiety · Depression · Cognitive-behavioral therapy (CBT) · Mindfulness

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental condition that affects approximately 1 in 59 children in the

USA [1]. It is widely accepted that co-occurring psychiatric disorders are common in autistic adolescents and adults. One in two people on the spectrum is affected by a co-occurring anxiety or depressive disorder [2–4]. Among people with ASD who do not also have intellectual disability, anxiety and depression are among the most common co-occurring mental health problems.

Problems with anxiety and depression confer unique impairment, above and beyond what is associated with ASD. Among neurotypical adults, both anxiety and depression have been found to predict poorer quality of life [5]. Similarly, these co-occurring conditions have been associated with increased service use, caregiver burden, and decreased quality of life in ASD [6–8]. In adults with ASD, there is evidence that ASD severity moderates impact of anxiety such that anxiety has a greater adverse impact on outcome among people who are less severely affected by autism [8]. This finding, however, must be interpreted with some caution as it can be difficult to assess internalizing problems, both anxiety and depression, in people who are

This article is part of the Topical Collection on *Autism Spectrum Disorders: Treatment, Services, Outcomes, and Community Functioning in Adolescents and Adults*

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lower functioning or minimally verbal. Relative to anxiety in autism, there is little research on the experience or impact of depression.

Although there has been relatively little longitudinal research, prospective studies have shown that social communication impairment, a hallmark feature of ASD, predicts heightened risk of social anxiety longitudinally among typically developing children [9]. One of the few longitudinal studies with children with ASD found that anxiety predicted social communication impairment; however, social communication deficits did not increase risk for anxiety [10]. Much remains to be learned about the potentially transactional relationship between core features of ASD and anxiety and mood disturbance.

Given the frequency with which anxiety and depression co-occur in ASD, in conjunction with their unique impact on functioning, adult outcome, and quality of life, it is critical to consider how to best prevent and treat these disorders among adolescents and adults with ASD. The past 20 years has seen rapid proliferation of scientific and clinical interest in anxiety in autism, as exemplified by an approximately 30-fold increase in rate of publication on this topic [11]. Although research on depression has proceeded at a slower rate, there has been heightened basic and clinical research in this area as well [12]. At this juncture, there is a suitable research base to guide evidence-based care decisions related to treatment of anxiety and depression in adolescents and adults with ASD (Fig. 1).

Treatment of Anxiety and Depression ASD

Anxiety disorders are the most prevalent mental health condition among children and adolescents, and they are associated with significant impairment in family, social, academic, and adaptive functioning [13]. Cognitive-

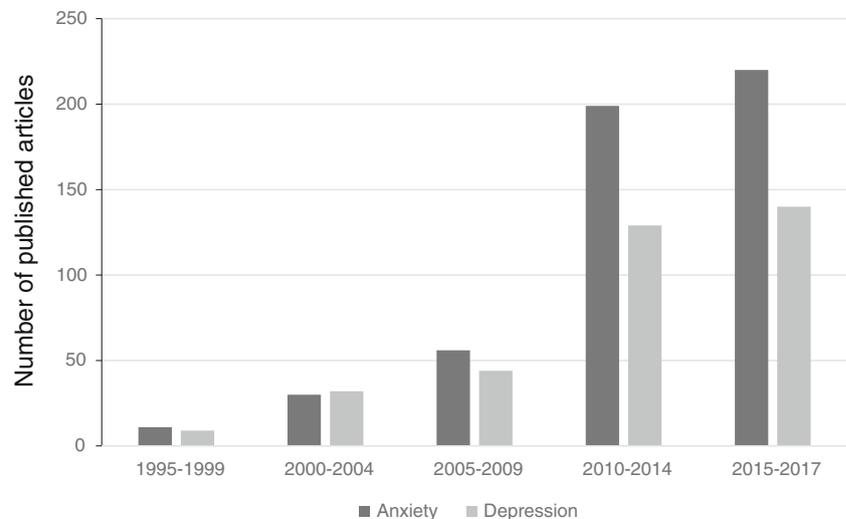
behavioral therapy (CBT), which involves exposure, modeling, and parental involvement, has been labeled a “well-established” evidence-based treatment for anxiety disorders among adolescents and adults [13]. Among adults, depression is the most prevalent mental health condition worldwide [14], and a recent meta-analytic review suggests that individuals with ASD are four times more likely to experience depression in their lifetimes than typically developing counterparts [12]. First onset of depressive disorder is often during adolescence and it is associated with significant impairment in global life domains [15]. Among adolescents in the general population, CBT and interpersonal therapy (IPT) have been deemed “well-established” evidence-based treatments for depression with medium effect size response rates, as well as “probably efficacious” for children [16].

Cognitive-Behavioral Therapy

The majority of existing research on co-occurring psychiatric conditions in ASD has focused upon anxiety reduction among higher functioning children and adolescents with ASD. To date, more than 10 randomized controlled trials (RCTs) of adapted CBT for anxiety have been published. CBT studies have been conducted in group [17], individual [18, 19], and mixed group/individual [20] modalities. Several systematic reviews and meta-analyses have recently been conducted [21–25], generally finding moderate to large treatment effects [21, 23, 24].

In comparison to anxiety, there has been far less research on the psychosocial treatment of depression in ASD. A recent meta-analysis of RCTs examining CBT use in ASD found that most studies only emphasized anxiety [26]. The few trials that targeted a problem other than anxiety involved treatment of anger, emotion dysregulation, insomnia, or OCD; none explicitly targeted depression [26]. Although it is often assumed

Fig. 1 Number of research articles published on treatment of anxiety or depression in 5-year increments (last block is 3-year increment). Articles were retrieved from PUBMED. Search terms were restricted to title or abstract (autism or Asperger and treatment and “anxiety”/“depression”). Articles that studies both anxiety and depression were included in each domain respectively



that CBT (with more general, rather than anxiety-specific, protocols) would also be beneficial to treat depression in ASD, there is limited direct evidence for this assumption. Interestingly, a recent quasi-experimental design of group CBT with adolescents and young adults with ASD found that depression improved whereas anxiety did not [27].

Mindfulness and Non-CBT Psychosocial Approaches

More recently, non-CBT approaches, such as mindfulness-based intervention (MBI), have been applied successfully with clients with ASD, with preliminary evidence suggesting that MBI has the potential to reduce the impact of co-occurring anxiety and depression [28•]. There is a sizable body of research suggesting that improved emotion regulation and increased emotional awareness are primary treatment mechanisms in MBI [29]. These mechanisms provide an attractive alternative for autistic adolescents and adults, as high-level cognitive strategies taught in CBT can be difficult to deploy during times of high distress. There is growing interest in utilizing and adapting MBI for adolescents and adults with ASD [28•, 30].

To our knowledge, only one RCT utilizing MBI with adults with ASD has been published. Spek and colleagues [31] utilized modified MBI group treatment with 42 adults with comorbid depressive and anxiety symptoms, and results included large effect decreases in anxiety and depression symptoms. Similarly, in a second open trial with 50 adults with ASD, reductions in anxiety and depression were observed and maintained at the 9-week follow-up [32]. Sizoo and Kuiper utilized a group-based MBI with autistic adults and found large effects in anxiety reduction and depression [33]. Of note, they used an unmatched and uncontrolled design, in which adults with ASD completed either group CBT or a group MBI program, and both were found to reduce depression with no significant difference between the conditions [33]. To date, there are no studies that utilize an individual MBI modality for adults with ASD that targets depression or anxiety. However, Conner and White conducted an open trial with an MBI that utilized individual therapy to target emotion dysregulation broadly; results supported both feasibility and preliminary efficacy [30].

MBI research with adolescents with ASD has primarily involved parent training to reduce problem behaviors (e.g., aggression) [34–41]. These studies support the utility of both group and individual parent-assisted MBI with children and adolescents with ASD. Much of this research reports promising results with respect to reduction of aggression and problem behaviors, but none have studied co-occurring depression and anxiety as primary outcomes [35].

Other psychosocial interventions targeting core ASD symptomatology have demonstrated indirect effects upon depression and anxiety symptoms. For example, the PEERS social skills group program for adolescents and young adults

[42] has been shown to reduce depression and suicidality among teens [43] and social anxiety symptoms have likewise decreased significantly for young adults following PEERS [44]. Beyond psychosocial treatments, medication utilization for anxiety and depression symptoms is high in this population, especially among those with co-occurring ID. One survey found that at least 50% of adolescents and adults with ASD were prescribed antidepressants [45]. In a recent evaluation of Medicaid claims data, adults with ASD who had depression or anxiety were actually less likely to receive psychosocial intervention than adults with depression or anxiety without ASD, yet more than twice as likely to be on multiple psychotropic medications [46]. This is noteworthy given the limited research base on their impact, and also given there are no FDA-approved medications to treat anxiety and depression in ASD [47].

Common Treatment Modifications for Adolescents and Adults on the Autism Spectrum

Regardless of the intervention approach, it is generally agreed that some adaptation is helpful to make the content more relevant and digestible for clients with ASD. It is our understanding that there are more similarities than differences across studies and protocols, with respect to content and delivery adaptations. Such adaptations include heightened parental involvement, increased use of structure and visuals (worksheets, role plays, visual cues, and prompts, etc.), concrete examples and language, and increased psychoeducation on emotions and anxiety. Moree and Davis [48] identified four common modifications for CBT with children with ASD and co-occurring anxiety: (1) concrete tools and supports; (2) use of hierarchies that also address ASD symptoms; (3) incorporation of special interests; and (4) parental involvement.

Clinicians may choose to weight some CBT-based therapy more heavily on the behavioral side, particularly for those individuals with reduced verbal competency, and those who struggle with cognitive flexibility or generalizing learned skills across situations. In such scenarios, behavioral strategies may be more valuable than cognitive approaches, and might focus on building adaptive behaviors, structuring time and providing accountability, identifying and working toward life goals, increasing social opportunities and other rewards, and to some extent supporting healthy behaviors relevant to sleep, exercise, and nutrition. Such foci may be particularly helpful for emerging adults or transition-age youth moving from highly structured education systems, often with services/supports, to minimally structured, experientially impoverished lives essentially “overnight” [49].

Common modifications for MBI with adolescents and adults with ASD include the elimination of metaphors and poetry and changing lengths of meditations to account for slow processing and attentional capacity [30–32]. Many

interventions also incorporate an emphasis on social problems and other core ASD characteristics while targeting the reduction of anxiety or depressive symptoms. Core symptoms of ASD have been included with anxiety symptoms on symptom hierarchies [19], and group-based skills training and practice can be used to leverage heightened social interest as well as anxiety reduction [20]. While parental involvement in treatment typically decreases from childhood to adolescence, individuals with ASD are likely to depend more upon parents or other caregivers into adulthood. Therefore, including parents and caregivers in interventions has been recommended as a means to increase generalizability of core concepts taught in the therapy session [50]. Additional time to structure and plan practice tasks is often warranted to combat executive functioning deficits (e.g., planning, time management). For instance, a therapist might, in collaboration with the client and his parents, make a concrete plan for completing homework and provide a structured worksheet to complete and return at the next session. We summarize the most commonly seen adaptations in Table 1.

Identifying and Engaging Common Factors

Despite the growing body of research demonstrating the efficacy of psychosocial treatment for anxiety and depression in people with ASD, this research base has generally adopted a fairly traditional focus on clinical response, rather than engagement of targeted mechanisms of action. Owing, in part, to an appreciation of the lack of clear boundaries distinguishing different psychiatric disorders, intervention research has experienced a shift toward identification of mechanisms underlying psychopathology,

which may or may not be tethered to particular diagnoses. Consistent with this shift in thinking about psychopathology is a call from the National Institute of Mental Health for experimental therapeutics approaches that involve identification of the candidate mechanism before evaluation of clinical impact. Such target-based approaches are thought to promote a richer understanding of mediators and moderators of treatment change, as well as greater transdiagnostic portability [51]. To inform future treatment research in this area, we pull from the extant treatment literature to propose specific constructs, or mechanisms of action, that warrant consideration (Fig. 2). These candidate mechanisms are couched in the Research Domain Criteria (RDoC) matrix, espoused by the National Institute of Mental Health [52]. RDoC provides a framework for the consideration of psychological constructs that may be informative across psychiatric disorders, broken down into the following five major domains: cognitive systems; negative valence systems (related to aversive situations including fear, anxiety, and loss); positive valence systems (related to motivation, reward seeking, etc.); systems for social processes; and arousal/regulatory systems. Although RDoC emphasizes the integration of multiple levels of information including genetics, neural functioning, and physiology, below we primarily focus on behavioral research and emphasize components of the RDoC matrix that might be most relevant to anxiety and depression in ASD.

Cognitive Systems

Several constructs within the cognitive systems domain of RDoC have been considered in anxiety and depression

Table 1 Common modifications when treating anxiety or depression in clients with ASD

Domain	Modification
Content	<p>Focus on positive character attributes of client during treatment, in consideration of chronic nature of ASD</p> <p>Address ASD core symptoms/deficits during treatment (e.g., in developing exposure hierarchy, targeting social problems)</p> <p>Use supplemental group training for additional skills practice/modeling</p> <p>Use of peers or similar-age others for modeling, and skills practice</p> <p>Increased focus on developing emotional awareness/insight</p>
Delivery	<p>Increased reliance on parents (throughout treatment, and with adolescent/young adult clients)</p> <p>Psychoeducation on relationship between autism and anxiety/depression</p> <p>Slower pace of treatment (to allow for processing time and repetitive practice)</p> <p>Inclusion of special interests in treatment (e.g., to teach and incentivize)</p> <p>Eliminate or reduce use of metaphors (for some clients)</p> <p>Highly structured sessions, clear expectations</p> <p>Use of visuals for teaching and support during session (e.g., handouts)</p> <p>Additional time for in-session practice and planning at-home practices</p>

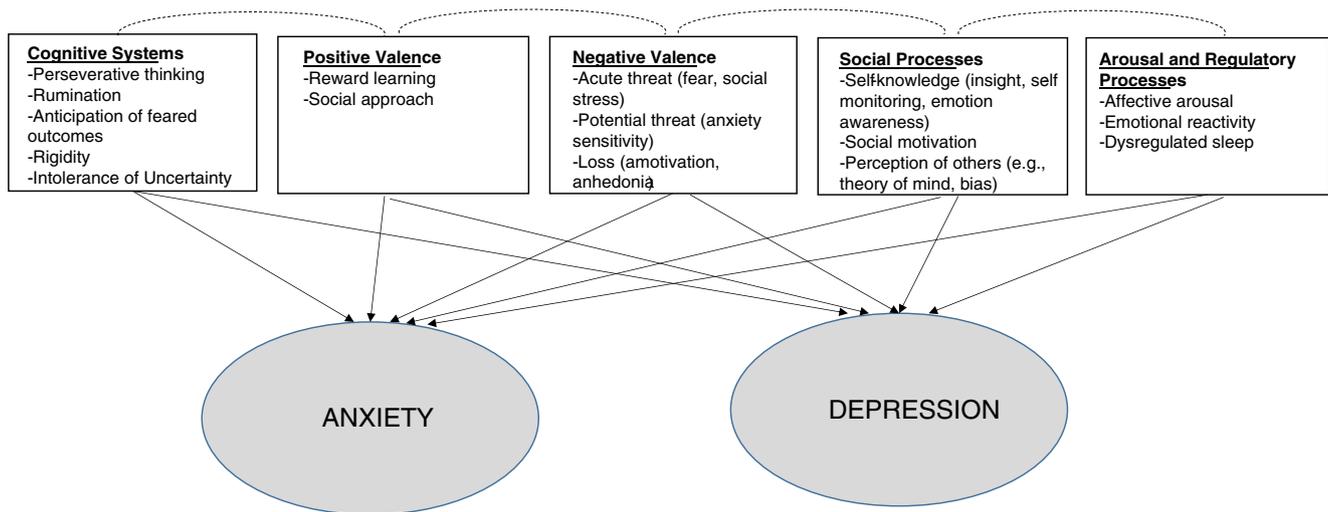


Fig. 2 Candidate treatment mechanisms associated with NIMH RDoC domains

research in ASD. These include perseverative thinking and rumination, rigidity, intolerance of uncertainty, and fear of bad outcomes or negative evaluation by others. Indeed, some of these processes are already targeted in treatment research: most of the CBT programs evaluated to date in ASD make reference to isolating processes such as testing the probability of the feared (bad) outcomes during cognitive restructuring [19, 53, 54].

Other constructs that have been linked to anxiety and depression, namely indecision and perseverative thinking, have not yet been well-addressed in the treatment literature. People with ASD often struggle with decision-making [55], especially with day to day decision-making and when the decision must be made quickly. The decision-making approach of young people with ASD tends to be characterized by a drive to avoid potential loss [56]. This is different from the general neurotypical stance of seeking (or approaching) potential reward, even in the face of risk. Although a risk avoidance technique is logical, it is not always ideal for everyday social interactions in which some level of risk is inherent [55]. To the extent that aberrant decision-making leads to behavioral avoidance, it may be linked to anxiety or depression via reduced opportunity for rewarding experiences that promote social growth [57].

Diminished reward sensitivity and approach motivation have been long-associated with anhedonia and clinical depression, as well as other internalizing disorders [58, 59]. In the adult ASD population, greater self-reported capacity for social reward was strongly associated with loneliness in the specific context of elevated social impairment; loneliness in turn predicted depression [60]. Within the same study, an interactive effect was observed in which *diminished* sensitivity to social reward was also associated with loneliness, independent of the degree of social impairment. These findings suggest that

interplay between cognitive features and environmental context (e.g., social opportunities) may moderate internalizing symptoms in ASD.

Perseverative and passive (unproductive) thinking on negative topics (generally called rumination) is robustly associated with the onset of depressive disorders in the typically developing population [51]. Rumination correlates with more “autism-specific” markers of perseveration, such as insistence on sameness, across ASD and general samples [61, 62••, 63•], and ruminative thinking has been shown to prospectively predict greater depressive symptoms in children with ASD [64]. Gotham and colleagues recently observed similarity in a potential neural signature of rumination across adults with ASD and typically developing depressed adults [65]. They concluded that depression treatments in ASD are likely to profit from following models used in other ruminative populations. Finally, intolerance of uncertainty has been suggested as a mediator of anxiety in people with ASD. Boulter and colleagues [66] found that intolerance of uncertainty was elevated in youth with ASD, relative to peers without ASD. They also found support for intolerance of uncertainty as a mediator between ASD and anxiety; however, given the use of a non-experimental design, neither causation nor temporal precedence could be established.

Positive and Negative Valence Systems

In contrast to the variety of cognitive constructs that have been explored in research on anxiety and depression in ASD, the RDoC domain of positive valence systems and negative valence systems has not been widely studied. Negative valence systems have most often been considered in relation to potential threat, which underlies the majority of CBT-based anxiety treatment and is targeted directly in ASD treatment protocols

that include exposures [17, 19]. However, one study examining attention bias to threatening stimuli found no significant differences in bias between ASD and non-ASD groups and no association between bias and anxiety [67].

The RDoC construct of loss offers another avenue for future work attempting to identify intervention targets, insofar as it relates to such concepts as anhedonia and amotivation. Anhedonia, the inability to feel pleasure, is more prevalent in ASD relative to typically developing groups, and is thought to be a primary contributor of depressive symptoms [68]. Loss, as it refers to the occurrence of negative life events, has also been reported in adults with ASD; negative life events were also correlated with overall depression and anxiety [69, 70]. The frequency of these events and their impact on internalizing symptomatology may be related to negative attributional styles or patterns of cognitive rigidity and rumination unique to ASD [61, 71].

Within the positive valence systems, social motivation models of ASD have suggested that approach motivation and reward learning function differently in ASD, such that social stimuli are less rewarding for individuals on the spectrum, which results in decreased neural specialization for efficient processing of social stimuli [72]. Although social approach and reward have not often been evaluated in treatment studies, children with ASD have been found to self-report less social interest but *more* approach to social stimuli during a behavioral task, compared to children without ASD [73]. Additional work has established relationships among social communication and facial emotion recognition deficits, social interest, and loneliness [60, 74•, 75••]. An emerging body of evidence indicating that social reward varies within ASD (e.g., sub-groups based on social reward and motivation) and the extent to which social approach and reward might both underlie anxiety and depression and be responsive to intervention suggests this is an important, untapped avenue of research. New work also indicates that, even within the context of social orienting, individuals with ASD and individuals with depression may share a visual attention bias away from *positive* emotions specifically, which represents another area to explore for links to emotional well-being [76•].

Systems for Social Processes

Regarding the RDoC domain of systems for social processes, relevant targets of treatment for depression and anxiety in individuals with ASD have included self-monitoring, emotion recognition, insight, and theory of mind (i.e., expressed empathy). Few studies have sought to isolate and evaluate these constructs as components of treatment for anxiety and depression. In a recent study, Pallathra and colleagues examined social motivation, social cognition, social skills, and social anxiety in adults with ASD; the authors reported nonsignificant associations between these behavioral components of

social functioning and anxiety, suggesting a multidimensional model of social functioning [77••]. Social motivation was associated with both social skill and social anxiety, which suggests the potential mechanistic import of social motivation.

Self-monitoring, wherein individuals are taught skills to manage their own behavior, has been shown to successfully improve social/adaptive/academic difficulties in individuals with ASD, although there is large variability in implementation [78]. CBT, which integrates elements of self-monitoring and emotion recognition, has successfully been shown to reduce anxiety in children with ASD [19]. Furthermore, modifications to CBT, such as the addition of social skill work (i.e., didactic lessons, peer modeling, behavioral rehearsal, etc.) also show promise in targeting symptoms of anxiety in conjunction with social skills [20, 79].

Considering the association, though debated, between social communication impairment and anxiety in individuals with ASD [9•, 10], attention should also be given to underlying mechanisms of social skills training (SST) in treating anxiety and depression in individuals with ASD. SST addresses social processes holistically, integrating didactic lessons, peer modeling, and behavioral rehearsal. Findings regarding the efficacy of SST to address anxiety and depression are mixed; several reviews of SST highlight unsuccessful attempts to address anxiety [80] and depression [81] as secondary treatment targets. In contrast, researchers examining the impact of a theater-based SST intervention reported a concurrent decrease in anxiety in individuals with ASD [82] and group-based SST contributed to reduced depression linked to increased social contact [43]. In each of these studies, outcomes addressing systems for social processes (i.e., emotion recognition, empathy, social motivation, insight, etc.) were measured using behavioral and questionnaire instruments and the interventions were multicomponent, which does not permit us to unpack the relative impact of isolated constructs or mechanisms.

Arousal and Regulatory Systems

Emotional reactivity falls within the arousal and regulatory systems domain of the RDoC. Conceptualized as the tendency to experience strong, often sudden, negative emotion, emotional reactivity is tethered to emotion regulation in typically developing [83] and ASD [84] samples. Emotion dysregulation, or difficulty altering one's emotions in adaptive or goal-directed ways, has been shown to be impaired in many psychiatric disorders, including anxiety and depression, in people without [85] and with ASD [86]. There have been recent strides made in the valid assessment of emotion dysregulation in people with ASD [84]; as such, emotional reactivity/emotion dysregulation are prime candidates for further exploration in treatment research. In a recent two-site open trial of a therapy developed to improve emotion regulation in

adolescents with ASD, of 17 treatment completers, all showed meaningful improvement on at least one index of emotion regulation and most (94%) had meaningful reduction in depression, anxiety, or problem behaviors [30].

Sleep is another primary focus of the arousal and regulatory systems in the RDoC framework. Dysregulated sleep has been linked to anxiety and depression across clinical populations, with suggested bidirectional effects [87]. As sleep problems are highly prevalent in ASD and have been associated with behavioral problems [88], this is an important direction for future study as an intermediate and moveable mechanism in ASD treatments for anxiety and depression.

Conclusions

Among adolescents and adults with ASD, both anxiety and depression are highly prevalent. These co-occurring conditions confer additional impairment and therefore warrant targeted treatment. There has been rapid growth in psychosocial treatment research in this area, though most of this work has focused on the application of CBT to anxiety. In recent years, other approaches, such as mindfulness-based treatments, have been garnering more research attention. Based on the state of this research, there is reason to be optimistic about our ability to successfully treat anxiety and depression in clients with ASD.

An experimental therapeutics approach to treatment development [89••] holds that a specific disease mechanism must be identified and found to be modifiable *prior to* evaluation of treatment efficacy, operationalized as change in more distal, clinical outcomes. Given the heightened federal focus [52] on experimental therapeutics and a growing scientific appreciation of the utility of transdiagnostic treatments, we have endeavored to identify the most promising candidate mechanisms related to treatment of anxiety and depression in patients with ASD. Our hope is that this review will serve as a guide for future treatment research in this area, and note that neither the RDoC domains nor the constructs housed within them are orthogonal to one another; many are inter-related (Fig. 2).

We are making progress toward understanding why and under what conditions treatment works [90]. As treatment research for co-occurring problems in people with ASD matures, we encourage early identification of putative mechanism(s) of change. It is equally important to consider study designs (e.g., longitudinal; use of multiple and multi-unit assessments of key mechanisms and outcomes; sufficiently large sample size to explore moderation) that will allow us to answer critical questions related to “why, when, and for whom” treatment effects are seen. Finally, given the pervasiveness and chronicity of both anxiety and depression among individuals on the autism spectrum, resources should be

allotted to prevention efforts and longer term follow-up studies to better understand developmental course.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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