МЕДИЦИНСКОЕ СОПРОВОЖДЕНИЕ
MEDICAL SUPPORT

Integrating Treatment for Autism: Psychiatric Comorbidities and Comprehensive Treatment

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Autism Spectrum Disorder (ASD) treatment becomes more convoluted when additional mental disorders are present. Comorbidities with ASD discussed in this review include attention deficit hyperactivity disorder (ADHD), anxiety, depression, disruptive mood dysregulation disorder (DMDD), psychotic and bipolar disorder. As these disorders typically affect multiple endophenotypes, from genetics to behavior, treatment must aim to target multiple layers, all the while minimizing side effects. Evidence-based therapies for ASD and comorbidities can range from psychosocial interventions to psychotropic medicines, with a varying degree of effectiveness for pairings of comorbidities and combinations of treatment. This review aims to create a brief overview of ASD comorbidities and discuss treatment options based on prior evidence-based research. Appropriate treatment is dependent on specific symptomatology, but evidence suggests that integrative-targeted treatment is typically more effective than stand-alone treatments.

Keywords: autism, comorbidities, endophenotypes, integrative medicine, psychosocial interventions, psychopharmological treatment, drug treatment.

Интеграция помощи людям с РАС: коморбидные состояния в психиатрии и комплексная терапия

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Сопутствующие психические заболевания осложняют процесс терапии при расстройствах аутистического спектра. В данной статье обсуждаются такие коморбидные состояния, сопутствующие РАС, как синдром дефицита внимания и гиперактивности, тревожность, депрессия, деструктивное расстройство дисрегуляции настроения, психотические и биполярные расстройства. Так как данные заболевания, как правило, затрагивают множество эндофенотипов, от генетического до поведенческого, то и терапия должна быть многоцелевой с максимально сниженными при этом побочными эффектами. Вмешательства с доказанной эффективностью при РАС и коморбидных состояниях могут варьировать от психосоциальной коррекции до лечения психотропными препаратами с различной степенью эффективности в зависимости от сочетания коморбидных состояний и комбинаций терапевтических стратегий. В данном обзоре поставлена цель краткого представления коморбидных состояний при РАС, а также обсуждение возможных вариантов терапии, основанной прежде всего на доказательных исследованиях. Подбор терапии зависит от симптоматики в каждом конкретном случае, но данные свидетельствуют о большей эффективности интегративно-целевой терапии по сравнению с терапией отдельных коморбидных состояний.

Ключевые слова: аутизм, коморбидные состояния, эндофенотипы, интегративная медицина, психосоциальная коррекция, психофармакологическая терапия, медикаментозная терапия.

ASD & Mental Comorbidities

ASD can become even more complex to treat when comorbidities are present. Mental comorbidities with ASD can come in many forms, but for the purposes of this paper we will focus on the following: ADHD, anxiety, depression, DMDD, psychotic and bipolar disorder. ASD and comorbidities originate from genes, the environment and the interaction of the two. Because of this, when treating autism and its comorbidities, one should consider targeting multiple layers (endophenotypes) to improve ASD and co-occurring neurodevelopmental disorders.

The terroir model draws a parallel to the layers of the earth, where symptoms (phenotypes) are the observable on the surface of the earth, and genes are earth's core. Between these layers are interacting levels composing the endophenotype. Level one refers to DNA and mRNA where gene modification is a potential treatment solution. Level two consists of cell modulation and physiological processes, which are targeted with biomedical and epigenetic treatments. Level three is composed of reshaping neuromodulators, brain structure and brain function. Targeted treatment for both levels two and three consists of pharmacotherapy, while levels three and four are targeted by speech and language therapy, occupational therapy, and cognitive-behavioral therapy (CBT). Lastly, level four treatment aims to change cognition through behavioral interventions, and family support and structure [14]. Although this model has associated treatment types with one or two epigenetic layers, typically treatments will indirectly affect more than one level of the endophenotype. Combining treatments can maximize the endophenotypes targeted, making for a more comprehensive treatment.

Although it is important to note that singular treatments targeting only one symptom are typically less effective then combining a multitude of treatment techniques to target multiple symptoms, one must also consider the interactions of multiple treatments and monitor any additional or increased negative side effects. When dealing with medications, prescribers must be aware of polypharmacy and potential risks that coincide. However, combined interventions that target different mechanisms can often produce a number of complimentary results.

Specialists delivering treatment must also consider barriers that individuals and families may run into. There are regulatory barriers, such as drug treatments not yet approved in the home country — in fact, some of the drugs mentioned in this paper are only available in the United States. There are also insurance barriers when it comes to both drug and psychotherapy treatment [56]. Stigmatization and lack of racial and cultural-matched treatment providers can also prevent individuals, often minorities, from seeking treatment [31; 37; 49]. It's important for physicians to recognize both biological and societal factors that may affect a patient's treatment.

Comorbid ADHD

In 2013, a shift in the field occurred when ADHD was permitted as a possible comorbidity of ASD in the

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DSM-5. 40—70% of children with ASD have a comorbid ADHD diagnosis, making it the most common ASD comorbidity [2]. With some notable overlapping symptoms, it is unsurprising that in a latent class analysis, ASD symptoms did not occur without ADHD symptoms [52]. However, besides the obvious heightened inattention problems that come with a comorbid ADHD diagnosis, there are also other troubling behaviors and functioning that are amplified, such as increased anxiety, worse working memory and decreased empathy [6]. Looking at similarities across the endophenotypes can help illuminate why some of these deficits might be exacerbated in a comorbid population.

From genetics to cognition, ASD and ADHD share many commonalities. There is a 50—72% overlap among the driving genetic factors in ASD and ADHD [30]. Both familial and twin studies have supported the tight genetic tie between the two disorders [40; 42]. On a neuronal level, through measuring centrality with fMRI, similar abnormalities were found in the precuneus, a region of the brain involved in visuospatial processing, episodic memory and affective responses to pain [3; 8]. Di Martino et al.,[8]- also found that individuals with comorbid symptoms had similar ADHD-like abnormalities in the basil ganglia (while those with ASD only did not), illuminating the idea that we must approach treatment for those with just ASD versus comorbid ASD and ADHD differently. We also see overlapping impairments in social and executive functioning across the two groups [1]. Now that we have outlined some associations between the origins and deficits in ASD & ADHD, the question becomes, what are some possible ways to treat it?

Stimulants

The most common two stimulants include amphetamines and methylphenidate. There is a limited amount of research on the risks and benefits of amphetamines in individuals with ASD and ADHD, but Reiersen & Todd [41] found that while amphetamines tend to have a higher efficacy than methylphenidate, they also more often lead to increased anxiety, irritability and aggression. Methylphenidate is shown to improve hyperactivity, and possibly inattention (the meta-analysis revealed significant, but not clinically relevant benefits) and it did not negatively impact the core symptoms of ASD [50]. Because of the reduced side effects, some recommend methylphenidate, a dopamine reuptake inhibitor, as the stimulant of choice for ADHD management in individuals with the comorbid ASD diagnosis [23].

Atomoxetine

For those who do not tolerate stimulants well or are uninterested in using a controlled substance, there are also non-stimulant options, such as a norepinephrine reuptake inhibitor, atomoxetine. In a meta-analysis of participants ranging in age from five to seventeen with comorbid ASD & ADHD, atomoxetine was shown to improve hyperactivity, impulsivity and overall ADHD [36].

Across the studies, irritability, nausea and decreased appetite were more commonly experienced in children with ASD compared to typically developing children. One study in particular combined a 10-week parent training paired with atomoxetine and, it proved to be more effective than placebo, with the only troubling side effect being decreased appetite [15].

Alpha-2 Adrenergic Antagonist

Following directly behind The British Association for Psychopharmacology's recommended first-line treatment of methylphenidate is a class of sympathomimetic agents called alpha-2 adrenergic antagonists (for example, guanfacine). These agents work by targeting abnormalities in the prefrontal cortex, which is the area associated with attentiveness and executive functioning.

The most recent research on guanfacine has focused on the extended-release form. Compared to the placebo control group, extended release guanfacine was found to be more effective in reducing hyperactivity, impulsivity and distractibility [45]. The treatment group saw a 43% decline on the ABC hyperactivity subscale, while the placebo group only saw a 13.2% decrease. Adverse side effects consisted of drowsiness, fatigue and decreased appetite. In a follow up analysis, the effects of extended release guanfacine on secondary measures of oppositional behavior, anxiety, repetitive behaviors and sleep disturbance were also examined [38]. Results showed significant decreases in oppositional and repetitive behavior, but there were no significant differences between the extended release guanfacine and placebo group for anxiety and sleep disturbances. Scahill et al. (2015), concludes that extended release is more tolerable and effective in an ASD and ADHD comorbid population than placebo and short release guanfacine.

When treating a patient with comorbid ADHD and ASD, there are a variety of medications to choose from. One must consider the efficacy and tolerability of the substance, in addition to parental and patient preferences. Providers should consider treatments that not only target ADHD symptoms, but also those that have no effect or improve ASD symptomatology.

Comorbid Anxiety (including Obsessive Compulsive Disorder (OCD))

Obsessions in OCD manifest similarly to insistence on sameness and preoccupation in ASD. Likewise, compulsions in OCD appear similarly to rituals/routines in ASD. OCD occurs in those with ASD with a 2.6-37.2% prevalence, and at a two times higher rate than in typically developing children [38]. However, despite these similarities and overlaps there are also notable differences between OCD and ASD, which could contribute to the lowered efficacy of CBT for those who have a comorbid ASD and OCD diagnosis versus OCD-only [35]. Limitations of CBT on a comorbid ASD population can

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stem from the lower language and cognitive capabilities those with ASD sometimes experience. Modifying CBT and Exposure Response Prevention therapies to better address the strengths and weaknesses associated with ASD has shown observable differences [35].

The recommendation to modify traditional CBT practices to accommodate ASD symptomatology is also applicable to the broader category of comorbid ASD and anxiety disorders. A systematic review gathered that adaptations may include longer sessions to allow for absorption and appropriate pacing, use of social stories, relaxation strategies, tangible reinforcements, video modeling, games to convey concepts and engage the child, and a parent and school component [55]. Adapted CBT has primarily been tested with high functioning adolescents — perhaps due to the shift of increased expectation and awareness of societal relationships during this period of life, and more developmentally appropriate cognitive capabilities to properly participate in the therapy. More research is needed on the effectiveness and adaptations of CBT for adults with ASD and anxiety, as there are specific issues that arise later in life connected to the disorders, such as issues with romantic relationships and substance use, that CBT could potentially address [27].

There are many pharmacological treatments for those with anxiety-only; however, the four studies that evaluate pharmacological treatments for ASD and anxiety are "outdated, included heterogeneous groups of children who do not precisely characterize the anxiety phenotype, and employ either a retrospective chart review or open-label design" [54]. SSRIs are sometimes used to treat comorbid ASD and anxiety, and those will be discussed further in the following section dedicated to SSRIs.

Comorbid Depression

Depression in an ASD population can prove difficult to diagnose, as most measures are not apt to capture the range of communication abilities and atypical presentations of depression in ASD. However, a recent national survey reported that 49% of their ASD sample of 185 people between the ages of 14 to 80 met the clinical ranges for depression [17]. Depressive symptoms are important to treat at a young age because internalizing symptoms were associated with poor emotional regulation in school and also lead to lower life satisfaction and greater social difficulties in early adulthood.

Comorbid Suicidal Ideation

In the same national survey mentioned above, of the 185 people with ASD, 36% reported suicidal ideation [17]. A systematic review of 13 studies showed the rates of suicidal ideation fell between 11—66% while suicidal attempts were between 1—35% [16]. These rates are higher than the rates of the general population. For example, in Taiwan, suicide attempts were greater in an ASD population of adolescents and young adults compared to their typically developing counterparts (3.9%:.7% respectively; Chen et al., 2017). Additionally, it is highly likely that having a comorbid diagnosis is related to suicidal ideation and attempts, but there are a couple of research limitations that hinder the ability to isolate these relationships. For example, in Hedley & Uljarević's [16] systematic review, the 13 studies primarily utilized self-report or record review, which does not allow for an accurate temporal assessment of comorbid symptoms and suicide ideation or attempts. Furthermore, the measures used across the 13 aforementioned studies to capture comorbid symptomatology were inconsistent and have not been validated for an ASD population [16]. That being said, a Japan-based study found that those with ASD who received services were less likely to attempt suicide [26].

Comorbid Depression Treatment

Treatment for depression typically involves CBT and/or antidepressants, but these have not been tested thoroughly across age groups and certainly not to their fullest extent in an ASD population. Group CBT was implemented as a randomized controlled trial (RCT) that compared 20 participants with ASD between the ages of 3 to 18. Results showed that those in the treatment group experienced a significant decrease in depression from pre to post-intervention (as measured by the DASS), while the waitlist control group did not (Santomauro et al., 2017). In adults, mindfulness-based therapy, social skills and vocational skills training lead to decreased depression (Sizoo & Kuiper, 2017; Hillier et al., 2011). More research is needed on children and adolescents with ASD and depression before anything definitive can be said about the effectiveness of psychosocial interventions.

Selective Serotonin Reuptake Inhibitors (SSRIs)

High usage rates of psychotropic medicines for people with ASD are reported across age groups. One study reports that out of 2,853 children between the ages 2 to 17, 27% took at least one psychotropic medication. Out of those who had a comorbid diagnosis, 80% took at least one psychotropic medication [7]. We see even higher rates in a study examining adolescents and adults with ASD where 57% reported taking psychotropic medication, with an increase to 64% four years later [9]. 81% of those with a comorbid diagnosis took a prescription medication.

There are a variety of SSRIs that have been tested for ASD including fluvoxamine, sertraline, fluoxetine and citalopram. Some were thought to improve core ASD symptomatology, such reducing RRBs, while others target depression, anxiety, and other linked comorbidities.

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Serotonin has become a focus in treating ASD because levels are consistently dysregulated in the ASD population, and when corrected, they have proven to improve global functioning and decrease rituals and routines [29]. Adverse effects, such as irritability and agitation, are one of the main deterrents for the use of SSRIs in an ASD population.

Comorbid Psychotic Disorder and Bipolar Disorder

Those who have bipolar disorder (BP) sometimes experience psychotic symptoms. BP, psychotic disorders and ASD have similar genetic risk factors, which is why some studies have chosen to examine all three disorders at once. Whole-genome studies have revealed some similarities [4]. Copy Number Variants and a few rare alleles (NRXN1, 22q11.2, 1q21.1 and 15q13.3 deletions) are all associated with schizophrenia and ASD. Single nucleotide polymorphism alleles (such as SHANK 3), are associated with all three disorders. This evidence leads the authors to conclude that specific genetic loci and allies may increase the risk of comorbidity. In further support of the interconnectedness of these disorders, having a diagnosis of one, typically means a higher risk of having the other. In a case control study of 9,062 17 to 27-year old's with ASD in Sweden, an ASD diagnosis was highly associated with an increased risk for psychotic and bipolar disorders. The risk was the highest for those with non-ID ASD, and lowest for the sex and age matched sibling controls [46]. Furthermore, Vannucchi et al., [53] found that relatives of patients with ASD had double the risk of being affected by BP.

Prevalence rates differ slightly based on which combination of comorbidities is examined. Kincaid et al., [28] complied data from seven studies and found that diagnosed ASD was prevalent in 1—52% of the psychotic sample. In adults with Asperger's Syndrome, a bipolar diagnosis was common in 6-21.4% of the systematic review cases [53]. Lastly, one study examined all three disorders and found that out of 129 adults with ASD, 7% had bipolar disorder with psychotic features, and 7.8% had schizophrenia or another psychotic disorder [48]. It is important to differentiate between all the possible comorbid diagnoses because different treatments may be indicated.

Currently, there are no studies that explore treatment for a person with ASD, bipolar disorder, and psychosis despite its relatively high prevalence. This could potentially be because misdiagnosis often occurs with some of the symptoms being indistinguishable from one disorder to the next. Potentially due to the indistinctness and common genetic origins, antipsychotics are used to treat both disorders when comorbid with ASD. It is also suggested to pair treatment with CBT to assist with the anxiety and emotions that may accompany the disorders.

Comorbid Disruptive Mood Dysregulation Disorder (DMDD)

DMDD is a new addition to the DSM-5. It was created because children were previously being labeled with bipolar disorder even though the symptoms present differently in a young population, and the treatment for BP has different effects on children than adults. For example, typical treatment in adults like mood stabilizers, such as lithium, lead to some exaggerated side effects in children, such as gastrointestinal discomfort, weight gain, headaches and tremors [43]. Criteria for meeting a DMDD diagnosis insists that the child must be at least six years old and symptoms must begin before age 10, with symptoms being present for at least a year. DMDD manifests through severe temper outbursts at least three times a week with reactions being bigger than expected, a sad irritable or angry mood almost every day, and troubles with functioning in more than one context (i.e. at school, home, and/or with friends).

Across studies, the prevalence of DMDD in children with ASD land somewhere in the mid 40's percentage range. In 2015, Mayes et al., found that 45% of children between the ages 6 to 16 with ASD experienced DMDD often, or very often, compared to 3% in the general population. A subsequent Mayes et al. [32] study looked at children ages 2 to 16 and found that DMDD symptoms do not differ from preschool to school age in children with autism as they do with ADHD and oppositional defiant disorder. Despite the high prevalence of DMDD in ASD, there have not been studies that specifically look at treatment options for this comorbid subgroup.

Antipsychotics

Antipsychotics are commonly used to treat schizophrenia and bipolar disorder and can also target ASD symptoms. Antipsychotics are categorized as either typical or atypical and there are benefits and drawbacks associated with each. Typical antipsychotics, such as haloperidol (a dopamine receptor D2 blocker), are associated with a high risk of causing extrapyramidal symptoms (EPS), especially in children. As shown through a randomized double-blind placebo control study (RDBCT), haloperidol has been efficacious in improving social withdrawal and stereotypy, but long-term usage often led to dyskinesia and sedation [13]. In a 12-week RCT study, 30 children and adolescents with ASD were treated with haloperidol or an atypical antipsychotic, risperidone. Those dosed with risperidone saw greater improvement with behavioral symptoms, impulsivity, language skills and impaired social relations [34]. Although there are also many side effects associated with atypical antipsychotics, they come with less EPS risk. Additionally, there have been a multitude of RCTs for risperidone and for aripiprazole proving efficacy in those with ASD [10], so for the purposes of this paper we will focus further on those.

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Risperidone

Risperidone composes 19.3% of psychopharmacological prescriptions for children with ASD 0 to 18 and 7.2% for adults over age 19 in the USA [24]. Risperidone is the most common drug prescribed for children with ASD between the ages of 0 to 18 across all countries, besides the UK and Japan. Risperidone was also the most commonly prescribed for adults with ASD across countries, besides Spain, Brazil and Mexico. Risperidone works by blocking postsynaptic dopamine and serotonin receptors, which may explain its efficacy compared to typical antipsychotics and placebos. Seven RCT's were examined in a systematic review of children and adolescents up to 17 years old. Overall, irritability scores (according to the ABC irritability subscale) and response rates were significantly greater for the treatment groups over the placebo [11]. Lethargy/social withdrawal, stereotypic behavior, hyperactivity/noncompliance, and inappropriate speech as measured by the ABC also showed significantly greater mean changed scores than the placebo group. Adverse events reported by this treatment group include increased appetite, drowsiness, somnolence, fatigue, anxiety, hypersalivation and elevated prolactin levels. However, no serious adverse events were reported.

Similar efficacy of risperidone in adults was also observed. Taylor [51] reviewed two placebo-controlled studies of adults with ASD, where the treatment group was more effective than the placebo in reducing irritability, repetitive and self-injurious behavior, physical aggression and property destruction. Increase appetite, weight gain and sedation are listed as side effects in the adult population as well.

Aripiprazole

Aripiprazole, a partial DA D2 and 5-HT1A agonist, acts similarly to risperidone but comprises only 11% of psychopharmalogical prescriptions in 0 to 18-year old's, and 9.6% in those 19 and older in the United States [24]. In a prospective study comparing the use of risperidone and aripiprazole in children and adolescents, researchers saw significant decreases in scores across the ABC subscales, suggesting both are equally effective [12]. Additionally, adverse effects did not significantly differ between groups. Two RCT studies were reviewed on the use of aripiprazole in children and adolescents with ASD [21]. Irritability, hyperactivity, and stereotypy measured by the ABC all showed improvements for the treatment group over the 8-week intervention program. Side effects included weight gain, sedation and tremors. In a Japanese sample of children with ASD ages 6 to 17, aripiprazole decreased parent-reported irritability in a 8 week- RDBCT [25]. In adults with ASD, case studies revealed that aripiprazole improved mood and behavior [51]. Behavioral outcomes, specifically social interaction, self-injury, compulsions, irritability and aggression, showed marked improvement; however standardized measures were not used across studies to capture the outcomes, so definite statements on aripiprazole in adults cannot be made.

Conclusion and Future Directions

CIMs can be implemented alongside the drug and psychosocial treatments mentioned previously. Depending on symptoms, there is a large range of CIMs that those with autism and comorbidities can utilize. According to a systematic review of 20 studies, 28—95% of children with ASD are treated with complimentary alternative medicines [CAMs; 22]. The most frequently used CAMs are special diets or dietary supplements. Hendren [18] aggregated a review of CAM treatments in ASD that have proven to be the most efficacious. The list is composed of melatonin, omega-3 fatty acids, multivitamin/micronutrients, NAC, and possibly memantine, digestive enzymes, methylcobalamin. CAMs become CIMs when used alongside conventional medicine. When combined with conventional psychopharmacology, families should consult with practitioners to review potential interactions and side effects of the CIMs approach.

From psychopharmological medicine to psychosocial intervention to CIMs, there are many combinations of treatments for ASD. Although this review outlines a number of evidence-based interventions that target symptoms in ASD and comorbidities, one must work with their doctor to explore their individual risk factors and benefits associated with each treatment type. Even if no comorbidities are present, the heterogeneity of ASD alone, and ever-changing symptom presentation with age make treatment difficult. There is still a lot unknown about the genetic and environmental origins of ASD, and until those gaps in research are filled, practitioners need to rely on the treatment evidence reviewed and their best judgment to provide families with their best suggestions for integrative treatment.

ASD is not a stand-alone disorder. Comorbidities create challenges for differential diagnosis and for targeting successful treatment. Inadequately identified and treated comorbidities lead to poorer outcomes for individuals with ASD. Effective treatment involves targeting multiple layers of the disorder including medical, behavioral, pharmacologic, ancillary and relationship-based therapies. As our ability to identify subcategories and biomarkers becomes more sophisticated, we may be able to better match treatments to neural systems. Brain structure and function, genetics, and biomarkers of epigenetic processes may play an increasing role in identifying the most effective psychotropic medications, behavioral interventions and biomedical supplements to effectively treat subtypes ASD and related comorbidities. Ultimately, clinical trials of reasonable size that include symptom clusters and/or biomarkers have the potential to examine efficacy of treatments in these specific subgroups, improving treatment precision [19].

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