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LEADING ARTICLE

Quality of Life in Children and Adolescents with Autism Spectrum Disorders: What Is Known About the Effects of Pharmacotherapy?

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Abstract A diagnosis of autistic spectrum disorder (ASD), now estimated to affect one in 88 children, requires deficits in social communication and interactions, and restricted interests and/or repetitive behaviors. Almost all children with ASD have deficits in adaptive skills, many have intellectual disability, and others have co-occurring psychiatric disorders or symptoms. Thus, this complex disorder has shown to have a substantial impact on patients' quality of life (QoL) and that of their families. Medication treatment is considered by clinicians and families to address problems with functioning due to psychiatric problems, and, as such, one-third of children and adolescents with ASD take at least one psychotropic medication and many use complementary and alternative medicine. This paper reviews what is known about the benefits and risks of psychotropic medications on the QoL of children with ASD. Although scarce, there are studies of psychiatric medications in autistic patients that include QoL measures, such as the pediatric studies of aripiprazole for irritability and one adult study of oxytocin. The aripiprazole study showed a positive effect on QoL in treated patients, as did the oxytocin study. Several other psychotropic medications are used in the treatment of children with ASD, and although information is available on the risks and benefits of each, we do not have specific data on the QoL impact of these medications. The aripiprazole and oxytocin studies exemplify how researchers can include QoL measures and use this information to guide clinicians. Additionally, we will recommend areas of further study in pharmacotherapy and QoL research in the context of treating children with ASD.

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1 Introduction: Quality of Life (QoL) and Autistic Spectrum Disorder (ASD)

The core features of autistic spectrum disorder (ASD) are impairment in social communication and interaction, and restricted interests and/or repetitive behaviors [1]. As a group, children with ASD are genetically and phenotypically heterogeneous [2]. Common comorbid symptoms include physical symptoms such as insomnia, eating and digestive difficulties, and allergies, along with psychiatric symptoms of anxiety, hyperactivity, inattention, irritability, and aggression. Psychiatric symptoms, whether part of ASD or a reflection of independent psychiatric comorbidity, increase disability. Quality of life (QoL) is universally accepted as a multidimensional construct combining the objective and subjective impact of an illness and its treatment; it is often thought of in three domains: disease state and physical symptoms, functional status, and psychological and social functioning, although details of this definition are still under discussion [3–5]. Thus, children with autism have difficulties in all the core areas of QoL: physical, functional and social-emotional.

Measurement of QoL has been standardized by tools such as the Health-Related Quality of Life Questionnaire (HR-QoL), the World Health Organization's QoL measure (WHOQOL-BREF), and the European QoL measure (EuroQoL-5D or EQ-5D) [6, 7].

Although there is a paucity of empirical data on QoL in children with ASD, a recent review of available measures found that children with ASD aged 8–12 years old report lower QoL compared with their peers and highlighted some of the difficulties in measuring QoL in children with ASD [8]. For example, children with autism had a tendency to give a literal interpretation to QoL questions, had difficulty expressing their emotional well-being, and a tendency to focus on a specific event instead of answering questions on their general well-being [14]. Furthermore, the priorities of children with autism; for example, time to enjoy their area of interest, were not reflected in current QoL measures and thus demonstrated a need to develop an autism condition-specific measure [8]. Despite these findings, two QoL questionnaires demonstrated validity in ASD children (8–12 years old): the Pediatric Quality of Life Inventory (PedsQL) and Kidscreen [8]. The Health Utilities Index (HUI3) is a QoL measure that correlates well with changes in adaptive and cognitive functioning in children with ASD [9]. Also, adolescents with ASD but without intellectual disability reported lower QoL than same-aged peers with diabetes mellitus, especially in the areas of leisure time, friendships, and affective and sexual relationships [10]. Studies of ASD adults show that lower QoL extends into adulthood as well, even for more able patients with ASD [11, 12].

Additionally, the caregivers of ASD children have lower HR-QoL scores than the general US population [13]. Family QoL can be measured by the Family Quality of Life-2006 (FQOL-2006) instrument and the Caregiver Strain Questionnaire (CGSQ), which has been shown to be reliable and valid for assessing caregiver burden for caretakers of children with autism [14, 15]. Parents of children with ASD have a higher prevalence of mental health problems, stress, physical health problems, and exhaustion than parents of children without ASD [16, 17]. Salient factors contributing to parental stress include severity of core disability, age of child, and extent of behavior problems; in addition, conduct problems, hyperactivity, and lack of pro-social behaviors had the most influence on maternal QoL [18].

2 The Effect of Psychopharmacology on QoL

Three pharmacologic trials of patients with ASD include QoL measures. One study of fixed dose aripiprazole (5, 10, or 15 mg/day) for the treatment of irritability in autistic children ($N = 218$; age 6–17 years) included the PedsQL and the CGSQ measures and showed that the subjects receiving aripiprazole 15 mg/day demonstrated statistically significant improvement versus the placebo on the mean PedsQL Combined Scales Total score (least-squares mean treatment difference [TD] 8.2; 95 % confidence interval [CI] 1.2–15.2) and on the CGSQ Global Score (TD −1.1; 95 % CI −1.9 to −0.3) [19]. Changes observed with aripiprazole 5 mg/day and 10 mg/day were not significantly different from the placebo [19]. In a separate, 52-week, open-label, flexible dose (2–15 mg) study of aripiprazole for the treatment of irritability in children with ASD ($N = 330$; ages 6–17 years), the PedsQL and CGSQ were used to measure changes in QoL in each group [20]. Subjects who took aripiprazole for the first time had higher QoL life scores with treatment and aripiprazole was superior to placebo on QoL measures as well [20]. A post-hoc analysis of the effect of aripripazole on QoL using the combined data from these two studies demonstrated aripiprazole superiority to placebo in improving QoL overall and specifically on three subscales as follows: the emotional, the social, and the cognitive functioning subscales ($p < 0.05$) [21].

One randomized controlled trial (RCT) of oxytocin versus placebo in adults with ASD used the WHOQOL-BREF emotional and social subscales to measure QoL as a secondary outcome to the intervention of oxytocin; the results suggested improvements on the emotional subscale [22]. Interestingly, there was no significant difference in the primary outcome measures of social function/cognition (Diagnostic Analysis of Nonverbal Accuracy) and repetitive behaviors (Repetitive Behavior Scale Revised) which shows that there is value looking at QoL as a separate measurement in the assessment of our interventions.

3 QoL Domains and Opportunities for Psychopharmacologic Research in Children with ASD

3.1 Physical Symptoms: Medical Co-morbidity

Disease state and physical symptoms is the first domain of QoL. Children with ASD often present with dental care problems (40–50 %), gastrointestinal dysfunction (as high as 70 % prevalence), feeding problems (up to 60 % prevalence), seizure disorders (8–42 % prevalence), and sleep disorders (44–83 %) [23]. Co-morbid medical problems add to caregiver burden, not only due to increased medical visits but also because the related discomfort can make the child more irritable. For medical disorders co-occurring with ASD, diagnosis can be more complicated, but medical management is the same as for other children and for GI distress, gluten-free diets and probiotics may be helpful [23, 24].

The prevalence of sleep disturbance among patients with ASD ranges from 40–86 % [25]. Insomnia is associated with hyperactivity, inattention, irritability, and aggression and thus it is important to quantify the impact of sleep disturbance on QoL. Also, young autistic patients often

stay awake for hours at a time, requiring supervision, which leads to exhaustion and caregiver burnout. In addition to behavioral techniques, five RCTs support the use of melatonin for sleep in ASD patients [26]. Melatonin improves sleep duration with a large effect size; however, patients continued to wake up during the night with the same frequency [26]. Minimal side effects were reported although this is a nutritional supplement that has not been extensively studied. Clonidine, also used for behavior problems, improves sleep architecture as well, though its use can be limited due to the side effect of sedation [26]. Using medications to treat insomnia in patients with autism has significant potential to improve QoL, but as yet no studies of medications for insomnia have included QoL measures.

3.2 Disease State: Psychopharmacology for Core Features of Autism

Pharmacology has had little effect on the core features of ASD. Risperidone reduces repetitive behaviors and selective serotonin reuptake inhibitors (SSRIs) have been studied for this indication [27, 28]. Oxytocin has shown some promise to improve social deficits in adults with ASD [22, 29, 30]. SSRIs are often prescribed to patients with ASD, especially those with comorbid anxiety disorders [31. One meta-analysis of SSRIs (fluoxetine, fluvoxamine, fenfluramine, and citalopram) did not find any studies that used a standardized measure of QoL, and there was no significant improvement in core and non-core features of autism, though there were some adverse events (seizure) [32].

Many parents and practitioners look to complementary and alternative medical (CAM) treatments, linked to non-empirically supported models of ASD, to reverse or minimize core features of autism (in QoL terms, disease state). Vitamin supplementation has only been studied in small studies with inconsistent results; trials have looked at vitamin C, folic acid, B6 and magnesium, and omega-3 fatty acids, among others [33–35. Following concerns about infectious etiology, anti-infective agents, antibiotics, and anti-fungals have been investigated with no clear support from well-controlled studies [36, 37]. A focus on possible neurotoxins began an interest in chelation, despite the lack of established efficacy and potential risk [38]. Another theory that the opiate agonist byproducts of casein and gluten cause CNS toxicity leads to casein-free and gluten-free diets [39]. This intervention is very commonly employed by parents yet it is difficult to maintain and costly. There are a few RCTs of dietary restrictions but very few studies have been double-blind and the impact on QoL and any measurable behavior is unclear [40].

Given the concern that immune system dysfunction is related to autism, immune therapies are among the treatment initiatives; at present, no RCTs are available. There is no empirical or epidemiological evidence to support vaccines' contribution to autism prevalence [41, 42]. In summary, the objective data does not show that CAM interventions have impacted the core deficits of autism, but subjectively they can give caregivers a sense of empowerment; thus, we recommend empathic listening to caregivers and respectfully guiding families to access truly scientific information.

3.3 Psychological and Social Functioning: Psychopharmacology for Psychiatric Co-morbidity

In autism, a large part of the disease state and psychological and social functioning is manifested in behavioral symptoms and co-morbid psychiatric illness. It is important to establish the relationship of psychiatric symptoms to ASD in order to appropriately target psychopharmacologic and non-pharmacological interventions and improve the QoL of affected individuals. Recent studies have begun to quantify the impact of psychiatric disorders on children with ASD. For example, parents of children with ASD reported higher rates of total anxiety, social anxiety, and panic disorder in their children compared with parental reports on children without ASD; futhermore, greater anxiety and ASD-like behaviors predicted for a lower QoL [43]. In children with ASD with and without co-morbid attention deficit and hyperactivity disorder (ADHD), symptoms of ADHD in autistic patients are negatively correlated with QoL [44].

Coury et al. [31] and the Autism Treatment Network (ATN), examined the rates of psychotropic medication use in ASD children and adolescents and found that 27 % of over 2,000 children in their sample were taking one or more psychotropic medications, and in the adolescent population, 66 % were taking one or more psychotropics. In the Coury et al. study, 85 % of children on psychotropic medication had a comorbid psychiatric diagnosis. This demonstrates the importance of understanding the impact of psychotropic medications on the QoL of autistic children and their families.

As reviewed above, pediatric aripiprazole studies in children with ASD have included QoL measures and have shown a benefit in QoL in treated patients. Additionally, risperidone has demonstrated efficacy in treating irritability and aggression in children with ASD and has a FDA indication for use in children with ASD (age 6–17 years) [45]. Weight gain, glucose intolerance, and dystonic reactions are concerning side effects, among others. Given both its potential benefit and concerning side effects, research on the QoL impact of risperidone would further inform parents and clinicians in the decision-making process to treat irritability.

Many children with autism have excessive activity and impulsivity. For these children, their symptoms of ADHD increase parental stress and decrease their adaptive

functioning and QoL scores [44, 46]. Additionally, ADHD symptoms are a factor related to victimization and bullying, an issue for nearly half of children with ASD; thus, ADHD symptoms represent an important target of intervention by psychotropic medications [47]. Methylphenidate was superior to placebo in a Research Units on Pediatric Psychopharmacology (RUPP) study (2005a), yet the response rate in patients with ASD was 50 % (lower than the nearly 80 % in non-ASD patients) [48]. Irritability was the most common reason for intolerance, but side effects of insomnia and decreased appetite were also common; this again highlights the potential benefit of QoL measures to potentially underscore the impact of psychotropic intervention on the patients' and parents' subjective sense of well-being.

Two placebo-controlled trials of clonidine in ASD children found it to be effective and well tolerated [23, 49]. One open-label study also found guanfacine to be helpful in ASD children who did not respond to methylphenidate [50]. Atomoxetine, often useful in patients with co-morbid anxiety and ADHD, showed improvement in an RCT and a prospective open-label study of children with ASD; hyperactivity and inattention improved in 75 % of the patients but 13 % were much worse due to irritability [51, 52]. The data reviewed supports psychotropic interventions of stimulants and alpha-2 agonists to target hyperactivity and impulsivity in autistic children, yet more information is needed to understand the overall impact on QoL.

Anxiety disorders are common in ASD patients, with approximately 40 % prevalence in this population and an established negative correlation with QoL [43]. The largest study of 149 patients age 5–17 years examined citalopram for repetitive behavior in a 12-week, double-blind, placebo-controlled study using the Children's Yale-Brown Obsessive Compulsive Scale modified for Pervasive Developmental Disorders (CY-BOCS-PDD) and the Clinical Global Impression of Improvement (CGI-I) assessment, which showed no improvement in the citalopram group versus placebo in repetitive behaviors, and some behavioral activation was seen [53].

In summary, the evidence is weak for serotonin reuptake inhibitors on ASD-related symptoms and QoL effects, though their lower risk profile and efficacy in the general population warrants further studies in children assessed to have ASD and comorbid anxiety disorders or depression.

4 Future Directions for Pharmacology and Autism: Challenges of QoL Research

4.1 QoL Definition

The definition and use of the term QoL is not universal. At times QoL is used when discussing a patient's functioning, such as Vineland scores or improvements on the Aberrant Behavior Checklist (ABC), yet these are not a measure of overall QoL. For example, the Cochrane reviews use the term 'quality of life' when discussing improvements on other measures. Measures of adaptive skills and behavior may have a role in understanding the impact of psychotropics on individual factors related to QoL but there needs to be further investigation and standardization of this approach.

4.2 Subjective and Objective Aspects of QoL

Another challenge to QoL measurement is that it contains a subjective component. Children and the psychiatrically impaired are variable reporters of their well-being. Additionally, caregivers report on QoL and it will require clarification whether they accurately report QoL on behalf of their children. For example, Tavernor et al. found that some components of QoL measurement did not accurately portray QoL priorities in children with ASD; for example, time to spend on their area of interest, and areas such as 'leisure time with others' was less important to a subset of patients, but that did not reflect an area of diminished quality of life because their interests and priorities were elsewhere [8].

4.3 Heterogeneity of the Disorder

The autistic population is heterogeneous, both genetically and phenotypically. There has been consensus on the diagnostic definition of autism in the new DSM-5, namely, the diagnosis will combine, into a single category, autism spectrum disorders, including autism, pervasive developmental disorder, Aspergers syndrome, and childhood disintegrative disorder [1]. We accept that there is a spectrum within ASD, and QoL inquiry will have to be adapted for different levels of functional and communication abilities.

4.4 Clarification Regarding Co-morbid Diagnosis

In autism, a large part of the disease state is manifested in behavioral symptoms and co-morbid psychiatric illness. One common question when evaluating for medical management of behavioral symptoms is whether there is a comorbid diagnosis. Traditionally, hyperactivity, anxiety, obsessive-compulsive symptoms and phobias had been subsumed by the autism diagnosis [54]. The updated definition in DSM-5 allows for a co-morbid diagnosis of ADHD in patients with ASD [1]. Clarification of comorbidity may explain the variability in medication response in these subgroups (autistic without comorbidity vs. autistic with comorbidity). Appropriate rating scales to discern comorbid diagnoses such as a version of the Kiddie

Schedule for Affective Disorders and Schizophrenia (KSADS) called the Autism Comorbidity Interview-Present and Lifetime Version (ACI-PLV) have been developed but more research is needed [55].

4.5 Communication and Language Problems

Using a measure of subjective sense of well-being, such as those in QoL research, is particularly challenging in the autistic population whose core deficit is communication. For example, in our studies we found that patients who scored below a 7-year-old language level on vocabulary tests often had difficulty with abstract questions. Despite this concern, as above, we recommend use of the validated measures, PedsQL and Kidscreen.

5 Conclusion

In summary, the heterogeneity of ASD makes the study of medications in this population challenging, but as demonstrated, it is feasible. Treatment delivery and caregiver burden is measurable and should be considered more prominently in research of therapeutics because these factors are reflected heavily in efficacy. It is clear that in order to improve the QoL of patients with ASD, pharmacotherapy must be coupled with multimodal therapies to give patients and their families the greatest number of tools to manage their daily challenges.

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