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The Quality of Life (QoL) in Attention Deficit Hyperactivity Disorder (ADHD)

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Additional information is available at the end of the chapter

Abstract

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by inattention, impulsivity, and hyperactivity of core symptoms, affecting 3-10% of school age children, as well as 4% of adults.

Quality of Life (QoL) is an individual perception in regard to his/her position in life, in the context of culture and value systems in which they live, and in relation to their goals, expectations, standards and concerns. Then it has a multidimensional concept, the core of which consists of the physical, psychological, cognitive, and social aspects of functioning.

Several studies on QoL in ADHD have been published pointing out that QoL domains in ADHD have been found to be negatively affected compared to the healthy persons. This situation suggests that ADHD not only affects academic achievements of a person but it also has a deteriorating effect on all aspects of life, including social and occupational. Mostly used pharmacological agents are atomoxetine, methylphenidate and other stimulants related to QoL and ADHD context. These agents of ADHD treatments have been correlated with an improvement in QoL scores. Non-pharmacological interventions and their effects on QoL in patients with ADHD or the effectiveness of combined treatment modalities should be carried out in the near future.

Keywords: Attention deficit hyperactivity disorder, quality of life, children, treatment

1. Introduction

Quality of life (QoL) and its evaluation have become an increasingly important measure of outcome in all age groups of mental health clinical work and research [1]. WHOQoL group describes QoL as "the individuals' perception of their position in life, in the context of culture

and value systems in which they live, and in relation to their goals, expectations, standards and concerns" [2]. QoL is a multidimensional concept, the core of which consists of the physical, psychological, cognitive, and social aspects of functioning [1].

Attention-deficit/hyperactivity disorder (ADHD) is a psychiatric disorder characterized by inattention, impulsivity, and hyperactivity that affects 3–10% of school age children [3]. Although most commonly thought of as a childhood disorder, ADHD affects children, adolescents, and adults. It persists in adolescence in approximately 80% of patients, and approximately 4% of adults are affected with ADHD [4]. ADHD is associated with a significant impairment of cognitive, emotional, and psychosocial functioning [5]. Also, children with ADHD can develop problematic relationships with families, and this pattern may continue into late adolescence and adulthood [6].

Several studies on QoL in ADHD have been published. Available studies confirm that ADHD impairs QoL in the sufferers [7]. QoL has the potential to be an important outcome measure. Understanding the impact of ADHD on QoL can be informative on a number of levels. In this chapter, we provide a review of QoL in adults, adolescents, and children with ADHD. We will be addressing the definition of QoL, providing an overview of what ADHD involves, and discussing four main issues:

1.   The impact of ADHD on QoL

2.   The relationship between ADHD symptoms and QoL

3.   The effects of ADHD treatments on QoL domains

4.   Appendix: The QoL measurement tools (generic and health-related scales)

2. The Quality of Life (QoL)

Quality of life (QoL) is a term explaining a satisfaction of life and fulfillment of one's expectations within the social and cultural milieu in which one lives and works. This QoL definition includes physical and mental health, independency levels, social relations, environmental issues, activities, individual beliefs, point of views of life itself and health, expectancy, and habits. All QoL definitions consist of physical, psychological, and social domains [1]. Health-related quality of life (HRQoL), on the other hand, is a multi-dimensional definition that consists of the parts of the QoL domains of the affected person by a disease. HRQoL attempts to measure to what extent the patient's activities are affected on a daily basis due to the disease [2]. In medical literature, it is observed that the terms QoL and HRQoL are used interchangeably. In this section, QoL and HRQoL terms will be used as synonyms in issues related to the quality of life.

The term QoL seems to have existed in sociological and medical terms since antiquity. Aristo and subsequent philosophers noted that the main purpose of life was reaching the optimized state allowed by life itself [3]. Hippocrates, building the foundations of medicine, taught his pupils that they must take responsibility for increasing the state of well-being to the highest

point during treatment procedures [4]. Excluding these general teachings, the term QoL was first reported in medical literature in 1960 with Long's article titled "On the quantity and quality of life." Six years later, it was again used in the editorial section of *Annals of Internal Medicine*, "Medicine and the Quality of Life" [5]. In subsequent years, QoL has been at the center of many debates, discussing how to define it, how to measure it, and which scales have the highest levels of validity [6].

Because QoL assessments are a crucial health parameter, it has been necessary to develop QoL measurements for children. Child QoL studies began in the 1980s. Herndon et al. (1986) evaluated the quality of life of 12 children with severe burns that affected physical functioning. This study conducted an evaluation based on the degree of the burn and how it affected psychosocial adjustment [8]. Two studies, conducted by Ditesheim and Templeton (1987) and another one reported by Henning et al (1988), are the very first studies in evaluating children's QoL [9, 10]. These first QoL studies of children were important in leading to the development of QoL scales in child age groups.

QoL scales are evaluated generally under two main headings; a general (generic) evaluation of well-being and the QoL developed after a specific disorder. They have superior and limiting aspects from one another. Generic QoL scales are created by comparing two people: one with any disorder to one who is healthy. Therefore, generic QoL scales have advantages in terms of applicability to public health studies, and comparison studies enabling the evaluation of subjects with disease and subjects without. However, the low sensitivity of generic QoL scales and their long-term evaluation phases can be seen as negative aspects. On the other hand, disease-specific QoL scales are valid only during the evaluation of the disease they have been developed for. This increases the internal consistency of the scale, as well as the sensitivity and specificity. However, a negative aspect of disease-specific QoL scales is, because they are only valid for a single disease, there is the question of which scale should be used for patients with multiple diseases [7]. Both generic and health-related QoL scales are available for evaluating QoL in adults and children with ADHD. All measurement tools mentioned throughout the text can be seen in the appendix.

3. Attention deficit hyperactivity disorder

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder consisting of inattention, hyperactivity, and impulsivity, unsuitable for the child's age and developmental level. By far the most common disorder in childhood, it causes impairment in social, cognitive, academic, and emotional domains.

Epidemiological studies have pointed out that ADHD prevalence in children throughout the world is at a 3–10% rate. A large number of studies have shown that the symptoms of ADHD and functional impairment continue during the adulthood period. With age, however, its prevalence decreases. The adult ADHD prevalence rate is 4% [11]. Community-based studies have shown that the frequency of ADHD in boys is 2 to 3 times higher than in girls, and this rate increases up to 9 times in clinical sample studies. The inattention subtype of ADH is seen

more frequently in girls, whereas the combined subtype of ADHD is seen more dominantly in boys. Because girls have more prominent inattention symptoms and they have less conduct disorder, they are admitted to the hospital at a lower rate [12].

ADHD, though its etiology is still not clearly understood, is a disorder in which genetic and environmental factors play crucial roles. Family, twin, and orphan studies support the importance of genetic factors in the etiology of ADHD. The heritability rate of ADHD has been found at a 76% rate in genetic studies. Genetic predisposition to ADHD is identified by the combination of the effects of many genes. Environmental factors that lead to ADHD, on the other hand, are more influential in those who have a genetic predisposition to disease [13]. Neuroimaging studies have revealed that there is a relationship between a delay in cortical maturation and ADHD. Previously, a dysfunction located in the prefrontal-striatal pathways was thought to play a crucial role. However, later studies have shown that the etiopathogenesis of ADHD is a widespread dysfunction in a number of locations such as the frontoparietal-cortical pathways, corpus callosum, anterior cingulate cortex, and cerebellum. These areas are responsible for functions such as cognitive processing, attention, motor control, executive functions, response inhibition, reward, and motivation. Neuropsychological problems and behavioral symptoms of ADHD are considered to be a result of structural and functional abnormalities in fronto-striatal-cerebellar circuits [14]. Findings obtained from neuropsychological evaluations and neuroimaging studies are very important but not sufficient to be used in the diagnosis of ADHD. Thus, ADHD is still a clinical diagnosis based on detailed history, clinical observations, and a physical and neurological examination. Clinicians should refer to the information from parents and teachers regarding the symptoms of children. It is important to determine the severity of the symptoms before and after treatment with valid and reliable rating scales [13].

Children, adolescents, and adults diagnosed with ADHD have a high rate of comorbid psychiatric disorders. Studies have rated this comorbidity from 46% to 76%. Oppositional defiant disorder (40–60%), conduct disorder (10–20%), anxiety disorder (30–40%), and mood disorders (20–30%) are the most frequently seen comorbid disorders [15]. Alcohol and substance abuse are two problems patients face in their adolescence or adulthood. The presence of comorbid psychiatric disorders during the progress of ADHD negatively affects both the treatment process and the prognosis.

Even though ADHD is mostly diagnosed during childhood, follow-up studies have pointed out that 60–80% of patients continue to have symptoms of ADHD during adulthood [14]. It is known that during the transition to adolescence and adulthood, the symptoms of ADHD vary. Hyperactivity decreases during and after adolescence, and restlessness, feelings of discomfort or risky behaviors become dominant instead. However, in adulthood, symptoms such as difficulty in maintaining attention, forgetfulness, an inability to organize, an inability to complete plans, frequent change of jobs, marital problems, and changes in mood are seen [16].

The treatment of ADHD is a multifaceted approach that includes psychosocial interventions as well as pharmacotherapy. For adults, cognitive-behavioral therapy (CBT) is seen as an effective intervention method to treat ADHD [17, 18] or as an added approach to the ADHD medication as a supplement, to being effective in ADHD treatment [19, 20]. Similarly, behav-

ioral management is also the most commonly used psychosocial approach in children with ADHD and has different forms for parents (such as behavioral parent training [BPT]), for teachers (such as training of classroom behavior management), and for children (such as summer treatment program [STP] and operant conditioning trails) [21, 22, 23]. STP is a multi-modal intervention, developed by Pelham et al. (1996), consisting of parent training, classroom implementation, practicing and tutoring of academic and sport skills, and social skill training [22]. Using these psychosocial approaches with pharmacotherapy could result in giving lower doses of medication to children with ADHD [23]. In adolescents with ADHD, behavior therapy (BT) was found to be effective compared to the medication, though BT had brought about greater improvement on overall functioning measures than that of medication [24]. CBT is another psychosocial intervention used in adolescents, which mostly relied on behavioral principles and was shown as effective [25, 26].

Pharmacotherapy is needed for many ADHD patients to control the symptoms and to decrease functional deteriorations. The first step in medication for the treatment of ADHD is stimulants. Stimulants are known to be generally safe and effective, and their clinical response rate is considered to be about 70%. Among non-stimulant medications, those frequently used are atomoxetine, alpha-2 agonists (clonidine and guanfacine), tricyclic antidepressants, and bupropion. Beginning the treatment in the very early stages of the disease and using effective dosage positively affects its prognosis and it leads to fewer problems in adulthood [27].

4. The impact of ADHD on QOL

Difficulties stemming mainly from the core symptoms of ADHD (inattention, hyperactivity, and impulsivity), affect many aspects of the lives of children and their families. It has also been long known that there is a relationship between a wide range of developmental, cognitive, social, and academic insufficiencies and ADHD [28]. Children and adolescents with ADHD experience more difficulties in social relations than that of their non-ADHD peers, especially in terms of establishing a relationship [29]. Also, ADHD in adults has been found to have specific and disabling effects on substance abuse, driving, divorce, lost years of schooling, unemployment, underemployment, poor self-esteem, and as a risk for other disorders [30]. Thus, a QoL assessment is especially important in disorders of a chronic nature that cause difficulties in almost every aspect of life such as ADHD. Studies examining the relationship between ADHD and QoL have gained momentum because QoL has become more prominent among health-related indicators.

Evaluating QoL in adults or children with ADHD has ultimately been possible by using generic QoL scales. A study conducted by Mick et al. (2008) showed that the psychometric properties of "Quality of life enjoyment and satisfaction questionnaire (Q-LES-QSF) [31]," one of the generic QoL scales, had internal consistency at a 0.88 rate in adults with ADHD, showing that it would be appropriate for evaluating QoL in ADHD [32]. Studies carried out in adults with ADHD have shown evidence of lower levels of QoL when compared to non-ADHD controls. In a study where the QoL of older patients with ADHD were evaluated with 148 adults aged

over 50 years, the quality of life levels, determined by using EurQoL [33], the generic QoL scale, and life satisfaction levels were found to be significantly lower than that of population normative results due to an important decrease in QoL aspects such as mobility, self-care, general activity, pain/discomfort, and anxiety/depression [34]. Similar to this report, a study conducted by Kooij et al (2005) with 1813 adults who had ADHD-DSM-IV symptoms that were obtained from self-report evaluations demonstrated psychosocial impairments [35]. This study revealed that inattentiveness and hyperactivity scores were significantly associated with the measures of impairment, evaluated by using the General Health Questionnaire (GHQ-28) [36], one of the generic QoL scales. Even after controls for the GHQ-28, it was concluded that ADHD is not merely a child psychiatric disorder that persists into young adulthood, but is an important and unique manifestation of psychopathology during the entire lifespan [35]. These findings support the idea that ADHD has significant effects on the QoL measured by generic QoL scales and other questionnaires evaluating daily functions and other aspects of life throughout the world.

As far as children with ADHD and their QoL measurements using generic QoL scales are concerned, a large number of studies pointed out similar findings with that of the adults' reports. A study reviewing other studies related to children with ADHD and their QoL, Danckaerts et al. (2010) revealed that there were a total of 36 QoL and ADHD studies, and 29 of them evaluated the QoL of children with ADHD, using generic QoL scales [37]. Some of these studies have pointed out that there is an important decrease in all measurable areas [38, 39, 41], as well as only the "psychosocial areas" [42, 43] of QoL domains in patients with ADHD compared to healthy subjects. Taking a closer look at these findings, a study, conducted by Varni et al. (1999), showed high reliability in assessing the QoL of children aged 5–16, including 72 with ADHD, 66 cancer patients, 57 cerebral palsy patients, and 3,256 healthy subjects, through the use of the Pediatric Quality of Life Inventory (PedsQL), a generic QoL scale [38]. Similarly, Escobar et al. (2005) conducted a study consisting of 237 children between the ages of 6 and 12, where 124 of them had ADHD, 93 of them had asthma, and 120 were healthy subjects [39]. In this study, QoL assessment was examined with the Child Health Questionnaire (CHQ) [40] scale. The results indicated that children with ADHD showed impaired psycho-social functioning (compared to the asthma group) and an impaired psychosocial and physical functioning (compared to the healthy group). Differences between the ratings for children with ADHD and asthmatic children were smaller than that of the ADHD group and the healthy children.

Another study reported an important difference in connection with QoL between children aged 8–12 with ADHD and healthy controls [41]. In this study, all subscale scores of PedsQoL-parent forms and "psychosocial health" and "total scale" scores of PedsQoL-children forms were found to be significantly lower in ADHD group than that of the healthy controls. Kandemir et al. (2014) examined 76 ADHD children and 59 healthy subjects aged 7–16 years, using PedsQL. As a result, the PedsQL-child scale psychosocial health subscale and total scale scores of the ADHD patients were significantly lower than the control group [42]. Similarly, another study, using CHQ, revealed that ADHD has a deteriorating effect on multiple aspects of QoL [43].

There may also be a distinct difference between parents' reports and their children's with respect to QoL measurements. In a review, 36 QoL studies conducted between the years 1998 and 2008 were evaluated, concluding that parents evaluated their children's QoL parameters lower than their children rated themselves [37]. During the evaluation of QoL parameters and ADHD's effect on it, the question arose of whether or not ADHD subtypes make a difference. According to the assessment of ADHD subtypes and their effect on QoL parameters, Landgraf et al. (2002) found that children with ADHD combined type had a poorer QoL than children with ADHD inattentive type, both in the area of emotional-social well-being and in how they functioned at home [44]. As shown, a great number of factors could affect studies' findings of ADHD and QoL and could lead to different results. Among these factors are the following: sampling's age group, using different types of QoL scales, choosing proxy or self-report scales (whether filled out by parents or children), and different cultural contexts.

There are also a great number of studies evaluating QoL domains through ADHD-specific QoL measures in both adults and children. Brod et al. (2006), for instance, revealed that adults with ADHD had lower QoL scores, when compared to controls and subthreshold groups, using Adult-ADHD Quality of Life scale (AAQoL), a disease-specific QoL [45]. Another report showed that Taiwanese adult subjects with ADHD had a poorer quality of life than that of controls [46]. It also has been pointed out that ADHD subjects took longer to fall asleep, had lower sleep efficiency, and had shorter periods of uninterrupted sleep, which were consistent with subjective complaints. Alongside this, actigraphic measures of ADHD subjects showed continuously elevated day-time activity levels that resulted in a 24-hour pattern that was more stable and less variable than in controls [47].

Gjervan et al. (2012) assessed the relationship between ADHD symptoms and specific QoL areas in 149 adults with ADHD. In this study, there was a negative correlation between all of the components of QoL, and the inattention and hyperactivity scores, though this correlation was most prominent between inattention scores and vitality scales and between hyperactivity symptoms and mental health scale scores. This study concluded that inattention was only significant as a predictor of emotional outcome scores and hyperactivity was significant as a predictor of both mental health outcome scores and social functioning scores. A relationship between age/sex and aforementioned mental components was not found [48]. In contrast to this report, a study revealed the predictors of QoL, reporting a difference in the QoL scores of different sexes and pointing out that the QoL predictors were income levels for men and inattention symptoms for women [49]. Because findings have revealed that the QoL and its effects on sexes differ, there is a need for further evaluation of other environmental issues and their roles in future studies.

Studies carried out with children and adolescents using ADHD-specific QoL scales have highlighted similar conclusions as adult studies. A study conducted by college students showed that the ADHD group reported a lower quality of life compared to the non-ADHD groups [50]. Another study, a pooled analysis of a total of 136 girls and 658 boys (from one Canadian sample and four European samples) with ADHD showed impaired QoL levels [51]. In conclusion, ADHD is associated with a variety of functional impairments in every aspect

of daily life, from academic achievements to social and occupational areas in both children and adults, as well as a significantly lower quality of life than of those without ADHD.

5. The relationship between ADHD symptoms and QoL

5.1. Symptom severity

A large number of studies in both adults and children with ADHD have shown that there is a negative correlation between ADHD severity and QoL parameters. A study revealed a relationship between a deteriorated QoL and ADHD symptom severity and unemployment in patients aged over 50. Both the severity of ADHD symptoms and inattention symptoms have been found to be correlated with the general activity levels of QoL scale scores and current health status sub-scores [34]. Similarly, a negative correlation was reported between the number of ADHD symptoms (ASRS) and the AAQoL total score [52]. Another study pointed out that the ADHD-RS-IV scores of 725 adults with ADHD were correlated with an improvement in both ADHD symptoms and its health-related QoL domains. In this study, inattention symptoms were found to be more predictive of QoL scores than that of hyperactivity/impulsivity symptoms [53]. In a study of 369 university students with ADHD symptoms, determined by using the "Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)" criteria, it was reported that their satisfaction with life scale (SWLS)'s scores were negatively correlated with all the other measures. Among males, poor social functions were the best predictor of dissatisfaction with life, whereas among females, it was poor emotional control. This implied that both ADHD symptoms and associated problems are significantly related to a lower satisfaction with life, arguing that ADHD symptoms and associated problems were found to be negatively related to subjective well-being [54]. Similarly, Brod et al. (2006) reported a negative correlation between adult self-report scale (ASRS) scores and QoL, where more severe symptoms of ADHD were associated with lower levels of QoL [45]. Another study evaluated the quality of life of 127 Israeli young adults who were living in community residences, diagnosed with borderline intelligence quotient, and attention-deficit/hyperactivity disorder. They studied the subjects with regard to their personal data, disability data, and social ecology data. Overall, they discovered that the QoL was associated with their inclusive education, the total attention-deficit disorder symptomatology score, the monthly income, the amount of participation in leisure activities, and having a personal friend. Two significant predictors of QoL were found to be attention-deficit disorder symptomatology score and monthly income. Additional analyses indicated that among younger residents, the two significant predictors were inclusive education and a high monthly income, whereas the predictors for older residents were a low level of medical disability and a low attention-deficit disorder symptomatology score [55].

Similar to studies of adults, studies of children with ADHD pointed out a negative correlation between symptoms of ADHD and QoL domains. In their two studies, Wehmeier et al. (2010, 2012) showed a correlation between the ADHD rating scale and CHIP-CE [56] scores, another generic QoL scale, where both were similar in both genders, with low scores at baseline

measurement and increased to a moderate level at endpoint assessment [29, 51]. Another study called ADORE, the ADHD Observational Research in Europe, made an important contribution to the evaluation of QoL using parent report forms (PRF) of the Child Health and Illness Profile-Child Edition (CHIP-CE) scales. With the participation of 1,500 parents from 10 European countries, children with ADHD between the ages of 6 and 18 were evaluated. In their conclusions, higher ADHD scores were found to be a predictor of lower QoL scores [57]. Studies using the CHQ-PF-50 scale for evaluating QoL found a statistically significant relationship (from small to moderate range) between QoL and ADHD, where both inattention and hyperactivity symptoms were found to be strongly related to psychosocial health subscale scores [43, 58]. All in all, assessing the above-mentioned results, a negative relationship between ADHD symptom severity and QoL, independent from age, is noticeable.

5.2. Functional impairment

The evaluations of QoL and functional impairment have many similar and different aspects from each other. In adults, ADHD determined by using self-report evaluations was found to be correlated with not graduating or being unemployed and these subjects were much more likely to experience relationship problems than those without ADHD diagnosis [59]. Brod et al. (2012) examined the burden of illness and QoL in 24 patients over the age of 65 and compared the findings of population data of younger adults with ADHD. Older ADHD adults showed a significantly greater impairment in productivity and a better life outlook than younger ADHD adults. In addition, 63% of participants had experienced problems such as financial difficulties, academic failures, poor working performance, and social isolation accumulated over a lifetime of living with ADHD [60]. A community-based study evaluating middle-aged adults with ADHD revealed a correlation between ADHD symptoms and both depression-anxiety scores and functional deterioration (as determined in "health," "subjective well-being," "building of social relationship skills," and "maintaining a healthy relationship" measures). After controlling depression-anxiety symptoms, the relation found between ADHD and functional deterioration was to remain [61]. Similarly, ADHD in young adults (ages 18 to 30) was found to be associated with significant impairments in multiple functional domains [62]. In another study, conducted with 3,400 university undergraduates, those with self-reported ADHD had significantly lower grade point averages, poorer emotional stability, and greater academic and social concerns than students who had never been diagnosed with ADHD [63]. Another study revealed that social functions were the best predictor of dissatisfaction with life, whereas among females it was poor emotional control, and both ADHD symptoms and associated problems are significantly related to a poorer satisfaction with life [53].

Detecting problems at the functional level is mainly carried out by clinicians, while the evaluation of QoL is done by the patient or their parents or caregivers. Rimmer et al. (2007) reported a mild correlation between functional impairment evaluated by a clinician and a QoL assessment carried out by children with ADHD or their parents [64]. In conclusion, studies reported that ADHD causes deterioration in the functioning of patients. However, in each

study, the affected life domains were found to be different. This situation could very well stem from the chosen samplings' age groups.

5.3. Comorbidity

A large number of studies pointed out that mental diseases accompanied by ADHD are common, and this affects individuals' QoL levels [37, 65-67, 69, 70]. A high level of psychiatric disorder comorbidity was reported by Lensing et al. at a 70.9% rate in adults with ADHD. QoL scores were found to be negatively affected in those who had comorbid psychiatric disorder. Also, these patients' QoL scores have been found to be lower in terms of their current health status, general activity levels, and mobility [34]. A study examining the effects of depression symptoms on QoL scores in adults with ADHD revealed that a total of 131 Korean soldiers were included, and ADHD symptoms were found to be affected by the symptoms of depression. However, depression symptoms had an indirect effect on QoL scores as a mediator [65]. Similarly, a study evaluating ADHD symptoms and anxiety-depression scores in 1382 of young persons between ages 19 and 30 found that there was a correlation between ADHD symptoms and anxiety or depression scores. The presence of depression or anxiety symptoms was found to have a negative effect on QoL scores [66]. In another study conducted with 319 prisoners where the psychopathology and QoL were evaluated, 68 of them were diagnosed with ADHD [67]. This showed that patients diagnosed with ADHD had more psychiatric comorbid disorders. This study also revealed that although prisoners with ADHD had similar risk factors than non-ADHD prisoners, their mental health, mental summary, emotional role limitations, and social functioning scores, as assessed by SF36-QoL [68], the generic QoL scale, were significantly lower than those of non-ADHD. Liew and Cavanna (2013) showed that those with ADHD with Tourette syndrome (TS) had a lower HR-QoL level than that of patients without it. They set out to compare tic severity and health-related quality of life (HR-QoL) ratings between adult patients with TS versus patients with TS plus ADHD. Comparing 40 patients with only TS to 32 patients with TS plus ADHD using standardized self-report measures of adult ADHD (Adult ADHD Severity Scale), tic severity (MOVES), and disease-specific HR-QoL (Gilles de la Tourette Syndrome Quality of Life Scale, GTS-QoL), they found a highly significant difference in tic severity as measured by the MOVES scale, with the TS plus ADHD group reporting higher scores. Likewise, there were significant differences in GTS-QoL scores, with the TS plus ADHD group demonstrating worse HR-QoL perception. Adult patients with TS and comorbid ADHD tended to have higher tic severity and poorer HR-QOL compared to patients with only TS. As a result, clinicians treating adults with TS should screen their patients for residual ADHD symptoms in order to ensure that appropriate management is provided to prevent potential behavioral difficulties and other functional impairments [69]. A study was reported in relation with psychiatric comorbidity, age, and sex in subjects up to age 18 with treatment-naive ADHD. Results of this study were evaluated after being categorized as dimensional and categorical. A lower self-reported QoL was associated with females, older subjects, more symptoms of anxiety, and trauma-related disorders (in dimensional approach terms), and with comorbid diagnoses of trauma-related disorders and oppositional

defiant disorder (ODD)/conduct disorder (CD)(in categorical approach terms). A lower parent-reported QoL was related to older subjects and increasing number of symptoms of mood and anxiety disorders on one hand, and any diagnosis of mood and anxiety disorders and ODD/CD on the other. Consequently, researchers have emphasized that during the evaluation of QoL in ADHD, age and sex variables, as well as both parents' and children's scales should be evaluated altogether [70]. It can be concluded that comorbid psychiatric disorders accompanying ADHD have a negative effect on QoL perceptions.

6. The effects of ADHD treatments on QOL

The concept of QoL has helped us understand the effects of medical conditions on individuals, as well as increasing our awareness of how treatments of diseases affect patients' life domains. ADHD treatment options including psychosocial approaches and pharmacotherapies have been shown to be effective in ameliorating both ADHD symptom scores and QoL measurements in both children and adults.

6.1. Psychosocial approaches and QoL in ADHD

There are a few studies regarding psychosocial programs and their effectiveness in treating ADHD and improving QoL compared to the medication studies. Cognitive-behavioral therapy (CBT) group intervention approach, one of the psychosocial methods, was shown as effective in low self-esteem and self-efficacy domains in adults with ADHD [17]. In another randomized controlled study, including a CBT booster-trial group, a CBT group and a control group, CBT booster sessions were shown to be as effective on Chinese adults with ADHD [18], using WHOQoL, another generic QoL scale [71]. Another study showed that CBT combined with pharmacotherapy of ADHD resulted in improvements of overall functioning assessed by clinical global impression scale (CGI) as well as ADHD symptoms [19]. Similarly, CBT combined with usual ADHD medication improved both the self-rated ADHD symptoms and social and occupational functioning in comparison to ADHD medication alone [20]. The other psychosocial approaches added to the ADHD medication in adults were also reported to be effective, though medication was found to be superior to placebo and psychosocial programs [72]. On the other hand, a review examining the effects of psycho-education interventions on outcomes of children and adolescents with ADHD highlighted that programs focusing on the communication between children and their parents and/or teachers and coping skills of parents had some positive effect on the clinical outcomes [73]. BPT has been shown to be effective in parent-child conflicts to improve child oppositional behavior rather than ADHD symptoms themselves [21]. Teacher training for contingency management procedures such as strategy training and curriculum modifications as well as punishment techniques were also found promising in altering the level of ADHD symptoms [22]. CBT was also shown as more effective in adolescents with pure ADHD or in those with anxiety/depression symptoms comorbidity than that of adolescents with ADHD and in those with comorbid oppositional

defiant disorders [26]. Psychosocial interventions added to ADHD medication was reported to be effective in ameliorating the core ADHD symptoms and functional impairments accompanying it [74].

6.2. Atomoxetine (ATX) and QoL in ADHD

Medication use for ADHD treatment and its effects on QoL domains is a well-studied issue. In the literature, studies evaluating QoL and ATX have been noticeably more common than that of other agents. With randomized, double-blind, placebo-controlled studies, ATX had a positive effect on the QoL of both adults and children with ADHD as well as with open-labelled designed reports [29, 51, 53, 57, 62, 74-78].

For adults with ADHD, ATX is the only United States Food and Drug Administration (FDA)-approved, non-stimulant drug. In studies conducted with adults with ADHD, the improvement of ADHD symptoms and QoL domains have been shown in many adult ADHD trials in ATX treatment groups compared to the placebo group [62, 74-78]. These improvements were not only statistically significant, but also showed a clinically meaningful improvement in symptoms [79]. A double-blind, placebo-controlled study, during 12 weeks of ATX treatment consisting of young adults with ADHD, revealed more improvement in ADHD symptoms, executive functions, and QoL scores than that of the placebo group [62]. Similarly, in the first large sampling of placebo-controlled prospective studies, ATX group's QoL total scores and all subscores (except for life outlook subscale) were found significantly improved compared to the placebo group [75]. In the first placebo-controlled design of an Asian sampling study, ATX was found as safe and tolerable in adults with ADHD for 10 weeks. Compared to the placebo, ATX was more effective on ADHD core symptoms and showed more improvement in QoL scores than that of the placebo group [76]. The study examined the effectiveness of ATX in adults with ADHD, at 10 weeks of the treatment and at six months and total QoL scores and ADHD symptom rating scores evaluated by the clinicians and clinical global impression scale scores were found significantly improved over that of the placebo group [78]. The evaluation of adults with both ADHD and comorbid social anxiety disorder after 14 weeks medication with ATX revealed that QoL total scores, state anxiety scores, social anxiety scores, and clinical global impression scores were significantly improved in ATX group over that of the placebo group [80].

For children and adolescents, ATX has also been the most studied pharmacotherapeutic agent in ADHD and QoL. In a randomized, placebo-controlled designed study of Swedish children with ADHD, ATX treatment was found as effective on Child Health and Illness Profile (CHIP) QoL domains [74]. Similar to this study, Escobar et al. (2009) reported that ATX was superior to that of a placebo on CHIP-CE scores [81]. Another randomized, double blind, placebo controlled study, conducted among 180 children and adolescents with ADHD and comorbid ODD/CD for nine weeks, showed that ATX had a positive effect on QoL domains [82]. In another study of comorbid oppositional defiant disorder and ADHD, Dell'Agnello et al. (2009) showed that ATX was more effective on CHIP-CE QoL domains than that of a placebo [83].

Also, with open-label designed studies, ATX has been shown to cause an increase in the QoL of children with ADHD [84, 85]. Montoya et al. (2014) examined the prognostic factors of improvements of ATX treatment in children and adolescents with ADHD, concluding that a baseline level of impairment in health-related QoL could be an early prognostic factor of clinical outcomes of ADHD treatment [86]. Also, another analysis of pooled data (from 5 clinical ATX trials (four from Europe and one from Canada) of similar durations (8- to 12-week follow-ups) and with similar inclusion and exclusion criteria) evaluated whether gender makes a difference in QoL domains with ATX treatments. It showed that there were correlations between HR-QoL and ADHD core symptoms. Boys and girls were similarly impaired at baseline with minor differences in some of the subdomains. The treatment effect of ATX was significant in both groups for the risk-avoidance domain and its subdomains [51].

6.3. Stimulants and QoL in ADHD

There are relatively few studies related to QoL and stimulants such as methylphenidate (MPH), amphetamines and lisdexamfetamine dimesylate (LDX), although they are the most used agents in ADHD treatment. Adult studies with stimulants and QoL in ADHD unanimously pointed out the efficacy of these medications on ADHD symptoms and QoL measurements. Mattos et al. (2013) showed OROS-MPH, a long-acting methylphenidate, was found effective, in a 12-week, multicenter, open-label trial involving 60 patients. All subscales of QoL improved from baseline to week 12, as well as the total score of QoL. In addition, significant improvement was pointed out by the Clinical Global Impression-Improvement (CGI-I) scale, depression scale, state-trait anxiety scale, ADHD symptom rating scale [87]. The placebo-controlled study examined the sleep quality and its relation with MPH treatment in adult patients with ADHD. Then, pre-treatment and after-treatment of sleep parameters, activity, and circadian rhythm were evaluated [47]. Data obtained from ADHD subjects at the beginning were compared with healthy persons. Actigraphic sleep estimates revealed that ADHD subjects took longer to fall asleep, had lower sleep efficiency, and had shorter uninterrupted night sleep. In addition, ADHD subjects showed continuously elevated daytime activity levels, resulting in a 24-hour pattern that was more stable and less variable than in controls. With MPH treatment, a decrease was found in waking throughout the night sleeps, concluding that there was an improvement in sleep quality despite the reduction in total sleep time. Kooij et al. (2001) evaluated the effect of MPH and dextroamphetamine treatments on sleep parameters in 8 adults with ADHD in a case-control study [88]. Actimeters were used to assess nocturnal motor activity for six consecutive nights both at baseline and after three weeks of treatment. ADHD patients slept worse and showed significantly higher nocturnal motor activity at baseline compared with controls. When within-group changes were compared between ADHD subjects and controls, treatment with stimulants tended to be associated with a reduction of Activity Level and Movement Index scores and improved sleep quality in ADHD patients.

An open-labelled designed study examining effectiveness of long-acting amphetamines in adults with ADHD for eight months found strong responses to the amphetamine treatment. This study revealed that changes in the symptoms and treatment satisfaction mediate inde-

pendently the mental outcome of QoL but not the physical outcome. Inattention symptoms were found as strong mediators for QoL outcomes compared to the disruptive behaviors [53]. A positive correlation between improvement of executive functions and health-related quality of life scores in adults with ADHD treated with triple-bead mixed amphetamine salts (MAS) was pointed out according to the evaluation of two large-sampled, randomized, placebo-controlled and double-blind study results [89]. Similarly, another study in adults with double-blind, placebo-controlled design for seven weeks showed a significant improvement in all subscales of health-specific QoL scores compared to the placebo results [90].

LDX was also shown to be effective in both ADHD core symptoms and in QoL measurements in adults with ADHD who had significant impairments [91]. Adler et al. (2013) examined the effects of LDX on QoL in adults with ADHD and clinically significant executive function deficits (EFD). In this 10-week randomized placebo-controlled trial study, LDX was just as effective on QoL and EFD measurements [92].

Stimulants and their efficacies on QoL parameters in children and adolescents with ADHD were also reported in the literature. Forty-five of treatment-naïve children with ADHD, aged 8–14, were assessed, based on self, parent, and teacher reports at the baseline and at the end of the first and third months of MPH treatment, regarding changes in inattention, hyperactivity, impulsivity, depression, anxiety, and obsessive compulsive symptoms. Symptoms of inattention, hyperactivity, and impulsivity were significantly reduced following a three-month MPH treatment. There were significant decreases in depression, trait anxiety, and checking compulsion symptom scores. Moreover, parents reported significant improvements in psychosocial and total scores of quality of life [93].

Gerwe et al. (2009) showed that in their 8-week, prospective, open-label, non-interventional trial, the impact of therapy with OROS-MPH on functioning in four different areas of life (school, recreation, family life, and peer interaction), severity of disease, and quality of life (QoL) as well as tolerability, were investigated under daily routine care. In this study, 306 patients, aged 10.2±2.3 years, were either transitioned to OROS-MPH from short-acting, immediate-release MPH preparations, or treatment was initiated with OROS MPH in MPH-naive patients. In both groups, therapy with OROS-MPH was associated with significant improvements in daily functioning, severity of disease, and QoL [94]. Another double-blind, open-label study designed with placebo controls examined MPH effects on QoL, conducted with children aged 7–10 who have ADHD and developmental coordination disorder comorbidity, over the course of four weeks. QoL was evaluated by using both children self-reports and parents' proxy-reports. Pre-treatment scores of autonomic, social, motor, cognitive domains of QoL and general well-being scores decreased, and after MPH treatment, scores of health-related QoL domains improved compared to the controls [95].

Lisdexamfetamine dimesylate (LDX) was also shown as effective in QoL measurements. Banaschewski et al. (2014) evaluated the effectiveness of LDX on QoL in a total of 262 children, aged 6–17, with ADHD [96]. CHIP-CE Parent Report Form, as QoL evaluation, was found during the pre-treatment period as lower in 4 of 5 sub-scales as one standard deviation of

normative means. After a treatment of 30–70 mg/day LDX for 26 weeks, all QoL subscale scores were found to be improved compared to the baseline evaluation. After 26 weeks, 76 of 153 patients who used LDX continued to take the same dosage of LDX whereas 77 of them used a placebo instead of LDX. During this new six-week period, QoL scores of all patients who used placebos deteriorated, while there was no difference in QoL scores of patients who continued with the LDX agent. During a six-week period, there was a statistically significant difference in terms of "Avoidance Achievement," and "Satisfaction domains" of QoL scores between two groups (placebo and LDX).

Other pharmacological treatments undergoing clinical trials as are follows [30]:

• Long-acting clonidine hydrochloride (Clonicel) (is in Phase III).

• Pozanicline (ABT-089), a neuronal nicotinic receptor partial agonist, might prove to be promising, as research has shown that this drug significantly improves QoL (measured with AAQoL), improves the core symptoms of ADHD, and also reduces the overall work impairment in the adult ADHD population.

• Sofinicline (ABT-894), another nonstimulant agent, is in clinical trials for ADHD and no QoL data are yet available.

7. Conclusion and summary

QoL is one the most important variables for evaluating health issues. The QoL of subjects who have ADHD has been revealed as decreased in almost all areas of life compared to the healthy persons. This situation suggests that ADHD not only affects academic achievements of a person but it also has a deteriorating effect on all aspects of life, including social and occupational. These findings have the potential to be cornerstones of applying treatment choices and regulating follow-up of ADHD. To be well-understood, the strengths and weaknesses of QoL and ADHD studies are important for designing further studies.

Most studies evaluating the relation between ADHD and QoL seem to have used generic QoL scales. These scales are appropriate and useful to determine QoL in different disease groups or patients who have concurrent diseases. At the same time, it is undeniable that generic QoL scales might not be correlated with the symptoms of ADHD, indicating that there is a need for specific evaluation of core symptoms of ADHD and their probable effects on QoL domains. In this perspective for evaluating adults and adolescents with ADHD and their QoL, self-report ADHD-QoL scales such as "The ADHD Impact Module for Adults (AIM-A)," "The Adult ADHD Quality of Life Scale (AAQoL)," and "The Adult ADHD Quality of Life-29 (AA-QoL-29)" or "The Weiss Functional Impairment Rating Scale WFIRS," and "The ADHD Impact Module-Child; AIM-C" are profitable. For QoL of children with ADHD, it is recommended that both self-report and the parent proxy forms of ADHD-QoL scales be used including "The EuroQoL Five-Dimension Questionnaire-Parent-Proxy Version; Parent-proxy EQ-5D." Because the number of ADHD-specific QoL scales is very limited, an increase in the number

of ADHD-specific QoL scales that have high reliability and validity scores will be useful for further application and evaluation of QoL in ADHD.

According to the literature, ADHD symptoms continue through the life span in many of the patients. This situation recalls that following the treatment and symptoms of ADHD in patients with ADHD, the child, adolescent, and adult forms of scales need to be used. In addition, ADHD has one of the most frequently observed comorbidity rates among the psychiatric disorders. In assessing QoL in ADHD, the frequency of comorbidity stands out as an aspect to be taken into consideration.

ADHD treatment consists of both pharmacological and non-pharmacological interventions. There is a specific notification that psychosocial interventions for treating of ADHD in both adults and children are seen at a lesser extent compared to the medication use. It is crucial to examine the further psychosocial approaches and their effects on both ADHD symptoms and QoL in adults and children. The use of many pharmacological agents in ADHD treatments has been correlated with an improvement in QoL scores. However, the presence of a small number of randomized placebo-controlled studies with agents, except atomoxetine, draws attention. In addition, there is a need for further study, including comparisons with different pharma-cotherapic agents. In addition, non-pharmacological interventions and their effects on QoL in patients with ADHD or the effectiveness of combined treatment modalities should be carried out in the near future.

Appendix

QoL scales

QoL scales are evaluated generally under two main headings; a general (generic) evaluation of well-being, and the QoL developed after a specific disorder. Generic and health-specific QoL scales both have superior and limiting aspects from one another. Generic QoL scales are created by comparing two people: one with any disorder and one who is healthy. Therefore, generic QoL scales have advantages in terms of applicability to public health studies, and comparison studies enabling the evaluation of subjects with disease and subjects without. However, the low sensitivity of generic QoL scales and their long-term evaluation phases can be seen as negative aspects. Disease-specific QoL scales are valid only during the evaluation of the disease they have been developed for. This increases the internal consistency of the scale, as well as the sensitivity and specificity. However, a negative aspect of disease-specific QoL scales is that they are valid only for a single disease and there is the question of which scale should be used for patients with multiple diseases [7].

Studies of QoL scales first began in adult groups. For evaluating physical functions of adults in QoL measurements, activities such as working conditions, self-care, tasks within the family, the ability to walk up the stairs, and the ability to sweep the house are questioned. From these studies, there are several QoL scales for evaluating the adults' QoL domains. On the other hand, it has since become clear that the evaluation of children's QoL has many different aspects

than adult QoL assessments. Activities, for instance, are differently evaluated from children with parameters like being able to eat, going to the toilet on their own, being able to perform minor chores, and gaming activities. Although activities in school or relationships with friends are not crucially important in adults when assessing social functioning, in children activities in school, peer relations, game playing, and adjustments to school are very important. Areas of emotional and cognitive functioning, body image, autonomy, family relations, and expectations of the future should be assessed for each age group (adults, adolescents, and children) differently. For these reasons, during QoL evaluations, using adults' QoL scales to evaluate adolescents or using scales developed for evaluating adolescents or children is not deemed appropriate without making age-appropriate changes [58].

The question of whether or not the assessment of QoL of children should be made by children themselves or their parents has been discussed for many years. Some researchers argue that a subjective assessment is more valuable because it reflects the conditions of children from their own perspective, while others suggest that an objective assessment made by parents with proxy scales has more validity [7, 97]. In general, it is proposed that scales used for evaluating QoL should be filled by the individual himself. However, the necessity of using proxy-report scales instead of self-report scales in persons who are too old, too young, or too sick to fill out the forms themselves has brought about the discussion of who will fill out the QoL scales. In last decade, the idea that children, after 3 years of age, need to self-assess their quality of life as much as possible has become more dominant. If children or adolescents are too young or too sick to answer the questions, or if they do not wish to, then, to evaluate their QoL, the use of the parents' version of QoL scales is recommended. In this case, the negative aspects of using parents' scales should be considered, which are as follows:

- Parents will not be able to know precisely what their child is experiencing from the symptoms, the child's relationship with his peers, or about his concerns for the future.

- Being affected by other children while filling out the scales, or the possibility of being affected by their own expectations and hopes, stress, or mental states at that moment.

Where possible, the use of scales that can be compared between parents and children seems to be the most appropriate solution. However, because these scales are limited in number and the results of the parents and children are not always compatible with each other, there are difficulties in using combined parent proxy and self-reporting. When analyzing parents' and children's scales simultaneously, children, unlike their parents, did not seem to be affected by the cause of the disease or its treatment; they look at their disease more optimistically. Having friends and their ability to run and play are the more important issues for them than the necessity of basic skills and aptitudes. Besides this, it should be noted that the level of the cognitive development of the child affects the ability to fill out the scale [7].

Generic QoL scales

Some generic QoL scales used in adults and children and adolescents are as follows:

For adults

1. The Quality of Life Enjoyment and Satisfaction Questionnaire Short Form (QLESQ-SF): It has five domains of questioning, including physical health, mood, family relationships, ability to function in daily life, and taking any treatment or medication, via a Likert-type order from very poor to very good [31].

2. The EuroQoL-Five Dimension Scale (EurQoL-5D): This is a standardized instrument designed by EurQoL Group evaluating health outcomes and is comprised of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, each with three response levels: no problems, some problems, and extreme problems. It is also allowed to rate each dimension on a vertical visual analogue scale (VAS) from 0 (worst imaginable health state) to 100 (best imaginable health state) [33].

3. The General Health Questionnaire-28 (GHQ-28): This scale is a summary of GHQ and consists of four subscales: somatic symptoms, anxiety and insomnia, social dysfunction, and severe depression [36].

4. The Short Form-36 General Health Survey Questionnaire (SF-36): This is a short questionnaire with 36 items that measure eight of multi-item variables: physical functioning, social functioning, role limitations due to physical problems, role limitations due to emotional problems, mental health, energy and vitality, pain, and general perception of health. It uses a scale of 0 to 100, with higher scores representing a better quality of life [68].

5. The World Health Organisation Quality of Life Scale (WHOQoL): The WHOQOL has been developed collaboratively in several culturally diverse centers over four years and contains a multi-dimensional profile of scores across 6 domains and 24 subdomains of the quality of life. It assesses individuals' perceptions of their positions in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns [71].

For children and adolescents:

1. The Pediatric Quality of Life Inventory™4.0 (PedsQL™4.0): This scale was developed by Varni et al. (1999) and is used in children aged 2–18 years. There are both child forms for ages 5 and up, and parallel parent scales for all age groups. In addition, all forms of the scale for age groups 2–4, 5–7, 8–12, and 13–18 have been arranged to contain minor differences according to the age group's characteristics. It has four main domains, including physical, emotional, social, and school-related functioning. A large number of studies in different languages have been carried out to determine the reliability and validity of PedsQL™4.0. It is a Likert-type scale and it can easily be completed within 5–10 minutes [38].

2. The Child Health Questionnaire (CHQ): It was validated by Landgraf, Abetz, and Ware (1996) and was examined for its reliability and validity with a group of children, ages 5–18. It is available in many different languages (Arabic, Bulgarian, Chinese, Danish, English, German, Spanish, etc.). CHQ has 12 subscales and 2 summary scores. It has a child's form (CHQCF-87 items) and two types of parents' forms (CHQ-PF-28, and 50 items). However, these are not parallel versions. CHQCF-87 was developed to be com-

pleted by children aged 10 or older. CHQ is frequently used to assess the QoL of children with different diseases [40].

3. The Child Health and Illness Profile (CHIP): It was developed by Starfield et al. (1995), assessing five domains that include achievement, comfort, resilience, risk avoidance, and satisfaction with health and self. CHIP has three versions: an adolescent form (CHIP-AE; ages 11–17), an illustrated form for children (CHIP-CE; ages 6–11), and a parallel version to measure the parental perspective on children's health and well-being (CHIP-PRF) [56].

4. The Dutch-Child-AZL-TNO-Quality of Life Questionnaire (DUX-25): This scale was validated by Kolsteren et al. (2001) as a generic instrument with identical proxy and self-report forms. It has 25 items and is used for children aged 5 to 16 years [98].

5. TNO-AZL-Child Quality of Life (TACQOL) Questionnaire: It was developed by Vogels et al. (1998) and measures problems in seven domains: (1) bodily functioning (fatigue and pains), (2) motor functioning, (3) autonomic functioning, (4) cognitive functioning (school), (5) social functioning (peers, family), (6) positive moods, and (7) negative moods. All seven domains include eight items [99].

6. The Kinder Lebensqualitatsfragebogen (KINDL, German Quality of Life Questionnaire): It is a validated tool comprised of 24 items, created by Ravens-Sieberer and Bullinger (1998). It has six subscores: physical well-being, emotional well-being, self-esteem, family, friends, and school. Three versions (KID-KINDL; KIDDO-KINDL; KINDL for parents) were used according to the age group. KID-KINDL was used for children aged 6–11 years, KIDDO-KINDL for adolescents aged 12–17 years, and KINDL for parents of patients aged 6–17 years [100].

ADHD-Specific QoL Scales

Because the assessment of QoL with generic measures has the potential disadvantage of emphasizing areas of disability that are inappropriate to the disorder in question, there have been several attempts to construct new evaluation scales, for both adults and children. The generic QoL scales such as SF-36, for instance, may not be correlated with the symptoms of a specific disorder like ADHD, indicating the need for specific QoL instruments [101]. Health-related QoL scales are not purely related with the disease itself, but are also associated with other factors such as family, friends, and socioeconomic and cultural issues. This situation emerges as a complicating factor in evaluating the relationship between the disease and the QoL. Some disease-specific QoL scales used in adults, children, and adolescents with ADHD are as follows:

For adults:

1. The Adult ADHD Quality of Life Scale (AAQoL): This scale, validated by Brod et al. (2006), is a Likert-type scale consisting of 29 items distributed in the following four domains: life productivity (11 items), psychological health (6 items), life outlook (7 items), and relationships (5 items)[45].

2. The Adult ADHD Quality of Life-29 (AAQoL-29): It is a participant-reported outcome measure used to examine disease-specific functional impairments and quality of life in

adults with ADHD. The AAQoL includes "life productivity," "psychological health," "quality of relationships," and "life outlook" subscales. Higher scores on the AAQoL-29 indicate better functioning [75].

3. The ADHD Impact Module for Adults (AIM-A): AIM-A is a validated measurement of the quality of life in adults with ADHD. The AIM-A measures the following multi-item concepts: living with ADHD (10 items), general well-being (11 items), performance and daily functioning (10 items), relationships/communication (8 items), bothersomeness/concern (9 items), and daily interference (9 items). Like SF-36, it uses a 0-to-100 scale, with higher scores representing a better quality of life [102].

For children and adolescents:

1. The ADHD Impact Module-Child (AIM-C): This is a disease-specific HRQoL survey instrument, consisting of two core multi-item scales to assess HRQL impact on the child and family. The child scale includes 8 items that measure the well-being of the child, and the home scale includes 10 items that assess the impact on the family/parent at baseline and study endpoint. In addition, the AIM-C includes 10 clinical treatment questions, a 6-item school cooperation scale, 9 parent attribute/knowledge items, 4 economic impact items, and 4 demographic questions answered by the subject's parents [44].

2. The Weiss Functional Impairment Rating Scale (WFIRS): This scale evaluates ADHD-related functional impairment. It shares many similarities with measures of QoL. The self-report form of the scale (WFIRS-S) is appropriate for adolescents and adult reporting of functional impairment associated with ADHD. It contains 68 items spanning six functional domains: home, self-concept, learning and work, activities of daily living, social activities, and risky activities. The parent form of the scale (WFIRS-P) consists of 50 items to be filled out by parents. Each item is measured on a four-point Likert scale. It measures functioning across six domains: family, learning and school, life skills, child's self-concept, social activities, and risky activities [103].

3. The ADHD Quality of Life Scale (ADHD/QoLS): It was developed by Dolgun et al. (2005). The ADHD/QoLS is designed for children aged 8–12. It has 30 items and they are on a 5-point Likert scale with five responses ranging from completely false to completely true. The scale is comprised of three subscales: cognitive, social, and psychological [104].

4. The EuroQoL Five-Dimension Questionnaire-Parent-Proxy Version (Parent-proxy EQ-5D): This proxy version of EQ-5D was tested by Matza et al. (2005) in a sample of children with ADHD in the United States and the United Kingdom, measuring of ADHD symptoms based on the DSM-IV criteria. The EQ-5D scales were also significantly correlated with the ADHD-RS scales. The proxy version of the EQ-5D completed by parents was able to detect impairment in children diagnosed with ADHD in the United States and the United Kingdom. Significant correlations were found with an ADHD symptom measure and previously validated multi-dimensional QoL instruments. These results suggest that parent-proxy EQ-5D ratings are feasible and valid to be used as a part of an overall health outcome assessment in clinical studies of childhood ADHD [105].

Study	N & Mean age	Design & Duration	Drug & Dose	Questionnaire	Main outcomes
Wehmeier et al (2012) [36]	794 (136, girls, mean age 9.6; 658 males, mean age 9.7)	5 ATX follow-up trials (4 of Europe, one from Canada 8-to12-week meta-analysis	ATX, up to 1.8 mg/kg/day,	CHIP-CE-PRF, HRQoL, ADHD symptoms	ATX was effective in improving some aspect of HR-QoL in both genders, correlation between core symptoms of ADHD and HR-QoL were low to moderta in both gender.
Wehmeier et al (2011) [80]	180, children and adolescents (6-17 years)	Randomized, double blind, placebo controlled, 9-weeks	ATX, up to 1.2 target dose mg/kg/day,	KINDL-R	Positive effects of ATX on QoL (emotional well-being, self-esteem, friends and family, in children and adolescents with ADHD and comorbid ODD/CD).
Wehmeier et al (2010) [23]	794 (611:children, 183:adolescent)	5 ATX follow-up trials (4 of Europe, one from Canada 8-to12-week meta-analysis	ATX, up to 1.8 mg/kg/day,	ADHD-RS, CHIP-CE	Atomoxetine was effective in improving some aspects of HR-QoL in both age groups. Correlations between core symptoms of ADHD and HR-QoL were low to moderate.
Becker et al (2011) [22]	721, children and adolescents (6-17 years)	Open-label OBSEER study	Once-daily modified-released (MR) MPH	SDQ, KIND(parent, child or adolescent versions)	ADHD had low QoL, independent of core symptom severit. QoL lower in additional conduct disorder, medication was effective.
Gerwe et al (2009) [88]	306, mean age 10.2±2.3	Open-label, non-interventional study, 8 weeks	OROS-MPH, IR-MPH	Non-validated, simplified Likert type scales	The importance of a therapy that covers not only school-time, but also takes other areas of life into account. Initiating treatment with long-acting preparations, such as OROS(®) MPH in MPH-naïve patients might be a feasible option.
Prasad et al (2007) [76]	201	Open-label, 10 weeks	ATX, 0.5-1.8 mg/kg/day	CHIP-CE Parent Report Form ADHD-RS, CGI-S, CGI-I	CHIP-CE score was significantly higher for patients treated with ATX. ADHD-RS, CGI-S, and CGI-I scores were significantly different in favour of ATX.
Dell'Agnello et al (2009) [77]	139	RDBPC, 8 weeks	Atomoxetine, 1.2 mg/kg/day	CHIP-CE Parent Report Form, CGI-ADHD-S,	CHIP-CE scores for risk avoidance domain,

Study	N & Mean age	Design & Duration	Drug & Dose	Questionnaire	Main outcomes
				CPRS-R:S, CTRS-R:S	emotional comfort and individual risk avoidance subdomains were improved by ATX. An improvement in all the subscales of Conners was observed with ATX.
Escobar et al (2009) [78]	149	RDBPC, 12 weeks	Atomoxetine, 1.2 mg/kg/day	CHIP-CE Parent Report Form	ATX improved HRQoL by parents and in the risk avoidance domain by patients. A modest correlation of clinical severity with HRQoL was found in this clinical population.
Svanborg et al (2009) [79]	99	RDBPC, 10 weeks	Atomoxetine, 1.2 mg/kg/day	CHIP-CE Parent Report Form	ATX combined with psychoeducation had a positive effect on coping abilities of the patients and their families.
Perwien et al (2006) [75]	912, 6-17 years	Open-label, 10 week acute, 24 months	ATX	CHQ parent report form	Improvements in HRQL were found both acute and long-term treatment for psychosocial health.
Gurkan et al (2010) [87]	45, 8-14 years	Open-label, 3 months	MPH	PedsQL (parent, children forms)	Depression, trait anxiety and compulsion symptoms decreased and QoL improved along with ADHD symptoms
Flapper et al (2008) [89]	23, 7-10 years	Open-label, 4 week	MPH	DUX-25, TACQoL parent children forms	HRQOL scores improved in 18 children receiving MPH. The ADHD/DCD group also demonstrated a significant improvement in ADHD symptoms and motor functioning.

ADHD-RS-IV: ADHD Rating Scale-IV; YQoL-R: Youth QoL-Research Version; HR-QoL: Health-related quality of life; BRIEF-A: Behaviour Rating Inventory of EF-Adult; GEC: Global Executive Composite; CHIP-CE- PRF: Child Health and Ilness Profile-Child Edition-Parent Rating Form, Weiss functional impairment rating scale-parent report; ADHDRS-IV-Parent: Inv total score; TQoLA: Taiwanese Quality of life questionnaire for adolescents, SDQ: strengths and difficulties questionnaire, CHQ= The Child Health Questionnaire; RDBPC =Randomized,double-blind,placebo controlled; CHIP-CE = Child Health and Illness Profile-Child Edition ; TQOLQA=Taiwanese Quality of Life Questionnaire for Adolescents; PedsQL= Pediatric Quality of Life Inventory; DUX-25= Dutch-Child-AZL-TNO-Quality of Life Questionnaire; TAC-QOL=TNO-AZL-Child Quality of Life; MPH =Methylphenidate, CPRS-R:S: Conners Parents Subscale, CTRS-R:S: Conners Teacher Subscale,

Table 1. Studies of the impact of treatment on QoL of children with ADHD

Study	N & Mean age	Design & Duration	Drug & Dose	Questionnaire	Main outcomes
Altin et al (2014) [44]	18-30 years	randomized, double-blind, plasebo-controlled, 12 weeks	ATX	CAARS-Inv: SV total score, AAQoL-29, CGI-ADHD-S, CGI-I, CAARS and BRIEF-AV Self-Reports	Atomoxetine reduced ADHD symptoms and improved quality of life and executive functioning deficits in young adults compared with placebo.
Adler et al (2013) [97]	159, adults with clinically significant executive function deficits (EFD)	Randomized placebo controlled, 10 weeks	LDX, 30-70 mg/day,	EFD (BRIEF-A, GEC) ADHD-RS-IV, CGI-S, AAQoL, AIM-A	Aduls with ADHD/EFD exhibited self-reported improvement on QoL, AIM-A and AAQoL correlate with medium/large ES, these improvements parallel by improvements in EF and ADHD symptoms.
Durell et al (2013) [73]	445, 18-30 years	randomized, double-blind, plasebo-controlled, 12 weeks	ATX	the AAQoL-29	Score decreases from baseline to the 12-week end-point greater in ATX group for the AAQoL-29 total score and all the subscale scores, except "life Outlook subscale" score.
Goto et al (2013) [81]	391, adults from Japan, Korea, and Taiwan	Randomized, double-blind, plasebo-controlled, 10 weeks	ATX	CAARS-Inv: SV total score, QoL	ATX effective in improving QoL and executive function as well as ameliorating core ADHD symptoms in adult Asian patients
Mattos et al (2013) [90]	60, adult, mean age 31.1 years	Multicenter, open-label trial, 12 weeks	OROS-MPH	Adult Self-Rating Scale, AAQoL, STAI, HAM-D, CGI	A significant reduction on CGI-I, HAM-D, STAI, and ASRS scores was observed
Weiss et al (2010) [39]	725, adults,	QUEST study, open-label, 8 months	Long-acting mixed amphetamine salts extended release	ADHD symptoms, medication satisfaction mediate quality of life	Symptom change and satisfaction with medication independently mediate change in mental but not

Study	N & Mean age	Design & Duration	Drug & Dose	Questionnaire	Main outcomes
					physical quality of life outcomes. Attention is a stronger mediator of ADHD-specific quality of life outcomes.
Brown and Landgraf (2010) [91]	Adults	2 of randomized, double-blind, placebo-controlled trials,	(MAS (SPD465)	BADDS, AIM-A	Improvement in executive function correlates with reported improvement in HRQOL as assessed in 2 independent clinical trials
Adler et al (2009a) [83]	442, adults with ADHD and social anxiety disorder	Randomized, double-blind, placebo-controlled, 14 weeks	ATX, 40-100 mg	CAARS:Inv:SV, LSAS, CGI-O-S, STAI, SAS, AAQoL-29	CGI-O-S, STAI, AAQoL score changes greater in favour of ATX, STAI scores was comparable. SAS scores were similar with placebo.
Adler et al (2009b) [86]	501, adults	randomized, double-blind, placebo-controlled, 10 weeks, then 6-month trial	once-daily morning-dosed ATX	AISRS, CAARS:Inv:SV, CGI-ADHD-S, AAQoL	Once-daily morning-dosed atomoxetine is efficacious for treating ADHD in adults when measured 10 weeks and 6 months after initiating treatment.
Spencer et al (2008) [92]	274, adults (18-55 years)	Randomized, double-blind, plasebo-controlled, 7 weeks	MAS (SPD465), 12.5-75 mg/day	AIM-A, ADHD-RS-IV, CGI	Triple-bead MAS was significantly more effective than placebo in adult ADHD.
Boonstra et al (2007) [94]	39 normal controls, 33 adults with ADHD for baseline comparison 31 adults with	1) Baseline group comparison; 2) Double blind, placebo-controlled, cross-over medication	MPH, placebo	Actigraphy, sleep log data,	Sleep problems are inherent in adults with ADHD and that methylphenidate reduced total sleep time but improved sleep quality by consolidating sleep.

Study	N & Mean age	Design & Duration	Drug & Dose	Questionnaire	Main outcomes
		ADHD medication			
Adler et al (2005) [82]	384, adults from 31 sites	ongoing, 3-year, open-label study, up to 97 weeks	ATX	CAARS-Inv:SV	Significant improvement was noted with atomoxetine therapy, with mean CAARS-Inv:SV total ADHD symptom scores
Michelson et al (2003) [84]	280 (study 1), adults 256 (study 2), adults	randomized, double-blind, placebo-controlled, 10-week	ATX	Conners' Adult ADHD Rating Scale.	ATX as efficacious treatment for adult ADHD.
Kooij et al (2001) [93]	8 adults,	Open-label, 7 days	MPH (51 mg: 30-90 mg) for 7 cases, dextroamphetamine (30 mg) for one case	Activity level Movement index scores	Treatment with stimulants associated with a reduction of activity Level and movement index scores and improved sleep quality in ADHD.

CAARS-Inv: SV: Conners' Adult ADHD Rating Scale-Investigator Rated: Screening Version; AAQoL: Adult ADHD Quality of Life Scale; STAI:State and Trait Anxiety Inventory, HAM-D: Hamilton Depression Rating Scale, CGI: Clinical Global Impression, MAS: triple-bead mixed amphetamine salts, AIM-A: Adult ADHD Impact Module, ADHD-RS-IV: ADHD Rating Scale-IV, TASS: Time-Sensitive ADHD Symptom Scale, BADDS: Brown Attention-Deficit Disorder Scale, ASRS: Adult ADHD Self-Report Scale, GAF: Global Assessment of Functioning, CGI-I: Clinical-Global-Impressions-Improvement Scale, CGI-ADHD-S: Clinical Global Impression-ADHD-Severity, BRIEF-AV: Behavior Rating Inventory of Executive Function-Adult Version Self-Report, LSAS: Liebowitz Social Anxiety Scale, CGI-O-S: Clinical Global Impression-Overall-Severity, STAI: State-Trait Anxiety Inventory, SAS: Social Adjustment Scale-Self Report, AAQoL-29: Adult ADHD Quality of Life Scale-29, AISRS: Adult ADHD Investigator Symptom Rating Scale, CGI-ADHD-S: Clinical Global Impressions-ADHD-Severity, BADDS: Brown Attention-Deficit Disorder Scale, BRIEF-A: Behaviour Rating Inventory of Executive Function-Adult Version Self-Report.

Table 2. Studies of the impact of treatment on QoL of adults with ADHD

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