

The quality of life of children with attention deficit/hyperactivity disorder: a systematic review

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Received: 28 October 2008 / Accepted: 8 July 2009 / Published online: 26 July 2009
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Abstract Quality of life (QoL) describes an individual's subjective perception of their position in life as evidenced by their physical, psychological, and social functioning. QoL has become an increasingly important measure of outcome in child mental health clinical work and research. Here we provide a systematic review of QoL studies in children and young people with attention deficit hyperactivity disorder (ADHD) and address three main questions. (1) What is the impact of ADHD on QoL? (2) What are the

relationships between ADHD symptoms, functional impairment and the mediators and moderators of QoL in ADHD? (3) Does the treatment of ADHD impact on QoL? Databases were systematically searched to identify research studies describing QoL in ADHD. Thirty six relevant articles were identified. Robust negative effects on QoL are reported by the parents of children with ADHD across a broad range of psycho-social, achievement and self evaluation domains. Children with ADHD rate their

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own QoL less negatively than their parents and do not always see themselves as functioning less well than healthy controls. ADHD has a comparable overall impact on QoL compared to other mental health conditions and severe physical disorders. Increased symptom level and impairment predicts poorer QoL. The presence of comorbid conditions or psychosocial stressors helps explain these effects. There is emerging evidence that QoL improves with effective treatment. In conclusion, ADHD seriously compromises QoL especially when seen from a parents' perspective. QoL outcomes should be included as a matter of course in future treatment studies.

Keywords Attention deficit/hyperactivity disorder (ADHD) · Quality of life · Systematic review

Introduction

As medicine has moved on from a “life preserving” to a “health promoting” science [95], the concept of Quality of Life (QoL) has become increasingly important in the study of medical conditions, their impact and their outcome [18]. The QoL concept has been defined in many ways, but all definitions, to a greater or lesser extent, emphasize the ideal state as one of general well-being in which an individual's day-to-day functioning, across a wide range of domains, is unencumbered by the potentially adverse impact of disease or disorder. Leidy et al. [44] defined QoL as “an individual's subjective perception of the impact of health status, including disease and treatment, on physical, psychological, and social functioning.” This is compatible with the WHO QoL group's description of 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” [91]. Almost all QoL definitions and measures include physical, social and psychological domains (although similar domains are often labelled differently). A cognitive domain is also commonly included [24]. Although QoL is influenced by many proximal (i.e., family, friendship) and distal (socio-economic and cultural) forces, illness is one of the most potent influences [24]. In addition to the effects of physical illness on QoL, there is now substantial evidence that mental illness has major impact [7, 50, 70].

A comprehensive discussion of the issues relating to the QoL concept in child and adolescent mental health is beyond the scope of the current review but can be found in a recent paper by the authors [18]. However, a number of key conceptual and measurement are discussed below.

Both the DSM-IV-TR [1] and ICD-10 [96] diagnostic systems emphasize the importance of there being both

symptoms and impairment before a diagnosis of mental disorder can be made. However, the distinctions between symptoms and their associated functional impairments are often not as clear and one would wish and their relationships with QoL, remain under-specified. For example some QoL items, designed for patients with physical illness, tap psychiatric symptoms (e.g. “how often did your child feel really sad?”) or the types of impairment commonly associated with psychiatric disorders (e.g. “how often did he/she finish all of his/her homework?”). As a consequence there is significant potential for overlap between instruments designed to measure QoL and those used to measure either symptomatology or impairment. It is therefore vital that, as far as possible, we draw clear distinctions between symptoms (e.g., low mood or poor concentration) and their potential effects (i.e., functional impairment and reduced QoL) and then also between impairment on the one hand and QoL on the other. Otherwise there is a clear risk that apparent QoL effects are so closely related to symptoms and impairment that their association with the disorder will become a tautology.

Also the concept of “validity” of QoL instruments has been particularly difficult to define and measure due to the lack of an agreed and objective gold standard of QoL. Current approaches suggest the employment of quantitative (e.g. factor analysis) and qualitative (e.g. patient debriefing questionnaires and patient panels) techniques. While these procedures have been increasingly used in the development of instruments to measure QoL in children and young people the process has not yet been repeated in different patient groups. And in particular there has been little work conducted to demonstrate validity in children with mental health problems.

Another consideration concerns the usefulness of both generic and disorder-specific measures of QoL and the relationships between these two very different types of measure. Generic measures are designed to be more comprehensive in their coverage, but may as a consequence be less sensitive to treatment-related change. Disorder-specific measures, or modules, focus in on areas of particular concern in relation to a specific disorder and may therefore be more sensitive to treatment effects but do readily not allow comparison with other disorders.

While it is generally accepted that QoL is a multi-dimensional concept and that the core domains tap into physical, psychological, cognitive and social aspects of functioning it is still the case that different QoL measures define these domains in different ways and then go on to divide them up into different sub-domains. As a consequence there is a considerable degree of inter-instrument non-overlap and we cannot simply assume equal coverage by different measures or that all generic QoL measures cover the necessary ground. This often makes it difficult to

make direct comparisons between studies that have employed different instruments.

QoL is seen primarily as a patient-reported outcome [48, 79] with a key distinction being between independent assessment (e.g., he/she cannot concentrate and this stops him or her functioning at school and I think he/she should feel bad about this) and the “subjective” appraisal (I cannot concentrate, this stops me working at school and I feel badly about this and it impacts generally on how I feel about myself). In this respect a child’s own report seems essential to accurately capture their QoL. However, this is complicated by several issues. Young children (e.g., before the age of 7 or 8 years of age) may lack the understanding, insight or communication skills to provide valid self ratings [10]. This may be accentuated in the case of; children with learning disabilities; those for whom mental health conditions impact on their ability to reflect and report upon their internal state accurately (e.g., depression); or as is often the case with ADHD, where the child is unable to concentrate and apply themselves to answering a questionnaire. In these cases one may have to rely on a proxy rating by a parent or a carer. As a consequence measures of QoL designed for child populations usually have both a child and parent completed versions. Clearly a proxy rating will allow only a partial sense of the overall impact of the condition on QoL which may place important constraints on the validity of studies that do not directly ask the child about their QoL. It is also important to note that the levels of agreement between child and other informants are modest [39], especially with regard to the non-observable aspects of QoL. Parent/carer ratings may, however, provide an important alternative perspective to that of the child. However, this does raise important issues about how information from different informants is combined or compared.

The developmental aspects of QoL have not been well studied. It is likely that there will be major age-related differences in the way individuals value different aspects of QoL, the ways in which they can express these and the ways that these two factors interact. It is inevitable that in selecting an instrument for a particular age group one will have to trade-off the age specificity of item content with the benefits of potential comparability across ages [48]. If one focuses too much on adapting instruments for use by a specific age group then it is likely to become difficult to compare or to pool data collected from subjects of different ages. On the other hand, if an instrument does not cover the necessary constructs within an age then the validity of that instrument will inevitably be compromised. Careful piloting of proposed instruments within the age range to be studied is therefore essential. There are various ways that instruments can be tailored to make them more age appropriate. These include; ensuring that questionnaires are short and written in simple (age appropriate) language;

changing questionnaires into interviews [36, 63]; attempting to reduce the influence of the adult over the child’s responses during face-to-face administration; using pictorial response formats such as *smiley*, *neutral* and *sad* faces [17, 24, 34, 61]; using props and puppets [49]; computer-administered measures [23, 31]; and ensuring that an appropriate recall period is selected. Younger children can have difficulties with the time concepts such as 1 week or 1 month [63].

In addition to these general issues relating to the measurement of QoL in children there are issues which are more specifically related to mental health problems in children. Mental health disorders will interact in complex ways with QoL. Mental health difficulties impact on a person’s capacity to engage effectively in daily activities and this can have knock-on consequences for their general sense of well-being. A reduced sense of well-being can also impact on mental health by, for example, further lowering mood. In childhood, the effects of mental health difficulties on QoL are perhaps most obvious in the more severe or extreme forms of mental health problem (e.g. autism) or those that impact directly on an individual’s sense of self worth (e.g. anxiety and depression). However, there is growing evidence that the, so called, externalizing disorders such as oppositional defiant disorder and attention deficit/hyperactivity disorder (ADHD) also substantially reduce the QoL of children and young people in terms of their subjective sense of wellbeing and their capacity for everyday functioning.

The goal of this review is to address the issue of QoL in ADHD through a systematic review of the published literature. ADHD is a high prevalence disorder of childhood and adolescence marked by early onset, persistent and pervasive patterns of inattention, overactivity and impulsivity. It is associated with impairment across a range of domains. More specifically ADHD is associated with educational under-achievement [94], family-related and peer relationship problems [2, 3, 25] and increased anti-social and delinquent activity [72]. Long term adverse outcomes include increased risk of substance abuse [14], reduced vocational opportunities [5] and increased criminal activity [73]. ADHD is often comorbid with other disorders such as oppositional defiant disorder (ODD), conduct disorder (CD), depression and anxiety [11, 12]. ADHD can be successfully managed by a combination of stimulant medication and psychosocial approaches which reduce both symptoms and global levels of impairment. While generally well tolerated stimulant medication has a range of side-effects in a substantial minority of children [4, 6, 30].

Understanding the impact of mental disorder in general and ADHD in particular on QoL can be informative on a number of levels. QoL has the potential to be an important outcome measure. Indeed Spitzer and colleagues have

suggested that the main goal of healthcare is to improve patients *perceptions of their health* and the extent to which health problems *interfere with their QoL* [79]. It could be argued that QoL outweighs simple short-term symptom reduction as the most important treatment outcome for ADHD. If a treatment reduces symptoms but does not increase a child's QoL can that treatment be considered effective? Thus QoL, if able to be measured reliably could be an important outcome measure in both clinical research and routine patient care. On a more general level the use of QoL data by individual child and adolescent mental health services could assist with service planning and audit—and help focus attention on outcomes that patients themselves feel are important. Taking this one step further the assessment of QoL across different mental and physical health domains can allow for direct comparisons to be made between the impacts of these conditions on either individuals or populations—which in turn has the potential to provide an evidence base for a more rational reconsideration of the ways that resources are allocated within health services than is typically the case. QoL measurement is already acknowledged as being central to the calculation of cost-effectiveness of different treatments and hence to the choices between treatments, both at an economic level (e.g. reimbursement of drug treatment costs) and at an individual patient level [21].

In order that these goals can be achieved, with respect to ADHD, several key questions need to be addressed. These include; (1) what is the impact of ADHD on QoL? (2) What are the relationships between ADHD symptoms, functional impairment and the mediators and moderators of QoL in ADHD? (3) Does the treatment of ADHD impact on QoL? This paper will address progress to date in trying to find answers to these questions through a systematic review of the published literature pertaining to QoL in ADHD, identify gaps in knowledge and make suggestions about the future lines of investigation that will be required to further the field.

Methods

A systematic literature search was conducted using the following databases; Ovid MEDLINE (R), Cochrane database of systematic reviews, ACP Journal Club, DARE, CCTR, CMR, HTA, NHSEED, EMBASE and PsychINFO from 1988 to April 2008. Text word and thesaurus searches were used to minimize the chance of missing relevant articles. The following keywords were searched: child, childhood, children, pediatric, paediatric, adolescent; quality of life, QOL, HRQOL, health status, functional status, well-being; self-esteem, self-concept, self-competence and self-image; ADHD, Attention deficit

hyperactivity disorder, attention × disorder. The reference lists of identified papers and previous reviews of QoL in children were searched manually. Included were papers in one of five major European languages (English, German, French, Italian, Spanish). Other inclusion criteria were; publication in a peer reviewed journal; a study, of any design, focusing on QoL in children or adolescents with ADHD that contained at least some empirical data on QoL measurement in children or adolescents with ADHD and used a QoL instrument. Studies in adults were excluded. The titles and abstracts of all papers identified from the first search were read by two authors (MD, DC) where there was disagreement at this stage the paper was retained. The full text of those papers passing this screen was read independently by two of the authors (MD, DC). There was full agreement between these two authors at this stage. Data was extracted by MD and checked for accuracy by DC and E S–B. Where there were several publications from single studies these were included where there was not repetition in the data presented. Where there were meta-analyses these were included and discussed before the individual studies.

The results of identified studies are described in a descriptive manner with effect sizes reported where available. As a guide to interpreting the clinical meanings of these effect sizes Norman et al. [53] proposed that, in QoL research, a difference of at least half a standard deviation is required for a “clinically meaningful difference.”

Results

This broad search strategy resulted in a total of 1,445 articles (including duplicates) from which a total of 36 relevant articles were identified (Fig. 1, Tables 1, 2).

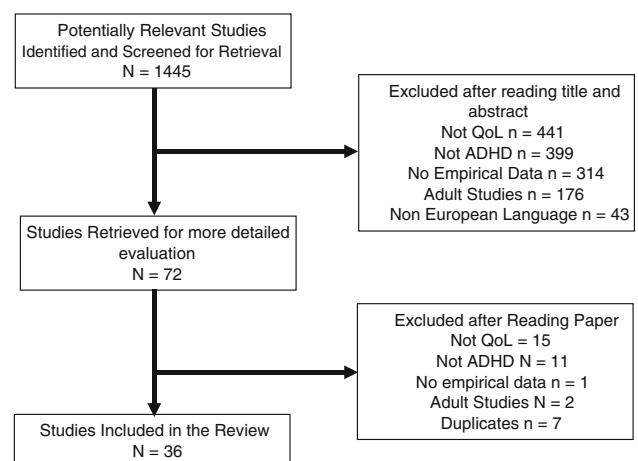


Fig. 1 QUOROM flow chart for literature search

Table 1 Case control and cross sectional studies, and baseline data from clinical trials that have measured quality of life in ADHD

Reference	Design	Measure	Rater	N	Main outcomes
Landgraf and Abetz [41]	Case control	CHQ	Child	56 ADHD, 278 healthy controls, 20 haemodialysis	Reliability and validity was reported as good. The QoL of the sample receiving haemodialysis treatment was poor compared to the healthy controls and patients with ADHD. The children with ADHD did not rate their QoL as different from that of healthy controls
Landgraf et al. [42]	Case control	CHQ	Parent		The ADHD sample showed significantly lower QoL than the healthy children on the overall summary score and the psychosocial and family subscales
Graetz et al. [29]	Case control	CHQ	Parent	248 ADHD, 113 inatt, 68 hyp/imp, 67 comb, 3,298 healthy controls	Compared with non-ADHD controls, all three ADHD-subtypes were rated as having lower QoL. Combined types were rated the most impaired on most subscales. Inattentive types were rated as more impaired than hyperactive-impulsive types on several scales
Landgraf et al. [43]	Cross sectional psychometric validation	AIM	Parent	81 ADHD	The scales exceeded standard criteria for item convergent and discriminant validity. No floor effects and minimal (2%) ceiling effects were observed. Cronbach alpha was 0.88 and 0.93 (Child and Home Scales), respectively. Statistically significant differences were observed on both home and child scales for ADHD inattentive versus ADHD combined with better ratings for inattentive children
Sawyer et al. [75]	Case control (population sample)	CHQ	Parent	308 ADHD, 53 MDD, 35 CD, 2,507 healthy controls	Children with ADHD had significantly worse QoL scores than children with no disorder across all domains. Differences remained after controlling for overlapping questions. Children with MDD were described as having more pain and discomfort and emotional problems than those with CD and ADHD. Children with CD and ADHD had greater behavioural problems than those with MDD
Bastiaansen et al. [7]	Cross sectional study in clinically referred children with psychiatric disorder	PedsQL	Parent	310 Referred children, ADHD 107	Different child psychiatric disorders impact differently on QoL. Children with attention-deficit had a better emotional functioning score than children with anxiety disorders. Their academic performance was significantly lower than for children with anxiety disorders and other disorders. Psychiatric comorbidity did not influence overall QoL
Klassen et al. [38]	Cross sectional	CHQ	Parent	131 ADHD compared to norms	Children with ADHD had comparable physical health but clinically important deficits in all psychosocial QoL domains. Poorer psychosocial QoL was correlated with greater parent-reported ADHD symptoms. Children with ≥ 2 comorbid disorders had worse QoL than those with no comorbidity in most areas and from those with 1 comorbid disorder in 3 domains. Predictors of psychosocial health included the number of comorbid conditions and parent rated combined ADHD symptoms
Matza et al. [45]	Baseline data from an RCT: ATX versus Placebo	CHQ	Parent	297 ADHD	QoL scores were significantly lower than national norms and were negatively correlated with clinical measures

Table 1 continued

Reference	Design	Measure	Rater	N	Main outcomes
Topolski et al. [82]	Cross sectional	YQOL-R	Young person	55 ADHD, 52 mobility impairment, 107 healthy controls	The adolescents with ADHD reported significantly lower QoL scores than the healthy control group (particularly in the Self and Relationship domains) and similar scores to those from the group with mobility impairment (a group previously demonstrated to have reduced QoL)
Bastiaansen et al. [8]	Longitudinal study in clinically referred children with psychiatric disorder	PedsQL	Parent	126 Referred children, 48 ADHD	38% of children showed neither symptom reduction nor QoL improvement, 33% of children showed both a clinically symptom reduction and QoL improvement. In 11% of all children, QoL improved while the level of psychopathology remained high and in 18% psychopathology improved while the level of QoL remained high
Escobar et al. [26]	Case control	CHQ	Parent	120 ADHD; 93 asthma; 120 healthy	Children with ADHD were rated worse than either asthmatic or healthy children for most Child Health Questionnaire domains. The greatest differences were found in behaviour, social limitations attributable to physical problems, emotional impact on parents, and family activities
Matza et al. [46]	Cross sectional	CHQ, CHIP-CE, EQ-5D	Parent	126 ADHD	EQ-5D scores were correlated with several domains of the CHQ-PF50 (e.g. Mental Health, Self-Esteem, Family Activities, Psychosocial Summary Score) the CHIP-CE (e.g. Satisfaction, Comfort, Academic Performance, Peer Relations) and the ADHD-RS scales
Matza et al. [47]	Cross sectional	Standard gamble utility interviews	Parent	43 ADHD	Comparisons between the various health states found the expected differences between untreated mild, moderate, and severe ADHD health states suggesting that parent standard gamble interviews are a feasible and useful method for obtaining utility in ADHD
Newcorn et al. [52]	Baseline data from an RCT: ATX versus Placebo	CHQ	Parent	293 ADHD 39% with ODD	Youths with ADHD and without comorbid ODD had reduced QoL compared to controls. QoL was lower in those with comorbid ODD
Pongwilairat et al. [59]	Case control	PedsQL	Child, parent	46 ADHD, 94 healthy children	Both the children with ADHD and their parents reported a significantly lower psychosocial QoL scores than controls and their parents. Children with ADHD also reported themselves to have a significantly low physical QoL score, despite being adjudged to be physically healthy
Rentz et al. [64]	Baseline data from an RCT	CHQ	Parent	921 ADHD	Internal consistency (Chronbach's alpha) at baseline was 0.88 for the Psychosocial Summary Score, ranging from 0.53 to 0.91 for the subscale scores. Construct validity was supported. Scales were responsive to change
Secnik et al. [76]	Cross sectional	EQ-5D, standard gamble utility interviews	Parent	83 ADHD	Parents' raw SG scores of their child's current health state were significantly correlated with inattentive, hyperactive, and overall ADHD symptoms and the EQ-5D visual analogue scale

Table 1 continued

Reference	Design	Measure	Rater	N	Main outcomes
Hampel and Desman [33]	Cross sectional	Kid-KINDL-R	Child	48 ADHD compared to norms	All domains of quality of life were impaired among children and adolescents with ADHD compared to normative data
Klassen et al. [39]	Cross sectional	CHQ	Child, parent	58 ADHD	Compared with population norms, across most domains, children with ADHD reported comparable health. Children rated their QoL significantly better than their parents in four areas (behaviour, self-esteem, mental health and family cohesion), and significantly poorer for one (Physical Function). Correlations between children and parents were relatively low. Discrepancies between parent-child ratings were related to the presence of a comorbid oppositional/defiant disorder, a psychosocial stressor and increased ADHD symptoms
Ralston et al. [61]	Cross sectional	CHIP-CE	Parent	1,478 ADHD, medication naive	Significant impairments on all CHIP-CE domains: (satisfaction, comfort, resilience, risk avoidance and achievement
Riley et al. [65]	Cross sectional	CHIP-CE	Parent	1,477 ADHD, medication naive	Internal consistency reliability was good-to-excellent (Chronbach's alpha >0.70) for all CHIP-CE domains and subdomains, with almost no ceiling and floor effects. Factor analysis was broadly supportive of the original structure with minor adjustments. CHIP-CE scales were moderate-to-highly correlated with measures of ADHD and family factors
Riley et al. [68]	Cross sectional	CHIP-CE	Parent	1,478 ADHD, medication naive	Factors significantly associated with a poorer QoL included: ADHD symptoms, conduct problems, peer relationship problems, having asthma, multiple other somatic symptoms, co-ordination problems, family factors (having a parent with a health or mental health problem possibly caused by the child's illness, child not living with both parents and maternal smoking during pregnancy)
Varni and Burwinkle [83]	Validation from cross sectional population sample	PedsQL	Child/young person, parent	72 ADHD, 66 cancer, 57 cerebral palsy, 3,256 healthy controls	Good reliability for the total scale score (Chronbach's alpha = 0.92 child self-report, 0.92 parent proxy-report). Distinguished between healthy children and children with ADHD. Children with ADHD self-reported severely impaired psychosocial functioning, comparable to children with newly diagnosed cancer and children with cerebral palsy
Hakkaart-van Roijen et al. [32]	Case control	CHQ	Parent	70 ADHD, 35 children with non-ADHD behaviour problems, 60 healthy controls	No significant differences between the groups on the physical summary score. ADHD patients scored significantly lower on the psychosocial summary score compared to children in the two other samples
Prasad et al. [60]	Baseline data from a clinical trial ATX versus standard clinical treatment	CHIP-CE	Parent	201 ADHD, 104 ATX, 97 standard clinical treatment	QoL was compromised at baseline on a summary score and satisfaction, resilience, risk avoidance and achievement domain scores

Table 1 continued

Reference	Design	Measure	Rater	N	Main outcomes
Yang et al. [97]	Baseline data from a naturalistic treatment study: MPH versus no medication	CHQ	Parent	119 MPH treated school-age children with ADHD, 129 healthy controls	The QoL of methylphenidate-treated children with ADHD was rated worse than that of the healthy children on the CHQ Psychosocial Summary Score and all of the CHQ psychosocial subscales
Flapper et al. [28]	Case control followed by open label trial (MPH)	DUX-25, TACQOL	Child, parent	23 ADHD + DCD, 23 healthy controls	Both child's self- and parent proxy ratings demonstrated lower overall QoL with subscale scores demonstrating lower functioning in motor, autonomic, cognitive, and social domains

CHQ Child Health Questionnaire, *CHIP-CE* Child Health Illness Profile-Child Edition, *DUX-25* Dutch Child AZL TNO Quality of Life, *EQ-5D* EuroQoL Five-Dimension Questionnaire, *GIPD* Global Impression of Perceived Difficulties, *PedsQL* Pediatric Quality of Life Inventory, *KINDL* Munich Quality of Life Questionnaire for Children, *TACQOL* TNO AZL Child Quality of Life, *YQOL-R* Youth Quality of Life Instrument-Research Version, *ADHD* attention deficit hyperactivity disorder, *inatt* inattentive type, *hyp/imp* hyperactive/impulsive type, *comb* combined type, *CD* conduct disorder, *MDD* major depressive disorder, *DCD* developmental coordination disorder, *ATX* atomoxetine, *MPH* methylphenidate

All except one of these papers described ratings made with generic measures of QoL. The nine generic measures used were; the Child Health Questionnaire [CHQ, 42], the Pediatric Quality of Life Inventory [PedsQL, 85], the Child Health Illness Profile-Child Edition [CHIP-CE, 66, 67], the Youth Quality of Life Instrument-Research Version [YQOL-R, 56], the Munich Quality of Life Questionnaire for Children [KINDL, 62], the Dutch Child AZL TNO Quality of Life [DUX-25, 40], the TNO AZL Child Quality of Life [TACQOL, 87], the EuroQoL Five-Dimension Questionnaire (EQ-5D, EuroQol Group 1990) and the Global Impression of Perceived Difficulties [GIPD, 88, 89]. All of these measures have been demonstrated to have acceptable psychometric properties. Having examined these instruments we feel that, notwithstanding the fact that authors of the GIPD have presented data supporting the reliability and validity data of their scale, the validity of the GIPD as a true measure of QoL is questionable as it is very general in nature. There are only five questions each of which asks about difficulties in a particular situation (in the morning, during school, during homework, in the evening, and overall difficulties) e.g. "Considering the past seven days, how difficult has the time spent in school been for you?" In view of these issues data related to the GIPD is not discussed further.

The disorder-specific measure was the ADHD Impact Module [AIM, 43] which has been psychometrically validated [43] but has not been subsequently used in any published studies. A second disorder-specific scale The *Weiss Functional Impairment Rating Scale* has been developed and initial studies suggest that it has strong internal consistency, a well established domain structure and is sensitive to change following treatment [90]. Correlations with the CHIP-CE (a broad based general measure of QoL) domains ranged from -0.32 to -0.72 (Weiss, personal communication). Although the Weiss scale was designed to focus on functional impairment it shares many similarities with measures of QoL. Studies using the Weiss scale are ongoing but have not yet been published.

Unfortunately the majority of studies in relation to child mental health in general and ADHD in specific have used only parent/carers as informants and not asked the child themselves about their QoL. Of the papers in this review 29 included only parent ratings, 2 included only child/young person ratings, and five included both parent and child ratings.

What is the impact of ADHD on QoL?

Identified case control and cross sectional studies of QoL in ADHD are described in Table 1.

Table 2 Treatment studies of quality of life in ADHD

Reference	Design	Measure	Rater	N	Duration	Main outcomes
Methylphenidate						
Yang et al. [97]	Naturalistic treatment (MPH vs. no medication)	CHQ	Parent	119 MPH treated school-age children with ADHD, 129 healthy controls	NA	Improvement of ADHD core symptoms after medication treatment predicted higher psychosocial QoL
Flapper et al. [28]	Case control followed by open label trial (MPH)	DUX-25, TACQOL	Child, parent	23 ADHD + DCD, 23 healthy controls	4 weeks	QoL scores improved in 18 children receiving MPH versus controls
Mixed amphetamine salts						
Sallee et al. [71]	Open label (MAS XR)	PedsQL	Parent	2,968 ADHD	7 weeks	Mean PedsQL total score improved significantly from baseline to follow-up
Wigal et al. [92]	RCT (MAS XR vs. ATX)	PedsQL	Parent	203 ADHD; 102 MAS XR, 101 ATX	3 weeks	Mixed amphetamine salts extended release and atomoxetine treatment both led to statistically significant improvements in QoL, but the difference between medication effects were only statistically significant for the school functioning subscale for which the improvement in the Mixed amphetamine salts extended release group was larger than that for the atomoxetine group
Atomoxetine						
Matza et al. [45]	RCT (ATX vs. Placebo)	CHQ	Parent	297 ADHD	8 weeks	Improvement in clinical symptoms was associated with corresponding improvement in QoL
Perwien et al. [57]	Post hoc analysis of three RCTs (ATX vs. placebo)	CHQ	Parent	647 ADHD	8 weeks × 2, 7 weeks × 1	Children who received atomoxetine had significantly greater improvement in QoL than the placebo. There were no significant differences between once-a-day and twice-a-day dosing. Improvement in QoL was predicted by treatment with atomoxetine, lower QoL scores, no prior history of stimulant use, and absence of oppositional defiant disorder
Newcorn et al. [52]	RCT (ATX vs. Placebo)	CHQ	Parent	293 ADHD, 39% with ODD	8 weeks	Youths with ADHD and comorbid ODD showed greater improvement in QoL on ATX than placebo. Treatment response was similar in youths with and without ODD, except that the comorbid group only improved at higher doses
Brown et al. [15]	RCT (ATX vs. Placebo)	CHQ	Parent	153	7 weeks	Parent reported QoL demonstrated a trend toward better response to ATX than to placebo
Perwien et al. [58]	Open label trial; extension of RCTs (ATX)	CHQ	Parent	912 ADHD, 312 completed long term trial and included in outcome analyses	24 months	Significant improvements were observed on the psychosocial summary scale, and all psychosocial domains but not the physical health domains following acute treatment with atomoxetine. The improvements on the psychosocial summary scale were either maintained or slightly improved after 24 months of treatment

Table 2 continued

Reference	Design	Measure	Rater	N	Duration	Main outcomes
Biederman et al. [13]	Post hoc meta-analysis of RCTs (ATX vs. Placebo)	CHQ	Parent	510 ADHD	NA	ADHD subjects treated with ATX showed significant improvements from baseline compared to those on placebo on most of the CHQ measures irrespective of the comorbidity with ODD
Cheng et al. [16]	Meta-regression analysis of RCTs (ATX vs. Placebo)	CHQ	Parent	1828 ADHD	NA	Parent reported QoL improved with ATX treatment
Prasad et al. [60]	Open label trial (ATX vs. standard clinical treatment)	CHIP-CE	Parent	201 ADHD, 104 ATX, 97 standard clinical treatment	10 weeks	QoL was compromised at baseline on a summary score, and improved during the 10-week study for both groups. Improvement in QoL was higher for patients treated with atomoxetine compared with standard clinical treatment at week 10
Wehmeier et al. [88]	Open label trial (ATX)	GIPD	Child, parent, physician	262 ADHD	24 weeks	It is questionable whether the GIPD is a true measure of QoL. Quality of life as reflected by the degree of perceived difficulties improved over time. Change in GIPD scores was greatest within the first 2 weeks. Children perceived the degree of difficulties as significantly less compared to parents and physicians. Agreement of ratings was highest between physicians and parents
GW320659	Open label dose titration (GW320659)	CHQ	Parent	51 ADHD	11 weeks	Significant improvements compared with baseline on 7 of the 12 subscales of the CHQ
<p>CHQ Child Health Questionnaire, CHIP-CE Child Health Illness Profile-Child Edition, DUX-25 Dutch Child AZL TNO Quality of Life, GIPD Global Impression of Perceived Difficulties, PedsQL Pediatric Quality of Life Inventory, TACQOL TNO AZL Child Quality of Life, ADHD attention deficit hyperactivity disorder, <i>inatt</i> inattentive type, <i>hyp/imp</i> hyperactive/impulsive type, <i>comb</i> combined type, ODD oppositional defiant disorder, DCD developmental coordination disorder, ATX atomoxetine, MPH methylphenidate, MA5 XR mixed amphetamine salts extended release</p>						

QoL in children with ADHD compared to healthy children

With two exceptions [75, 83] all of the studies which have investigated QoL in children or adolescents with ADHD have been conducted using clinical samples of referred children.

Self-report

Despite the considerable importance invested in the individual's self-perceptions by most definitions of QoL, only 7 studies of the QoL of children with ADHD that included child ratings were identified. Two studies used the CHQ, both of which failed to find a difference between ADHD and controls. Landgraf and Abetz [41] found that children with ADHD (9–16 years) reported their QoL to be very similar to that of healthy controls across the nine domains of the self-report version of the CHQ-CF87. Klassen et al. [39] also found that children and adolescents with ADHD (10–17 years old) rated their own QoL as no different from the general child population across most of the CHQ-CF87 domains. Compared to a healthy control group they considered themselves to be equal with respect to overall QoL, and on the role/social functioning, general health perceptions, bodily pain/discomfort, mental health, self-esteem and parental impact, slightly worse for physical function and behaviour and significantly worse only for family activities. The Klassen et al. study also compared child and parent CHQ ratings. Children rated their QoL significantly more positively than did their parents for their behaviour, self-esteem, mental health and family cohesion and significantly poorer for physical function. In general there was greater agreement between children and their parents for the physical subscales (with correlations between $r = 0.75$ and $r = 0.60$) than for the psychosocial subscales (between $r = 0.40$ and $r = 0.48$). Using the KINDL [62], Hampel and Desman [33] also found all domains of quality of life to be impaired in children and adolescents with ADHD compared to normative data.

In contrast to these findings with the CHQ and the KINDL several studies using different measures did find that children with ADHD self-report reduced QoL compared to healthy children. Topolski et al. [82] using the YQOL-R [22, 56], found that adolescents with ADHD (11–18 years) reported poorer QoL, compared with a control group without a chronic health condition, especially in the domains of self (belief in self, mental and physical health) and relationships (peers, friends, family, adults). These differences were no longer statistically significant, however, when a Bonferroni correction for multiple comparisons was applied. Pongwilairat et al. [59] using the PedsQL [86], in a Thai sample also found lower self rated

QoL in children with ADHD. The total score and the physical and psychosocial domain scores on the PedsQL reported by children with ADHD were all significantly lower than those reported by control children. These differences remained when corrected for medication status. Varni and Burwinkle [83] also found that, compared to healthy children, ADHD children (5–16 years) reported significantly lower PedsQL scores on dimensions of psychosocial health and small, but not statistically significant differences on physical functioning in a large population-based study. They also reported that the parent and child ratings were similar across all domains, that the inter-correlations of the PedsQL subscales between the two raters were in the medium to large range (between $r = 0.50$ and $r = 0.75$), and that the correlations in the physical domain were similar to those for the psychosocial domains [83]. Rimmer et al. [69] reported similar correlations ($r = 0.67$) between child and parent ratings on the PedsQL in an independent clinic based sample. Using the DUX-25 [40] and TACQOL [87] in a Dutch clinical sample of children with both ADHD and developmental coordination disorder (DCD) Flapper et al. [28] also found lower overall QoL in the ADHD/DCD group on both measures with subscale scores on the DUX-25 demonstrating lower functioning on the emotional and social domains and the TACQOL lower functioning on the motor, autonomy, cognitive, social and positive moods domains.

Parent rated

Twenty-three studies were identified that compared parent rated QoL in samples of children and adolescents with ADHD with that of normal controls or against existing normative data on QoL from standardized instruments. During the development of the parent version of the Child Health Questionnaire (CHQ-PF50), Landgraf et al. [42] reported that an ADHD sample were rated as having significantly lower scores on the psychosocial summary score and the psychosocial and family subscales (behaviour, mental health, self-esteem, role limitations-emotional/behavioural, parental impact-emotional and time, family activities and family cohesion), compared to their norm group. These findings were replicated in several clinical ADHD samples which used the CHQ and compared children with ADHD to either healthy controls [26, 32, 75] or US norms [15, 38, 39, 45, 46, 52, 57, 58, 64, 97]. Differences have been reported for both male and female subjects. The largest differences have been found on the family impact (family activities, parental time emotional), behaviour and role-emotional/behavioural subscales. The psychosocial summary scores for children with ADHD in the different studies are between 1.5 and 2 SD below the US norms. Comparing different ADHD-subtypes on the

CHQ, all three subtypes had worse scores than controls on most subscales although only the inattentive subtype were impaired on the physical subscales. There were other differences between the groups, for example, the combined and inattentive subtypes had significantly lower scores on the self-esteem and emotional impact subscales than the hyperactive-impulsive type and the combined subtype in turn showed worse scores on the, role/social functioning (due to emotional and behavioural problems, family activities and impact on parental time subscales than both the inattentive and hyperactive-impulsive subtypes [29]. Parents did not rate children with ADHD to have lower QoL on the physical domain in most studies [38, 45, 57, 64]. However, in a large community sample Sawyer et al. [75] did find small but significant differences on the parent-reported physical subscales of the CHQ-and the study of Escobar et al. [26] also reported a significantly lower physical summary score in children with newly diagnosed ADHD, compared to a control sample. Klassen [37] computed the effect sizes for several of the above studies, using the CHQ-PF 50 using the criterion of Norman et al. [53] clinically meaningful deficits in QoL were reported on all psychosocial and family subscales (mental health -0.55 , self-esteem -0.75 , parental impact time -0.85 , role-emotional/behavioural -1.22 , behaviour -1.44 , parental impact-emotions, -1.45 and family activities -1.67).

Using the PedsQL both Pongwilairat et al. [59] and Varni and Burwinkle [83] found children with ADHD to have similar parent rated QoL for physical health compared to healthy controls. This contrasts with the lower total and *psychosocial, emotional, social* and *school* subscale scores on the ratings of the ADHD group reported in the same studies.

In a pan-European ADHD observational study [ADORE, 59], the QoL of some 1,500 children with ADHD was dramatically lower at baseline, than that of norms for community youth, with mean scores on the parent report form of the CHIP-CE [67] between 1.5 and 2 standard deviations below community norms in all domains, except for the comfort domain. Scores were below 35 (mean of 50 with SD of 10) for the sub-domains, satisfaction with self, social problem solving, threats to achievement and academic achievement and between 40 and 35 for satisfaction with health, emotional comfort, family involvement, individual risk avoidance and peer relations. Only three sub-domains were near normal: physical comfort, restricted activities and physical activities. These findings were consistent across all ten participating countries [65]. Equally compromised QoL, as measured by the CHIP-CE, was found in 200 children with ADHD entering an open label treatment study in the UK [60].

Hampel and Desman [33] found all domains of parent reported QoL to be impaired among children and

adolescents with ADHD compared to normative data using the KINDL [62] and Flapper et al. [28] also reported reduced overall parent rated QoL in their group of children with ADHD and DCD on both the parent rated DUX-25 [40] and TACQOL [87] measures with subscale scores on the DUX-25 demonstrating lower functioning on the physical, home, emotional and social domains and the TACQOL lower functioning on the motor, autonomy, cognitive, social and positive and negative moods domains.

In two linked studies, one in the UK and one in the US, that used the EQ-5D parent version [27], very few of the parents of children with ADHD-related problems reported difficulties on the *physical* items (e.g. *mobility* and *pain/discomfort*) while the majority endorsed that their children had problems with emotions and in their abilities to carry out usual activities [46].

In summary, robust reductions in QoL of around 1.5–2.0 SD are reported across several different QoL measures and across a broad range of psycho-social, achievement and self evaluation domains by the parents of children with ADHD. Clearly these are large effects which are similar in size to those reported for the ADHD symptoms [93]. In general no strong effects of ADHD on physical functioning domain of QoL are reported. This negative impact is seen in both boys and girls and across the different ADHD-subtypes. Although not well studied the impact of ADHD on QoL appears to be less robust and broadly based when self-reported QoL is the main outcome. Children with ADHD rate their own QoL less negatively than do their parents and do not always consider themselves as having impaired QoL compared to healthy controls. These differences between parents and children may be related to the measures used. It is notable that while no group differences were reported for the two studies that have used the CHQ reduced self-reported QoL was reported in the four studies in which other QoL measures were used. Comparative studies would be helpful in identifying whether this is a consequence of the limited number of studies or the way in which the child completed CHQ has been constructed or worded (the same pattern of results was not found for the parent completed studies). However, it is also possible that the less robust findings are due to either a lack of self awareness or minimization of difficulties on the part of the ADHD child cannot be ruled out. Alternatively parents' ratings may be influenced by their own burden of care. There clearly needs to be more effort put in to studying self-reported QoL in those with ADHD and future studies should consider comparing ratings across different measures and comparing and analyzing the differences between child and parent ratings of QoL. It would also be of interest to use interviews in parallel with the standard questionnaires to investigate the meaning of different QoL scores and to tease out whether some questions are more sensitive/

important at picking up problems than others in this group of children and young people.

QoL in children with ADHD compared to children with other conditions

In order to assess the significance of the effects of ADHD on QoL it is useful to compare QoL in ADHD with QoL in other physical and mental health conditions. Whilst it would be possible to make indirect comparisons by comparing data from the many separate studies that have investigated QoL in different conditions this would result in a wide range of methodological problems. We have therefore restricted ourselves to studies that have made direct comparisons.

Three comparative studies have compared child self-reported QoL in children with ADHD and other medical conditions with conflicting results. Children with ADHD rated their QoL far better than children with end stage renal failure, not only on the physical subscales but also on role/social behaviour and mental health using the CHQ-CF87 [41]. On the PedsQL children with ADHD reported; significantly better physical functioning compared to children with newly diagnosed cancer and children with cerebral palsy; lower psychosocial health and social functioning (but similar total scores and emotional and school functioning) to the children with cancer and comparable total scores and psychosocial, emotional, social and school functioning to the children with cerebral palsy [83]. In the study by Topolski et al. [82] adolescents with ADHD reported similar scores on the YQOL-R to those from a group of adolescents with mobility impairment, who had previously been demonstrated to have reduced QoL compared to healthy children. It is interesting to note that as in the previous section, comparing child reported QoL between children with ADHD and healthy controls, it was only the study using the CHQ that reported the ADHD group to be generally better than those in the physical problems group.

Several studies have used parent proxy measures of QoL in comparative studies. Compared to children with asthma and sickle cell disease, children with ADHD were rated as having a lower QoL on the psychosocial subscales of the CHQ-PR50 while being given better scores on the physical subscales [45]. Escobar et al. [26] confirmed these findings also using the CHQ in a comparison between children with newly diagnosed ADHD and asthma. In the study of Varni and Burwinkle [83] the pattern of impairments reported by parents was different to that of the children themselves. Whereas the children with ADHD had reported similar total scores on the PedsQL to children with cancer and cerebral palsy their parents rated their overall QoL as superior to that reported by the parents of the two physical disorder groups.

There have been several direct comparisons of parent rated QoL between ADHD and other mental health conditions. In a large community sample, the QoL of children and adolescents with different mental disorders was compared after the exclusion of comorbid cases [75]. The results were all in the predicted direction. Children with ADHD had more behavioural and fewer *emotional problems* than those with major depressive disorder, and also had more *interference with family activities* and *impact on parental time* (effect sizes all ≥ 0.3 SD). *Interference with peer and school activities* or *emotional impact on parents* varied little for children as a function of different mental disorders. No significant differences were found between children with ADHD and conduct disorder. In the same study the scores of children with mental disorders (a majority of who had ADHD) were significantly lower on four of the five CHQ scales than for children with physical disorders (including asthma, diabetes and epilepsy). In a clinical sample, Bastiaansen et al. [7] did not find any overall differences in QoL of children with ADHD/disruptive disorders compared to those with other psychiatric disorders such as anxiety disorders, pervasive developmental disorders, mood disorders or even to those for whom help was being sought but who at assessment did not warrant a formal psychiatric diagnosis. However, children with disruptive disorders including ADHD showed significantly lower scores on the psychosocial sub-domain of the PedsQL than children in the other or no diagnosis category. Using the Dutch version of the CHQ PF-50 Hakkaart-van Roijen et al. [32] found that parents of ADHD children reported their children to have poorer QoL on the psychosocial summary score compared to the reports of parents of children with “non-ADHD behavioural problems.”

In summary, ADHD has been shown to have a comparable overall impact on QoL when compared to physical disorders. However, a closer inspection suggests greater impact on psychosocial QoL domains, and a lesser impact on physical QoL domains than common chronic physical illnesses. Initial evidence also suggests that ADHD has a comparable overall impact on QoL when compared to other mental health conditions. The available data is starting to suggest that different mental health disorders may impact on some QoL domains (e.g. peer and school problems and impact on parents) in similar ways while on other domains the impact varies depending on the disorder (e.g. children with ADHD had more behavioural problems and interference with family activities, but fewer emotional problems than those with major depressive disorder). However, data on these issues remains sparse and more studies are required before any clear statements can be made. Such data will be important not only to clinicians but also to health service planners who are required to make decisions about resource allocation between different parts

of comprehensive children's healthcare services and within different parts of child and adolescent mental health services.

Factors related to QoL in ADHD; Symptom severity, impairment, comorbidity, demographic and other factors

If we are to fully understand the nature of the QoL impairments in ADHD it is necessary to examine the factors that may drive a reduction in QoL.

Symptom severity

Several studies have investigated the correlations between symptom severity and QoL scores. Clearly an absence of correlation would be surprising and cast doubt on the relationship between ADHD and QoL. On the other hand a perfect or very high correlation would lead one to question whether the two concepts were in fact separable and whether measuring QoL adds anything to our understanding of the child with ADHD. A significant but moderately strong correlation supports the notion that QoL and ADHD symptoms are related but distinct constructs and that both may be required to give a full picture of a child's difficulties.

The scores on the *psychosocial* scales of the CHQ-PF50 have been shown to significantly negatively correlate with parent and clinician symptom ratings [38, 45, 64]. Correlations are usually in the small to moderate range (between $r = -0.21$ and $r = -0.60$), which suggests that these measures are tapping into related but distinct constructs. The highest correlations with symptom severity are found on *behaviour* and *family activities* subscales. The *psychosocial* subscales correlated equally highly with both the hyperactivity/impulsivity and the inattention symptom subscales [38, 45]. Correlations between the parent-reported QoL psychosocial scores and the teacher-reported *Child and Adolescent Symptom Inventory* were not statistically significant [38]. High symptom scores also predicted poor QoL on parent ratings using the CHIP-CE in the ADORE study [68]. Coghill et al. [19] using the EQ-5D found that utility scores deteriorated as severity increased and that patients with improved symptom severity since the last consultation had higher utility values (0.88) than those who did not improve (0.78). This suggested that patients who had reduced symptom severity valued their health state more than those whose symptoms did not improve. Similar results were reported by Matza et al. [47]. Used standard gamble (SG) utility interviews to assess parent preferences for health states of childhood ADHD. Parents' SG rating of their child's current health state was significantly correlated with inattentive, hyperactive, and overall ADHD symptoms ($r = 0.37, 0.36, \text{ and } 0.40$, respectively;

$p < 0.05$) and psychosocial HRQL domains, the mean utility score was 0.74 (on a utility scale ranging from 0 to 1). Secnik et al. [76] conducted a similar study in the UK and again found that parents' raw standard gamble scores of their child's current health state were significantly correlated with inattentive, hyperactive, and overall ADHD symptoms and the EQ-5D visual analogue scale.

Functional impairment

While it is possible to have a serious physical disorders such as diabetes, hypertension or cancer without there being any obvious functional impairment for ADHD, and most other psychiatric disorders, both symptoms and functional impairment are a prerequisite for diagnosis. Accordingly clinical guidelines have encouraged the measurement of both and instruments such as the Children's Global Assessment Scale (CGAS) [77] have been developed to allow impairment to be routinely measured in a clinical setting [80]. There are both similarities and differences between the concepts of impairment and QoL. Impairment is an objectively measured assessment of a deviation from the mean for a broad range of functional domains. QoL relates to similar domains but measures them subjectively against an internally rather than externally generated standard. Impairment is usually rated or measured by the clinician, QoL by the patient; impairment is integral to the illness; QoL is a broader assessment of the impact of illness [75]. Some of these differences are reflected in the differences between the CGAS and measures of QoL. As it involves making a single very general rating the CGAS, would not be expected to capture the diversity of QoL domains or the distinctiveness of the parent or the child perspectives. Using the PedsQL Rimmer et al. [69] found relatively low correlations between parent and child ratings of QoL and clinician ratings of severity using the CGAS (parent/clinician $r = 0.42$; child/clinician $r = 0.29$). Poor scores on the Clinical Global Impressions scale [CGI-S, 51], which indexes the severity of the disorder, were predictive of lower QoL as measured by parent ratings on the CHIP-CE in the ADORE study [68]. It is important to note that as some aspects of impairment are heavily reliant on self or proxy reports (e.g. ability to keep friends or build up close relationships) the boundaries between the impairment and QoL constructs are not always clear cut and much more work is required to more clearly define their boundaries and overlaps. However, as is the case for symptoms the finding of significant but not perfect correlations between impairment and QoL in ADHD adds some weight to the validity of the QoL construct in this context and that QoL is not simply a relabelling of impairment, as measured by tools like the CGAS, by a different name.

Comorbidity

Several studies have suggested that children with ADHD and a comorbid disorder have poorer QoL than those with ADHD alone. Newcorn et al. [52] compared youth with ADHD with and without ODD, and found that those with ODD generally had lower scores on the psychosocial summary score of the CHQ-PF-50, as well as on most subscales. The presence of a psychosocial stressor (e.g. parental separation/divorce; move; conflict with siblings or peers) was also related to a larger difference in the behaviour scale in this study, and higher parent-reported ADHD symptom severity was associated with more negative findings for self-esteem [52]. Within a sample of clinically referred children with ADHD multiple comorbid disorders was associated with poorer *psychosocial* QoL on the CHQ-PF50 than having either no or only one comorbid disorder [38]. The combination of comorbid ODD/CD and another comorbid disorder (e.g. tic disorder, depression, anxiety disorder but not learning disability) was also associated with significantly lower scores [38]. In a separate study by the same group discrepancies between parent and child reports of the CHQ behaviour and mental health scales were larger in the presence of ODD/CD [39].

In the ADORE study the association between 26 independent factors including comorbid problems and ADHD children's QoL was investigated using the CHIP-CE [68]. The presence of high emotional symptoms, conduct problems, peer relationship problems, coordination problems, asthma or two or more somatic symptoms, and having a parent with mental health or health problems, were all associated with poor parent-reported QoL on the CHIP-CE over and above the association between ADHD and QoL.

Demographic and other factors

In the ADORE study several other baseline variables, including several family factors, such as having a parent with a health or mental health problem possibly caused by the child's illness, child not living with both parents and maternal smoking during pregnancy were also associated with poorer QoL. Other factors such as the number of children living at home, a history of parental ADHD, maternal drug/alcohol abuse during pregnancy and low birth weight or prematurity were not associated with QoL scores on any domain/sub-domain. Living with both parents was, however, associated with a stronger sense of well-being [68].

In summary, the available data supports the validity of QoL measures as being associated with, but not completely overlapping with, ADHD symptomatology and impairment. Increased symptom levels and impairment predict poorer QoL. The presence of comorbid conditions

or psychosocial stressors is also predictive of poorer QoL in samples of ADHD children. Further studies are required to extend our understanding of the predictors and correlates of reduced QoL. These data should also be examined in detail to gain a better understanding of the overlaps between the various frames of reference (symptoms, impairment and QoL) and this information fed back so into efforts to refine the structure and scoring of current measures and the development of new and improved measures of QoL.

Is QoL in children with ADHD responsive to treatment?

If QoL measures are to be useful as outcome measures it is essential that they are sensitive and reliable measures of, change and are able to and capture changes that may occur in QoL after treatment. In their review of QoL measures in children and adolescents Solans et al. [78] reported that acceptable sensitivity to change has been reported for only 10% of the identified generic instruments (CHQ, KIDSCREEN, KINDL and Peds-QL). However, those that were tested were found to be sensitive to changes down to around 0.2 standard deviations. Of these four measures only the CHQ and the Peds-QL have so far been used in treatment studies of ADHD. Studies in paediatrics have generally supported the use of QoL as an outcome measure [84] although this remains a relatively understudied field that has only become popular to study in recent years. Within the child and adolescent mental health field we believe that QoL has only been used as an outcome in clinical trials for ADHD. The studies that were identified which measured treatment related changes in QoL in ADHD studies are described in Table 2.

We are unaware of any published clinical trials of psycho-social treatments for ADHD that have utilised QoL measures of outcome. However, early data from the longitudinal aspect of the ADORE study do suggest that over the first 3 months of treatment psychosocial treatments (mainly psychoeducation) are associated with an improvement in aspects of QoL, although these changes are not as great as those seen for pharmacological treatments [81].

Several studies have investigated the impact of medication treatments on QoL. Unfortunately as these studies have only recently started to appear in the literature and there are very few published studies describing the impact of either methylphenidate or amfetamines on QoL. There is, however, a fairly sizable literature on the effects of atomoxetine on QoL. All currently published treatment studies have used generic QoL scales rather than ADHD-specific scales.

Methylphenidate

There are no published controlled trials which have investigated the impact of methylphenidate treatment on QoL. In a cross sectional observational study of QoL, while both stimulant medicated and un-medicated children with ADHD had significantly lower total and psychosocial subscales scores on the PedsQL than healthy controls and these two groups did not differ from each other [59]. In another observational study Yang et al. [97] using the CHQ-PF50 also found the Psychosocial Summary Scores and all of the psychosocial subscale scores of children treated with methylphenidate were poor compared to healthy controls. However, they also reported that improvement of ADHD core symptoms after medication treatment was predictive of higher psychosocial functioning. This effect was independent of the child's current age, age at receiving diagnosis, age starting and duration of medication treatment but was not independent of ADHD comorbidity: The QoL of those children with a comorbid condition was less likely to improve even if core ADHD improved [97]. Flapper et al. [28] investigated the effects of methylphenidate at "optimal dose" in known responders in an open label trial on the parent and child rated DUX-25 and TACQOL. Children on methylphenidate rated themselves and were rated by their parents as having improved total QoL scores compared to their un-medicated state on both instruments and improved scores on the child reported physical and emotional subscales of the DUX-25, the child reported autonomy, cognitive, social, and negative moods subscales of the TACQOL and the parent-reported bodily, motor, autonomy, cognitive and social subscales of the TACQOL.

Amfetamines

One open label [71] and one randomized controlled double-blind trial (RCT) [92] have investigated the impact of mixed amfetamine salts on QoL. Both studies were sponsored by the pharmaceutical industry. In the open label study almost 3,000 subjects were treated with an extended release mixed amfetamine salt (MAS) preparation over a 7 week period [71]. QoL as measured by the total score on the parent rated PedsQL improved significantly from baseline to endpoint. Wigal et al. [92] measured QoL using the PedsQL during a randomized controlled double-blind laboratory school study comparing this same extended release mixed amfetamine salt preparation with atomoxetine. Both treatments resulted in statistically significant improvements in QoL from baseline to endpoint. The mean difference from baseline on the PedsQL for MAS was 7.9 unit points and for atomoxetine was 7.1 unit points ($p < 0.0001$). There were no differences between the two

medications with respect to the total ADHD scores or the ADHD symptom subscale scores. The two treatments did, however, differ with respect to QoL was seen on the school functioning subscale on which there was a greater improvement in the amfetamine treated group (34%) compared to the atomoxetine treated group (25%). The least square mean difference of 6.94 unit points (95% CI, $-2.45, 11.42$) indicated a positive effect of MAS over atomoxetine, a difference that was statistically significant [92].

Atomoxetine

This has been the most extensively studied ADHD medication from the perspective of QoL. Again all studies have been sponsored by the pharmaceutical industry. Combining data from three randomized double-blind controlled trials, Perwien et al. [57] documented that improvements on atomoxetine over and above those seen on placebo in the *psychosocial* summary score ($d = 0.55, p = 0.0001$), but not the *physical* summary score ($d = -0.11, p > 0.05$). Significant improvements were also found for the behaviour, family activities, parental impact time, role emotional/behavioural and mental health scale scores ($d = 0.26-0.55, p < 0.05$) of the parent rated CHQ-PF-50. Benefits were demonstrated after 7–8 weeks treatment. Lower baseline QoL scores, no prior stimulant use and absence of ODD were associated with improved QoL at endpoint. No difference was found between once or twice daily dosing schedules and there was no evidence to support a dose response curve for the doses tested. Response rates, defined as having a score within 1.5 standard deviations of the normative mean, were lower for QoL than they were for ADHD symptoms. A subsequent independent meta-regression analysis of nine randomized placebo-controlled trials with atomoxetine confirmed the improvement of QoL on the psychosocial summary score of the CHQ-PF50 in atomoxetine treated children and adolescents compared to placebo (Standardised Mean Difference 0.47, 95% CI 0.25–0.69) [16]. Both children with ADHD with and without ODD showed significant changes in the psychosocial summary score and on most subscales of the CHQ-PF-50 after 8 weeks of treatment with atomoxetine [52]. These findings were endorsed by a meta-analysis of the results of this and two other studies [13]. However, although the CHQ and symptom-based findings were generally similar, they varied to some extent as a function of group and dose, with some subscales separating from placebo in the 1.8-mg/kg/day dose group and not the 1.2-mg/kg/day group. This underscores the importance of looking beyond symptomatic control when evaluating treatments for ADHD.

Brown et al. [15] found only a trend toward a better response to active treatment with atomoxetine than to

placebo after a 7 week double-blind trial in children with ADHD, while significant improvements were found on both parent and teacher symptom ratings. The effect size relative to placebo was small ($d = 0.32$). With response defined as a total T-score below 60 on the CHQ, significantly more children responded to active medication (43.8%) than to placebo (22.2%). In a UK study, children were randomized to open label atomoxetine or standard current treatment [60]. Over a 10-week period, overall QoL in children with ADHD improved significantly, as measured with the CHIP-CE total score. A differential effect was found between the study treatments, in favour of atomoxetine over standard “treatment as usual” (mainly methylphenidate). In the atomoxetine group children’s mean total CHIP-CE score increased from 23.2 to 38.4, which is still more than one standard deviation below the norm of 50. After 10 weeks all five parent-reported sub-domains of the CHIP-CE (*satisfaction, comfort, risk avoidance, resilience and achievement*) were improved. Much less improvement was seen on the patient-reported Harter Self Perception Profile, with only one scale (social acceptance domain) showing significant change. Possible reasons for the larger improvement for atomoxetine than methylphenidate suggested by the authors are, a more persistent effect of atomoxetine, with less fluctuations and a possible additional effect on anxiety or tic symptoms [60]. It is also possible that whilst treatment with atomoxetine was optimized during the trial the treatments used in the “treatment as usual” was not.

There is little data on longer term treatment effects on QoL. Perwien et al. [58] report on the changes in the CHQ-PF-50 over a 10-weeks period and over 24 months open label treatment with atomoxetine. Significant effects were found for the psychosocial scales in the acute treatment phase and these were preserved over the long term, however, no additional improvement in QoL was observed between 10 weeks and 24 months.

Other medications

Using an unlicensed novel inhibitor of noradrenaline and dopamine reuptake (GW320659), a statistically significant improvement was observed in the *psychosocial* summary score of the shorter CHQ-PF-28 by DeVeauh-Geiss et al. [20].

In summary, there is emerging evidence that QoL improves following effective treatment. This evidence is, however, almost entirely limited to pharmacological treatments and to atomoxetine in particular and almost entirely based on parent report. Several issues still require to be addressed including; the overlap and interactions between improvements QoL and reduction in symptoms and an assessment of the clinical relevance of various degrees of change.

Discussion

QoL is being increasingly recognized as an important component of a comprehensive assessment of the impact on children and young people of health problems, in general, and ADHD, in particular. However, the QoL concept remains problematic in a number of ways, with multiple competing definitions and measurement approaches [18]. These issues complicate the interpretation of the existing data relating to QoL in ADHD. Notwithstanding these limitations, in the current review we have brought together the existing published data on QoL in ADHD. This allows us to assess the implications of these findings, reflect on issues of interpretation and identify areas for future study.

The current published evidence indicates that QoL is impaired in children with ADHD according to parental report. Across different measures of QoL parents consistently rate the QoL of their children with ADHD as between 1.5 and 2 SD below the appropriate population norms. Furthermore the evidence suggests that QoL impairment increases as the severity of disorder increases, and/or where it is complicated by the presence of comorbidity or psychosocial stressors. The most robust effects are found on the *psycho-social* and *achievement*-related measurement scales and those that assess impact on family life. Both inattentive and hyperactive/impulsive ADHD symptoms appear to be equally related to this reduction in QoL. Furthermore, there is evidence to support treatment effects on QoL that to some extent mirror their effects on ADHD symptoms, although with smaller effect sizes. While there is some evidence for child reported reductions in QoL this is less consistent than for parent ratings. There is also fairly consistent evidence that parents and children assess QoL differently, as evidenced by the, modest, correlations between parent and child reports, and that parents tend to rate their children with ADHD as having lower QoL than do the children themselves. While these may in part be related to the measures used (neither of the studies that used the child rated CHQ reported differences between ADHD and healthy children but all four of those that used other scales did) there are several other factors that could account for these findings. Inconsistencies between child and parent ratings of QoL may also reflect age, or sample differences as well as error or true differences. In contrast to children with other psychiatric conditions (e.g., depression), children with ADHD may have an over-optimistic view of their situation. A similar effect has been demonstrated in many studies of self-esteem and self-concept in children with ADHD where it has been hypothesized as being the result of a *positive illusory bias* [35, 55]. Children with ADHD are hypothesized to overestimate their own abilities and performance in order to protect a positive self-image [54]. Experimental studies have supported aspects of

this proposed mechanism [35, 54] and it may be important for similar studies to be designed with respect to child reports of QoL in ADHD. Klassen et al. [39] have suggested several other possible reasons for the discrepant findings between child and parent reports of QoL; children may want to conceal their problems; they may ignore them in an attempt to cope with them; they may undergo a process of adaptation to disorder leading to a shift in their internal standards leading to changes in evaluation; they may be making systematic mistakes in rushing through the questionnaires because of their impulsive cognitive style. The finding of larger discrepancies between self- and parent-ratings in children with comorbid ODD/CD and those with additional psychosocial stressors may support the first two hypotheses. This pattern of discrepancy between informants also raises a fundamental conceptual issue given that, in its purest sense, QoL has a strong element of self evaluation. If this view was taken to its logical conclusion the child's view would trump that of the parents. However, at this stage we suggest that a pragmatic approach should involve attempts to develop methods that allow the combining of both proxy and child ratings in order to provide a more comprehensive and integrated assessment [83]. There will, however, need to be more work exploring the psychometric properties of child-report instruments both in general and in ADHD specifically. Future research, including head to head comparisons of parent and child ratings and experimental studies, should also address the differing ways by which children and parents construct the experience and impact of ADHD on the child's QoL. Developmentally sensitive designs that can describe the impact of ADHD on QoL at different ages and the progression of QoL over time would also be very welcome. Large datasets, particularly those derived from community samples, should also be interrogated using data reduction techniques such as factor analysis to identify latent variables. Of particular interest will be studies that have used more than one measure of QoL whereby commonalities between different measures can be identified and possibly translated into new instruments with improved validity and reliability.

Relatively few child studies have compared QoL in ADHD either with QoL in other psychiatric disorders or with chronic physical disorders. Those studies that have been conducted have started to suggest that different disorders may result in different QoL profiles, however, more and larger studies will improve our understanding considerably.

More work is also required to improve our understanding of both the differences and interrelationships between the different levels of analysis that comprise a child's overall functioning (e.g. ADHD symptoms, associated functional impairment and QoL) as these concepts are

currently not well delineated either theoretically or on a practical level within the different measurement scales. Different questionnaires contain different mixes of items which tap into all three levels. This means that there is inevitably item-overlap between symptoms rating scales and QoL measures and it then becomes difficult to tease out any independent effects that the disorder or its treatment may be having on symptoms on the one hand and QoL on the other. This in turn begs the question as to whether an apparent treatment related change as measured by current QoL instruments actually adds anything to our understanding of treatment effects. Whilst we believe that measures of QoL can add considerable colour to the measurement of treatment outcome future research needs to address the contribution of these different elements in characterizing ADHD and its relationship to QoL. A major question to be addressed here would be; does the concept of QoL add any value to our understanding of ADHD over and above the concepts of symptoms and more specific functional impairment? One study [74], explicitly studied aspects of this overlap and reported that the removal of potentially overlapping (symptom) items made little difference to the relationships between mental illness and QoL that they had previously established. There is the potential for similar analyses to be conducted with existing datasets and this may help to provide a more definitive answer to this question. This may suggest ways that the existing measures of QoL could be refined for use with ADHD populations or scored differently when used in this group. This may also result in a clearer delineation of the key characteristics that lay at the core of QoL that are independent of both symptoms and general functional impairment.

Even within the currently limited research into QoL in children with ADHD there is a lack of consistency in terms of the instruments used to measure QoL. These different instruments have been organized into substantially different sub-scale structures and content [18] which has made it very hard to compare QoL across studies and disorders. These differences between the instruments and between researchers regarding their preferred measure are likely to reflect different opinions regarding the best conceptualization of QoL and emphasize the lack of an agreed core QoL paradigm. Sufficient data has not yet been published to perform a meaningful meta-analysis of studies and instruments from which steps could be taken towards the development of a core set of items that could in turn lead to the development of a common instrument. Of course as is frequently the case in psychological research the authors of the current measures of QoL will often have substantial academic and/or financial investment in their own tool and may therefore also be reluctant to engage in a process by which their own measure may be used less frequently in

future studies. While it is not possible at this stage to recommend one measure as being superior to the others it would be beneficial for studies to be conducted that compared different measures in head to head designs in order that their performance in different groups and different contexts can be described. Studies in children and young people with ADHD that combine questionnaire and interview methods would also be helpful to support the validity of these measures in this group.

Most studies to date have relied on clinic-referred samples, and thus have the potential for referral and Berkson's bias [9]. This has led to a reduced range in outcomes and associated limitations on the power of statistical tests. Further studies are required, to anchor these effects within the wider population.

Most studies have used parental reports both for symptom severity and QoL. This introduces the problem of shared-rater variance and may induce at least two possible sources of bias. This could result in a spurious association between ADHD symptoms and QoL and leaves both measures open to undue influence by parent characteristics: other than the very general data from the ADORE study mentioned above [68], we are unaware of any studies that have investigated the effect of parental mental health on measures of their child's QoL. Future studies should, as a matter of course, take independent ratings of QoL and symptoms. The choice of who should act as the second informant itself raises a number of issues. In the broader field of ADHD, teachers' ratings are often used to address this problem. However, the low correlations found between ratings of QoL by the child or parent and teacher-reported symptoms may be accounted for by the fact that teachers are interested in and observe different maladaptive and adaptive behaviours in the classroom than parents do at home, or that they often only see the children when they are medicated. On the other hand, it is also possible that parents may have exaggerated both symptoms and impact on well-being.

Finally, treatment studies have, to date, been extremely limited in their scope. Studies have focused almost exclusively on one treatment modality (pharmacological) and one molecule (atomoxetine). Stimulants (amphetamines, methylphenidate) are also recommended for the treatment of ADHD [4]. In view of the many measurement issues described above we are not yet at a stage whereby QoL measures can be considered as serious contenders as primary outcome measures in major clinical trials although this may change in the future. One particular psychometric issue that requires clarification in this respect is clarification of what constitutes a clinically meaning change for these measures. We do, however, strongly recommend that those designing and conducting future clinical trials, both pharmacological and psychosocial, should include

measures of QoL as secondary outcome measures. Although we are aware of several ongoing RCTs of stimulant medication that are using QoL measures at present no systematic published data from RCTs on the impact of methylphenidate on QoL in ADHD, only one RCT of amphetamines and none with psychosocial treatment, this needs to be addressed urgently. It should also be noted that the total number of individual children that have had their QoL measured as a part of the atomoxetine development program is less than it may initially appear to the casual reader. Several of the meta analyses have included data from the same trials and all of the children in the long term open label follow-up study described by Perwin et al. [58] were enrolled into the long term study following their having completed participation in an RCT and are therefore likely to be included in at least one other publication. The lack of systematic studies of psychological therapies either on their own or in multimodal combinations with medication is a further omission in our understanding of the impact of treatment on QoL.

Studies have, on the whole, had relatively short follow-up periods and it may be the case that some aspects of QoL will take more time for change and would therefore not be seen in these short-term clinical trials. However, Perwin et al.'s longer term study [58] failed to show any additional improvement in QoL after the acute treatment period.

There has been no systematic analysis of the extent to which changes in QoL are mediated by symptom changes, changes in functional impairment or other factors. This task is complicated enormously by the fact that the concept of QoL appears to be somewhat confounded in current scales with ADHD symptoms and functional impairment.

Although it is likely that QoL, in relation to medication response, will probably be influenced by a mixture of positive treatment responses and side effects the role of adverse events, in determining QoL following treatment, has not yet been reported in any of the published studies.

Most studies have either had strict inclusion and exclusion criteria that have not allowed the recruitment of those with comorbid disorders or have failed to control for comorbid disorders such as ODD, anxiety and depression, either at baseline or when assessing the responsiveness of QoL to treatment, even though it is recognized that several subscales of the QoL measures contain items on behaviour problems, depressive symptoms and anxiety. At the same time, it seems clear that some of the QoL effects demonstrated in ADHD are clearly distinct from ADHD symptoms, e.g. peer and family relation impact.

The ADORE study [61] collected naturalistic observational data on ADHD symptoms, impairment, comorbidity and QoL over a 2 years period on a large group of children and young people with ADHD who were receiving a wide range of pharmacological and non-pharmacological

treatments. Data from the longitudinal portion of this study has been submitted for publication and will help to address many of these issues. However, it is also essential that further well designed clinical trials which utilise both child and parent proxy completed QoL measures are conducted and in particular head-to-head studies of different treatment packages with a broad range of outcomes over extended periods of time, with multiple testing points are required. These studies should be designed in such a way to allow the exploration of the natural history of changes in QoL following treatment as well as the mediating effects of symptom reductions and other factors on longer term changes in well-being.

In addition to acting as an outcome measure QoL measures could be helpful within the clinical setting as an indicator of clinical need and assist the clinician in identifying areas of life that are particularly difficult for a child in order that appropriate support can be engaged. ADHD impacts on many aspects of life and although clinicians now have much more information regarding the best ways to reduce ADHD symptoms it is also important for us to always be alert to the associated difficulties faced by these children and to consider how best we can improve their lives.

In summary, published studies to a degree support an impact of ADHD on QoL, which is at least as great as seen for many physical disorders. These effects are greatest, and most consistent, with parent ratings than child-self ratings. Future research needs to distinguish QoL effects from those related only to symptoms and functional impairment; study the differences between child and parent perceptions of ADHD and its impact; identify common elements across the multiple measures currently in use; use population as well clinical samples; include independent ratings of QoL and ADHD symptoms; study the effects of a broader range of treatments in a way that allows the assessment of mediating and moderating factors.

Acknowledgments This paper is derived from a work group meeting of the European ADHD Guidelines Group which was supported by an unrestricted educational grant (costs of the meeting only) from: Elli Lilly, Janssen-Cilag, and Novartis & Shire.

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