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Health state utilities associated with adult attention-deficit/hyperactivity disorder

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Objectives: With growing awareness of the importance of adult attention-deficit/hyperactivity disorder (ADHD) treatment, cost-effectiveness analyses, including utilities, are needed to compare the value of treatment options. Although utilities have been reported for childhood ADHD, little is known about utilities representing adult ADHD. Therefore, the purpose of this study was to estimate utilities associated with adult ADHD.

Methods: Health-state descriptions of adult ADHD were drafted based on literature review, interviews with four clinicians, and clinical trial data. Health states were revised based on a pilot study with 26 participants. Final health states were rated in time trade-off interviews with general population respondents in London and Edinburgh, UK.

Results: A total of 158 participants completed interviews (mean age =47.0 years; 49.4% female; Edinburgh =80 participants). Mean (standard deviation [SD]) utilities were 0.82 (0.17), 0.68 (0.28), and 0.67 (0.28) for health states describing treatment responders (health state A), nonresponders (health state B), and untreated patients (health state C), respectively. Most participants rated health state A as preferable to B (n=92; 58.2%) and C (n=97; 61.4%). The majority rated B and C as equal (n=125; 79.1%). Paired Student's *t*-tests found that A had a significantly greater mean utility than B (t=10.0; $P<0.0001$) and C (t=10.2; $P<0.0001$).

Conclusion: The current study provides utilities that may be used in cost–utility models of treatment for adult ADHD. Results reflected clear differences between health states representing treatment responders and nonresponders/untreated patients. Current utilities were comparable to those previously reported for childhood ADHD.

Keywords: adult ADHD, utility, time trade-off

Introduction

A growing body of research indicates that symptoms of attention-deficit/hyperactivity disorder (ADHD) often persist into adulthood.[1–4] With increasing awareness of the need to treat adult ADHD, cost-effectiveness analyses are needed to demonstrate and compare the value of new and existing treatment options. A cost–utility model is a type of cost-effectiveness analysis that requires utilities, which are values on a scale with anchors of 1 (full health) and 0 (dead) to represent the strength of preferences for various health states.[5]

Although utilities have been reported for childhood ADHD, including values associated with various levels of treatment response,[6–9] little is known about utilities associated with adult ADHD. Two recent reviews reported no published utility values representing ADHD in adults.[10,11] Literature searches conducted for the current study also found no published work on adult ADHD utilities, but one conference presentation was located that reported adult ADHD utilities derived from SF-36® (Medical Outcomes Trust, Hanover, NH, USA) responses via the SF-6D scoring algorithm.[12] However, the six items from the SF-6D do not assess attention or other constructs that are specifically

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relevant to ADHD,[13] which suggests that it may have limited content validity for this particular condition. Therefore, the purpose of this study was to estimate utilities associated with adult ADHD using a direct utility elicitation method. Time trade-off (TTO) methods were used to obtain utilities for health states representing treatment responders, nonresponders, and untreated patients.

Methods

Overview of study design

Adult ADHD health-state descriptions (often called vignettes) were drafted based on literature review, clinical trial results, and input from clinicians. These health states were refined based on additional clinician interviews and a pilot study conducted with general population respondents in London, UK. Utilities were then derived in a TTO valuation study with general population participants in Edinburgh and London, UK.

The vignette-based approach was used because it is well-suited for obtaining utility estimates for specific conditions. Other commonly used utility assessment approaches may have limited applicability to ADHD. For example, generic preference-based instruments such as the EQ-5D (EuroQol Group, Rotterdam, the Netherlands) do not have dimensions assessing ADHD symptoms such as inattention or impulsivity. Furthermore, mapping an ADHD-specific questionnaire to a generic preference-based measure would be severely limited by the lack of overlapping content between these two types of instruments. In addition, no ADHD-specific preference-based measure is available for obtaining utilities directly from this population.

Health states

Three health states describing adult ADHD were rated in the TTO interviews: treatment responder (A), nonresponder (B), and untreated (C). All health states include a parallel series of statements in four areas: diagnosis of adult ADHD, treatment, symptoms, and impact on functioning. The responder and nonresponder health states both included the same statement indicating that treatment is being received. This treatment statement was nonspecific so that the utility values could be used to represent either pharmaceutical or nonpharmaceutical treatment arms in a cost–utility model. The nonresponder and untreated health states were identical except for the statement indicating whether treatment is received. The three health states are presented in the Supplementary material.

The health states were drafted based on literature review, interviews with clinicians, and clinical trial data. First, a literature review was conducted to ensure that the health states would be grounded in clinical research.[14–20] This review focused on identifying the key symptoms and functional impact of adult ADHD.[21–26] This literature was used to draft structured interview guides for the clinician interviews. Then, interviews were conducted with four clinicians who had experience with adult ADHD. All four had Doctor of Medicine degrees, while two also had PhD degrees. During interviews, the clinicians responded to questions regarding symptoms and impact of adult ADHD.

Pooled data from six clinical trials were examined to ensure that health states accurately described differences between treatment responders and nonresponders. The six trials were parallel double-blind placebo-controlled trials of atomoxetine for the treatment of adult ADHD. Patients were categorized as responders if they had at least a 30% symptom reduction from baseline on either the Conners' Adult ADHD Rating Scale (CAARS) total symptom score[27] or Adult ADHD Investigator Symptom Rating Scale (AISRS) total score,[28] plus a Clinical Global Impression-ADHD Severity score $\leq$3. The 30% symptom-reduction cutoff is commonly used as a threshold for categorizing adult ADHD treatment response across a wide range of clinical trials and outcome measures.[29–36]

Then, endpoint individual item scores were examined on measures of symptoms and function. Language from items distinguishing between responders and nonresponders was included in the health states. For example, the health states included a statement "trouble concentrating when people are speaking to you", which roughly corresponds to item 14 of the CAARS and item 5 of the AISRS. In the trials, responders had, respectively, mean scores of 0.67 and 0.74 on these two items, compared with 1.90 and 2.02 for nonresponders. Health states also included "trouble completing tasks and getting things done on time at work and at home", which corresponds to item 22 of the Adult ADHD Quality of Life Measure (AAQOL).[37] In the pooled trial data, responders had a mean score of 2.22 on this item, compared with 3.50 for nonresponders.

The responder health state says symptoms occur "once in a while" with "minimal consequences". The nonresponder and untreated health states say symptoms occur "often" with "real consequences". These phrases indicating symptom severity and impact were taken directly from response options of the CAARS, AISRS, and AAQOL. The specific response options were selected based on mean scores for responders and nonresponders in the six clinical trials described above. For example, the CAARS response option of 1 ("just a little,

once in a while") was used to represent symptom severity of responders, whereas the response option of 2 ("pretty much, often") was used to represent symptom severity of nonresponders. Similarly, the AISRS response option 1 ("minimal functional consequences") was used to represent impact in the responder health state, while 2 ("real functional consequences") was used to represent impact in the nonresponder health state. On the AAQOL, response option 2 ("a little") corresponded to responders, while 4 ("often") corresponded to nonresponders. For the current health states, symptom severity of untreated patients was assumed to be similar to that of nonresponders.

Health states were drafted based on the language in these clinical trial measures while taking into account clinician input and published literature. Draft health states were tested in a pilot study in London with 26 general population participants (13 female; mean age =42.2 years, 50.0% white) recruited through a newspaper advertisement. The draft health states were administered in a TTO interview to ensure that respondents were able to understand the health states and the interview task. Participants consistently reported that the health states were clear and easy to understand. Some participants suggested minor revisions in formatting, phrasing, and explanation of the TTO task, and the health states were edited accordingly. Health states were also edited to ensure that they reflected typical patients with ADHD as closely as possible, without overestimating or underestimating the impact of this condition. For example, an early draft of the nonresponder health state specified that the patient could not maintain employment. The statement was dropped during the pilot study because: 1) the statement appeared to represent a more severe impact than would be experienced by a typical patient; 2) the severity of the statement seemed to distract respondents from attending to the key symptoms and functional impairment of ADHD; and 3) unlike the other statements, it was not specifically tied to clinical trial measures.

Participants

Participants were required to be at least 18 years old, able to understand the procedures, able to give written informed consent, and residing in the UK. Inclusion criteria did not specify any particular clinical characteristics because interviews were intended to yield utilities that may be used in submissions to agencies like the National Institute for Health and Care Excellence (NICE), most of whom prefer that utilities represent general population values.[38–40]

Of the potential participants who responded by telephone to newspaper or online advertisements, 203 were reached for screening. Of the 203 screened participants, 199 were eligible, 174 were scheduled for interviews, and 160 participants attended and completed their interviews. Two of the 160 participants were unable to complete the utility interview procedures. Thus, a total of 158 interviews were completed.

Utility interview procedures and scoring

Interviews were conducted in private conference rooms in Edinburgh and London during October 2012. Procedures and materials were approved by an independent institutional review board, and participants provided written informed consent prior to completing study measures.

Health states were first rated using a visual analogue scale (VAS) intended to introduce participants to the content. Then, health-state utilities were obtained using the TTO method, which has previously been described in detail.[5] TTO interviews were conducted with a 10-year time horizon, which is consistent with the influential Measurement and Valuation of Health study that elicited valuations from the general public for EQ-5D health states.[41] NICE has recommended that, when EQ-5D utilities are not available, utilities for UK cost–utility models should be derived using methods similar to Measurement and Valuation of Health methodology.[42] In the current study, participants were offered choices alternating between greater and lesser durations in full health, varying in 1-year increments (ie, 9 years, 1 year, 8 years, 2 years, 7 years, etc).

For each health state rated as preferable to being dead in the TTO task, the utility value was calculated based on the choice in which the respondent is indifferent between y years in the health state being evaluated and x years in full health (followed by y–x years dead). The resulting utility estimate (u) is calculated as:

$$u = x/y.^{43} \quad [1]$$

If participants indicated that a health state was worse than dead (which seldom occurred in the current study), the interviewer altered the task so that respondents were offered a choice between immediate death (alternative 1) and a 10-year life span (alternative 2) beginning with varying amounts of time in the health state being rated, followed by full health for the remainder of the 10-year timeframe. For these negative utilities, the current study used a bounded scoring approach, which is commonly used to avoid highly skewed distributions.[5,43,44] This scoring approach limits

the score range of health states worse than dead between 0 and −1; formula:

$$u = -x/t \quad [2]$$

where x is time in full health and t is the total life span of alternative 2 in the TTO choice.

Statistical analysis procedures

SAS statistical software version 9.2 (SAS Institute Inc., Cary, NC, USA) was used for all analyses. Continuous variables including utilities were summarized in terms of means and SDs, and categorical demographic variables were summarized as frequencies and percentages. A series of independent *t*-tests (for continuous variables) and chi-square analyses (for categorical variables) were conducted to compare utilities and demographic characteristics of the samples from London and Edinburgh. Pairwise comparisons between health states, using *t*-tests, were conducted to examine differences in preference.

Results

Sample description

A total of 158 participants completed the interview. The sample had a mean age of 47.0 years (SD =14.4) and was 49.4% female. Ethnicity, marital status, employment status, and education level are summarized in Table 1. Only one participant reported being diagnosed with ADHD, but 33 participants (20.9%) reported knowing a friend or family member diagnosed with ADHD. A total of 35 participants (22.2%) reported being diagnosed with a mental health condition, including alcohol abuse (n=2), substance abuse (n=1), anxiety (n=18), Asperger's syndrome (n=2), and depression (n=26).

There were significant differences between the London (n=78) and Edinburgh (n=80) samples in ethnicity and marital status (Table 1).

The Edinburgh sample had a higher percentage of white participants while the London sample had a higher percentage of single participants.

TTO utilities and VAS scores

Mean (SD) TTO utilities were 0.82 (0.17), 0.68 (0.28), and 0.67 (0.28) for health states representing adult ADHD responders (health state A), nonresponders (health state B), and untreated patients (health state C), respectively (Table 2). There were no significant differences in health-state utilities between the London and Edinburgh samples. VAS ratings followed the same pattern of relationships among the three health states: A, 80.0 (SD =16.9); B, 47.1 (SD =17.2); and C, 44.4 (SD =20.4).

In the TTO interviews, 92 participants (58.2%) rated health state A greater than B, while 97 (61.4%) rated A greater than C. The majority of participants rated B

Table 1 Demographic characteristics

Characteristics	London (n=78)	Edinburgh (n=80)	Total sample (n=158)	*P*-value[a]
Age (years), mean (standard deviation)	44.9 (14.9)	49.1 (13.8)	47.0 (14.4)	0.068
Sex, n (%)				
Male	41 (52.6)	39 (48.8)	80 (50.6)	0.63
Female	37 (47.4)	41 (51.3)	78 (49.4)	
Ethnicity, n (%)				
White	55 (70.5)	77 (96.3)	132 (83.5)	0.0002
Black	7 (9.0)	0 (0.0)	7 (4.4)	
Asian	8 (10.3)	1 (1.3)	9 (5.7)	
Mixed	8 (10.3)	2 (2.5)	10 (6.3)	
Marital status, n (%)				
Single	42 (53.8)	22 (27.5)	64 (40.5)	0.0033
Married	24 (30.8)	37 (46.3)	61 (38.6)	
Other[b]	12 (15.4)	21 (26.3)	33 (20.9)	
Employment status, n (%)				
Work full time or part time	49 (62.8)	43 (53.8)	92 (58.2)	0.25
Other[c]	29 (37.2)	37 (46.3)	66 (41.8)	
Education level, n (%)				
Completed university degree	32 (41.0)	28 (35.0)	60 (38.0)	0.44
Did not complete university degree	46 (59.0)	52 (65.0)	98 (62.0)	

Notes: [a]*P*-values are for comparisons between the London and Edinburgh samples. Comparisons were performed with independent Student's *t*-tests for continuous variables and chi-square analyses for categorical variables. [b]Includes divorced, separated, and widowed. [c]Includes homemaker/housewife, student, unemployed, retired, and disabled.

Table 2 Time trade-off utility scores

Health states describing adult ADHD Mean (standard deviation)	London (n=78)	Edinburgh (n=80)	Total sample (n=158)	*P*-value[a]
(A) Treatment responder	0.83 (0.16)	0.82 (0.18)	0.82 (0.17)	0.58
(B) Treatment nonresponder	0.67 (0.29)	0.69 (0.28)	0.68 (0.28)	0.61
(C) Untreated	0.65 (0.30)	0.68 (0.27)	0.67 (0.28)	0.50

Note: [a]*P*-values are from *t*-tests comparing the London and Edinburgh samples.
Abbreviation: ADHD, attention-deficit/hyperactivity disorder.

and C as equal (n=125; 79.1%), although some rated B greater than C (n=23; 14.6%) and others rated C greater than B (n=10; 6.3%). *t*-tests comparing mean TTO utilities found that A was significantly greater than B (t=10.0; $P<0.001$) and C (t=10.2; $P<0.001$). The small difference between health states B and C was also statistically significant (t=2.1; P=0.037).

The great majority of the 158 respondents provided positive utility scores for all health states, indicating that the three health states were almost always perceived as preferable to being dead. Negative utility scores, which indicate that a health state was perceived as worse than being dead, were provided by one respondent for health state A, three respondents for health state B, and three respondents for health state C.

Discussion

Results reflected clear utility differences between adult ADHD health states representing treatment responders and health states representing nonresponders or untreated patients. Utility values identified in the current study were in a similar range to TTO utilities previously reported by Lloyd et al[7] for childhood ADHD. The current utility of 0.82 for a health state representing treatment responders who have symptoms "once in a while" with "minimal consequences" is between the values Lloyd et al reported for childhood ADHD with severity levels of "normal" (0.84) and "borderline to mildly ill" (0.79).[7] The current scores of 0.68 and 0.67 for health states describing nonresponders and untreated patients, respectively, are between the previously reported values for childhood ADHD with severity levels of "borderline to mildly ill" (0.79) and "moderately to markedly ill" (0.58).

While the vignette-based utility assessment method used in the current study is well-suited for identifying utilities associated with specific medical or psychiatric conditions, the limitations of this method should be acknowledged. For example, it is difficult to know the extent to which vignette-based utility values are comparable to utilities derived from other approaches, such as generic preference-based measures. In addition, the usefulness of resulting utility scores is limited by the content of the health states. For example, the current health states only reflected two levels of symptom severity (the nonresponder and untreated health states had the same descriptions of symptom severity). ADHD is a heterogeneous condition with a wide range of severity levels that could be represented in additional health states. In addition, patients' health-related quality of life is likely to be influenced by other factors that were not included in these health states, such as treatment-related adverse events. Therefore, the current study should be considered an early step in estimation of utilities associated with adult ADHD, and future research is needed to identify utilities of a wider range of health states representing more severity levels and specific treatment attributes.

The supporting information used when drafting health states could also have an impact on results. Although health states were drafted based on comprehensive supporting information drawn from literature review, clinical trial results, and clinician interviews, no patients with adult ADHD were directly interviewed. However, the clinical trial results included a patient-reported measure and a clinician-rated measure of all *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* ADHD criteria completed based on interviews with patients. Therefore, while it is possible that patients would report different symptoms than those reflected in the current health states, these health states should largely reflect the patient experience.

It should also be noted that the clinical trial results used to support the health states were from studies focused on a single pharmaceutical treatment (ie, atomoxetine). In these trials, the symptoms that were found to differ between responders and nonresponders covered a broad range of ADHD criteria, so it is reasonable to expect that these differences are representative of improvement that may be experienced with other ADHD treatments. Furthermore, respondents were not oriented to any particular treatment, and the responder health state did not specify any particular type of treatment ("You receive treatment for ADHD. This may include medication [tablets every day] and/or psychological treatment"). Still, it is possible that different treatments could have different effects on ADHD symptoms and,

thus, the improved symptoms described in the responder health state may not be equally representative of patients responding to pharmaceutical treatments other than atomoxetine. Fortunately, the use of published literature and clinician interviews as additional sources of health-state support help to ameliorate this concern.

Future studies may also examine adult ADHD utilities with different methodology. For example, NICE states a preference for utilities based on the EQ-5D in order to maximize consistency across appraisals. However, the guidelines indicate that there is flexibility in situations when the EQ-5D may not apply to a particular population or medical condition. With regard to the current study, the EQ-5D was not considered optimal for evaluation of ADHD health states because none of the five items assess attention or other ADHD symptoms. Therefore, the current study followed methods that NICE has recommended as an alternative: "direct valuations of descriptions of health states" with "the time trade-off method in a representative sample of the UK population… to retain methodological consistency with the methods used to value the EQ-5D".[42] Future research may determine the extent to which alternative methods, such as the EQ-5D or other variations of TTO interviews, would yield different utilities. One possible approach would be to add an ADHD-specific item to the EQ-5D. This approach, often called a "bolt-on", has recently been examined as a way to make the generic EQ-5D applicable to a wider range of specific medical conditions.[45]

Limitations associated with sample characteristics should also be acknowledged. The current study was conducted in two UK locations with a broad sample of respondents, without taking the respondents' health status into account. However, the sample was not recruited to be representative of the UK general population, and it is not known whether utilities may be different in a nationally representative sample. Still, despite demographic differences between the London and Edinburgh samples, there were no significant differences in utility between the two geographic locations, which suggests that health-state preferences may not vary greatly among UK samples.

A possible limitation of the current health states is that they named ADHD as the disease condition. Previous research has yielded mixed results regarding the impact of including the condition label in health states. Some research has suggested that including the condition label can affect utility values, while others have reported situations where the label did not affect values.[46,47] The impact of the label may depend on the specific medical condition and its severity. For example, one recent study found that a cancer label resulted in lower utilities, while the label of irritable bowel syndrome had no significant effect on utility.[48] In light of these mixed results, recommendations vary and it is common to include the condition label in health state descriptions. Although some researchers recommend excluding the label to avoid potential impact on utility values, it can also be argued that the label leads to more accurate representation of the health state because patients who live in a health state experience it with knowledge of the label. In the current study, it was decided to include the ADHD label to ensure that participants viewed all health states as true health conditions requiring treatment, despite the mild symptoms of the responder health state. Future research may examine the extent to which the ADHD label influences health utility values.

Another aspect of the study design that could influence results is that utilities were derived from preferences of general population respondents, instead of patients with adult ADHD. As frequently discussed in previous literature, both the general population and patient approaches have advantages and disadvantages, and there may be differences in utilities from the two types of samples.[5,49–51] The general-population approach is consistent with the most frequently cited methodological guidance provided by health technology assessment agencies.[38–40,52] Theoretically, general population values can be considered representative of a societal view that may be relevant for decision-making regarding public health care funding. On the other hand, patients with personal experience may have greater insight into the content of health-state descriptions and, therefore, patient utility valuations may reflect a more accurate understanding of the health states. It is not known whether patient-based utilities would differ from the utility scores reported in the current study.

Conclusion

Despite potential limitations, the current study provides utilities that may be useful for calculating quality-adjusted life years in cost–utility models of treatment for adult ADHD. It is hoped that future research can build on this study by providing a more detailed set of utilities, thus leading to more accurate modeling to demonstrate the value of various treatments for adult ADHD.

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Disclosure

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Supplementary materials

Table S1 Health state A: treatment responder

- **ADHD**
  - A doctor has diagnosed you with attention-deficit/hyperactivity disorder, which is sometimes called ADD or ADHD.
  - You first had these problems as a young child, and the problems have persisted into adulthood.
- **Treatments**
  - You receive treatment for ADHD. This may include medication (tablets every day) and/or psychological treatment.
- **Symptoms**
  - ONCE IN A WHILE, you have the symptoms below:
  - You have a little difficulty concentrating and keeping your attention focused.
  - You have problems organizing tasks and activities.
  - You procrastinate and have a little difficulty getting started on tasks.
  - You have a little difficulty finding important things like your keys or wallet.
  - You feel a little internal restlessness and tension, and you appear a little restless to others even when you are sitting. You fidget and have a little trouble sitting still.
- **Functioning**
  - Your ADHD has some MINIMAL CONSEQUENCES for your life.
  - Your ADHD symptoms have a minimal impact on your social interaction and relationships.
    - Once in a while, you have a little trouble concentrating when people are speaking to you.
    - If you are in a relationship with a spouse or significant other, your ADHD symptoms cause minimal difficulties, such as tension and arguments once in a while.
  - Your ADHD symptoms have a minimal impact on your productivity.
    - Once in a while, you have a little trouble completing tasks and getting things done on time at work and at home.
    - Once in a while, you have a little difficulty remembering appointments.

Table S2 Health state B: treatment nonresponder

- **ADHD**
  - A doctor has diagnosed you with attention-deficit/hyperactivity disorder, which is sometimes called ADD or ADHD.
  - You first had these problems as a young child, and the problems have persisted into adulthood.
- **Treatments**
  - You receive treatment for ADHD. This may include medication (tablets every day) and/or psychological treatment.
- **Symptoms**
  - You OFTEN have the symptoms below:
  - You have difficulty concentrating and keeping your attention focused.
  - You have problems organizing tasks and activities.
  - You procrastinate and have difficulty getting started on tasks.
  - You have difficulty finding important things like your keys or wallet.
  - You feel internal restlessness and tension, and you appear restless to others even when you are sitting. You fidget and have trouble sitting still.
- **Functioning**
  - Your ADHD has REAL CONSEQUENCES for your life.
  - Your ADHD symptoms have an impact on your social interaction and relationships.
    - You often have trouble concentrating when people are speaking to you.
    - If you are in a relationship with a spouse or significant other, your ADHD symptoms often cause difficulties, such as tension and arguments.
  - Your ADHD symptoms have an impact on your productivity.
    - You often have trouble completing tasks and getting things done on time at work and at home.
    - You often have difficulty remembering appointments.

Table S3 Health state C: untreated

- **ADHD**
  - A doctor has diagnosed you with attention-deficit/hyperactivity disorder, which is sometimes called ADD or ADHD.
  - You first had these problems as a young child, and the problems have persisted into adulthood.
- **Treatments**
  - You do not receive treatment for ADHD.
- **Symptoms**
  - You OFTEN have the symptoms below:
  - You have difficulty concentrating and keeping your attention focused.
  - You have problems organizing tasks and activities.
  - You procrastinate and have difficulty getting started on tasks.
  - You have difficulty finding important things like your keys or wallet.
  - You feel internal restlessness and tension, and you appear restless to others even when you are sitting. You fidget and have trouble sitting still.
- **Functioning**
  - Your ADHD has REAL CONSEQUENCES for your life.
  - Your ADHD symptoms have an impact on your social interaction and relationships.
    - You often have trouble concentrating when people are speaking to you.
    - If you are in a relationship with a spouse or significant other, your ADHD symptoms often cause difficulties, such as tension and arguments.
  - Your ADHD symptoms have an impact on your productivity.
    - You often have trouble completing tasks and getting things done on time at work and at home.
    - You often have difficulty remembering appointments.