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Cost Effectiveness Analysis of Atomoxetine Versus Behavioral Therapy Versus Combination of Both in Children with Attention Deficit Hyper Activity Disorder (ADHD)

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ABSTRACT

High prevalence of children diagnosed with Attention Deficit Hyperactivity Disorder (ADHD) in Mental Health settings for children, and substantial impact on children, their parents life, and society has made ADHD a major public health concern. To analyze the cost effectiveness of medication (Atomoxetine), behavioral therapy, and combined treatment of Atomoxetine and behavioral therapy for treatment of ADHD in children from payer perspective with time horizon: 12 weeks. A prospective trial based economic evaluation conducted on children (6 to 12 years), in psychiatric out patients clinic at Abasseya Mental Hospital (AMH), Cairo ,Egypt , and had a clinical diagnoses of ADHD as defined in the Diagnostic and statistical Manual fourth edition (DSM_IV). Were classified into three groups: medication only group, behavioral therapy group, and combined medication and behavioral therapy group . Each treatment had both a cost and an outcome associated with it. Cost effectiveness ratio comprising the average total cost per child per unit of outcome [three months-Quality Adjusted Life Years] "QALY" in each of the three groups. The combined therapy was associated with the highest cost effective ratio C/E Ratio of 7695.524 LE per QALY, medication therapy was 4381.927 LE per QALY, While C/E Ratio of behavioral therapy was 3337.339 LE per QALY. The sensitivity analyses: show that the utility values of all health states are crucial determinants of the cost-effectiveness results. Combined therapy associated with greatest health benefits and highest costs. Behavioral therapy was the least effective and cheapest option.

Keywords: Attention Deficit Hyperactivity Disorder, Abasseya Mental Hospital, Diagnostic and statistical Manual

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INTRODUCTION

Attention Deficit Hyperactivity Disorder (ADHD) is a condition of the brain that makes it difficult for children to control their behavior. It is a chronic neurobehavioral disorder that initially manifests in childhood and is characterized by hyperactivity, impulsivity, and/or inattention. These symptoms can lead to difficulty in academic, emotional, and social functioning[1]. ADHD has been a topic of intense scientific research in Western countries, but there is limited information about this phenomenon in the Arab region.[2] Because epidemiological studies on psychiatric disorders are quite rare in the Arab World.[3] Additionally, we do not have demographic and descriptive statistics for children and adults with the disorder; therefore, there are disparities in identification, access to treatment, and reports of the manifestation of ADHD and its comorbidities[4]. Depending on article reviews epidemiological studies on ADHD conducted in all the Arab countries from 1966 through 2009.[5] Founded prevalence of 0.5 to 0.9 % in community versus 5.1 to 14.9 % in school system using Structured interview in community versus Rating scales in school system with other Various instruments [3]. Thus ADHD rates in Arab populations were similar to those in other cultures [2]. ADHD substantially impairs the quality of life of affected children and adolescents as well as their family members [6-7]. It also poses considerable economic burden to the healthcare system and society worldwide [8]. Its high prevalence, chronicity, and substantial impact on daily life functioning for children, their parents, peers, and teachers had made ADHD a major public health concern[9]. Among all middle-income countries in the region, Egypt invests a smaller proportion of its gross domestic product on health care.[10] Investments in economic evaluation studies will help in allocating limited resources in the most efficient way to improve health care services[11]. Excess costs associated with individuals with ADHD due to health care and work absence, health improvement of children and adults with ADHD could save the excess costs to family and society [12]. There is no cure for attention deficit hyperactivity disorder (ADHD), but treatment can alleviate the symptoms and make the condition much less of a problem in day-to-day life. Standard treatments for ADHD in children include medications, education, training and counseling, but it is widely agreed a combination of those things is the best way to treat it [13].According to American Academy of Pediatrics, For elementary school–aged children (6–11 years of age), the primary care clinician should prescribe US Food and Drug Administration–approved medications for ADHD and/or evidence-based parent and/ or teacher-administered behavior therapy as treatment for ADHD [13].National Institution of Clinical Excellence (NICE)

recommended in school-age children and young people with severe ADHD, drug treatment should be offered as the first-line treatment. Parents should also be offered a group-based parent training/education program [14].Atomoxetine is a non-stimulant drug licensed for use in children of 6 years and over and young people for the treatment of ADHD. The precise mechanism by which it produces its therapeutic action in (ADHD) is not clear, but is thought to be due to selective inhibition of the pre-synaptic norepinephrine transporter, thus inhibit reuptake of noradrenaline[14]. Despite the predominance of pharmacological management of ADHD symptoms psychological interventions for ADHD have attracted the interests of clinicians and researchers as the main aim of all psychological interventions for ADHD is to improve the daily functioning of the child or young person by improving their behavior and family and peer relationships[14]. The analysis conducted by NICE[14] suggests that behavioral therapy interventions beneficially affects children with ADHD whether applied without medication [15-17] or in combination with routine ADHD medications [18-24].The quality of the clinical evidence supporting psychological intervention for children with ADHD evaluated by NICE as moderate to high [14]. Current practice in the treatment of ADHD differs. pharmacological, behavioral ,or combination of both interventions may all be used; the choice of treatment strategy among different available interventions to children with ADHD was identified by the health economist as an area with potential major resource implications [14]. Decision of treatment is depends on the symptoms presented, the preferences of the child and parents and services and resources local availability [14].

Aim of the study: To determine the cost effectiveness of three treatment alternatives (medication, behavioral, and combined medication and behavioral treatment) for attention deficit hyperactivity disorder in children.

The study design: The present study is a prospective trial based economic evaluation (cost effectiveness analysis) from the perspective of Egyptian Ministry of Health and Population (payer perspective) .the protocol was approved by institutional review board.

MATERIALS AND METHODS

Patients and Methods

All children in psychiatric out patients clinic at Abasseya Mental Hospital (AMH) Cairo, Egypt, who are 6 to 12 years of age (boys or girls) , and had a clinical diagnoses of ADHD as defined in the Diagnostic and statistical Manual fourth edition (DSM_IV) [25-26], confirmed by structured interview , and had an IQ of > 70 assessed by the the Stanford-Binet Intelligence Scale: Fourth

Edition for children (SB:FE) [27-28] which is a standardized test that assesses intelligence and cognitive abilities in children matrices, were eligible to participate.Exclusion criteria included Serious or chronic medical illness such as (diabetes mellitus ,TB, Cardiovascular or cerbrovascular diseases),Co morbid psychosis or bipolar disorder, history of seizure disorder, as this will involve extra medical costs that are difficult to be allocated and affects medication outcome Ongoing use of psychoactive medications other than the study drug.

Methods:

This study was conducted in accordance with the ethical standards of the investigative site institutional review board

1. Sixty four child (84.37% boys) enrolled in this study were subjected to the following:

a. History: patient's personal, family, and medical history were taken.

b. Clinical, and Psychiatric assessment to obtain the exact diagnosis, severity status and determine co-morbidity, intelligent quotient IQ-test was done for each patient, liver functions tests (are not recommended unless there is a clinical indication as recommended by NICE).

2. Patient's parent or primary care giver were asked to:

a. Fill in a socioeconomic sheet. (El Shakhs) [29]

b. Rate in Swanson, Nolan, and Pelham questionnaire (SNAP) Rating Scale developed by Swanson and colleagues [30-31]

c. Rate in The Revised Conners' Parent Rating Scale (CPRS-R) [32-33]

The Conners' Parent Rating Scale (CPRS) is a popular research tool in clinical settings for reporting childhood behavior problems (32). The present study used a revised CPRS (CPRS-R) [33]. Discriminated validity was strongly supported by statistically examining the ability of the CRS-R to differentiate ADHD individuals from nonclinical individuals and other clinical groups. For monitoring treatment effectiveness and changes over time, initial CRS-R ratings should be obtained prior to beginning therapy and before the child/adolescent is placed on any psychoactive agent. These initial ratings serve as baseline indicators of behavioral problems prior therapy, and progress can be evaluated by comparing these scores to those derived from later ratings. The Arabic version of the questionnaires was used as recommended by general secretary of mental health, Egypt.

3. Patients were classified according to the type of treatment they received into three groups (depended on psychiatric recommendation and parents preferences):

A. Group 1:

medication only group (20 child); was defined as intake of Atomoxetine daily with average dose of 0.5 mg/kg /day for titration period of two weeks , then dose is increased to a target dose of 1.2mg/kg/day (maximum 100 mg/day) taken once daily (34). Children taking medication regularly contacts with psychiatrists and mental nurse (healthcare professionals) , more frequently during the titration period.

B. Group 2:

behavioral therapy only group (21 child); sessions by psychologists or specially trained facilitator for 45 to 75 minutes were delivered for children and parents (between eight and 12 sessions for each) This is the routine clinical practice in child unit.

C. Group 3:

combined medication and behavioral therapy group (23 child); that is, behavioral therapy is delivered concurrently with medication .

4. Patients had been followed up monthly for 12 weeks to report compliance, adverse effects, tolerability, and discontinuation.

Non compliance was defined as missing intake of study drug on more than five consecutive days.

Discontinuation was defined as to stop attending behavioral therapy for more than five consecutive sessions.

Tolerability assessments included; Monitoring vital signs at every visit (blood pressure, pulse, weight, height) , Spontaneously reported adverse events to open ended question about any adverse events.

5. We assume that children showing clinically significant improvement with pharmacological or psychological treatment after 12 weeks will retain improved utility score for one year.

Time horizon: was 12 weeks as recommended by NICE 2011 [35], and Health Technology Assessment HTA NHS R&D HTA Programme review [36].Twelve weeks (school semester)at which most parents referred to outpatients psychiatric clinics as a result of educational difficulties

Discount rate:

No discount rate was applied ,as the study duration was less than one year, (discount rate 0%).

Outcome: was expressed as three months- weight Quality Adjusted Life Years (QALYs). Thus we need utility scores for health states of children with ADHD. Utility scores provide a summary score, typically between 0 (death) and 1 (full health), with the relative importance of changes in different dimensions of health being weighted according to people's preferences [36].

Utilities Associated with Health State

Utility values were obtained from a recent study by Lloyd et al [37]. The health states were defined based on the Clinical Global Impression-Severity (CGI-S). The CGI-S is a 7 point scale designed for clinicians to rate the severity of a patient's condition and is a common endpoint in clinical trials evaluating new treatments for ADHD [38].

Table 1: Clinical Global Impression –Severity scoring and utility values associated with the four health states estimated from the TTO method used in the analysis [37]

Definition	Score	Health state	Utility values associated with the four health (mean ±S.E)
'not ill at all'	1	normal state	0.839 ± (0.020)
borderline ill' or 'mildly ill'	2 or 3	mild state	0.787 ± (0.022)
'moderately ill' Or 'markedly ill'	4 or 5	moderate state	0.578 ± (0.028)
'severely ill' Or 'among the most extremely ill subjects'.	6 Or 7	severe state	0.444 ± (0.023)

CGI-Improvement (CGI-I)

The clinician compares the patient's overall clinical condition to the one week period just prior to the initiation of medication use (the so-called baseline visit).

Table 2: Clinical Global Impression –Improvement scoring used in evaluation of clinical condition improvement (37)

No change from baseline	Minimally improved	Much improved	Very much improved
4	3	2	1

Resources and Costs: The analysis adopted the perspective of the Egyptian Ministry Of Health (payer perspective),thus only direct medical cost were estimated this is consistent with Egyptian guideline recommendation [11]. As in most cases, data and information on indirect costs are lacking in Egypt[11].Health service costs consisted of intervention cost; Treatment medication (Atomoxetine), psychotherapy sessions costs, and Psychiatrist and mental nurse costs (professional staff costs).Atomoxetine wholesale price taken from tender lists of Abbasseya Mental Health Hospital, Egypt (LE126 per 30 capsules) in November 2013.Staff costs have been calculated based on clinical opinion, and real clinical practice using salary data of psychiatrist, psychologists and mental nurse according to ministry of health tarrifs , and estimates of client contact time (table 3).

According to real contact of patient with health care staff resources utilization per patient were calculated .Costs of Examinations: Clinical Psychiatric assessment, IQ investigations , diagnostic and follow up questioners (SNAP, CPRS-R) ,and other social services for the whole time of the analysis were omitted from the analysis, as these were common in the three strategies assessed.

Treatment of side effects associated with medication was not assumed to incur extra costs, as most side effects recorded (anorexia, nausea, insomnia headache, loss of appetite) were managed by physicians responsible for children monitoring. Treatment of side effects associated with medication was not assumed to incur extra costs, as most side effects recorded (anorexia, nausea, insomnia headache, loss of appetite) were managed by physicians responsible for children monitoring. We did not include other societal costs such as social benefit payment, and loss of productivity of parents ,thus was consistent with the approach used in the Economic modeling conducted by the National Institute for Health and Excellence [14].

Table 3: Hourly costs of staff input according to ministry of health Tarrifes

	Clinical psychologist	Mental health nurse	psychiatrist
Salary (LE)	1500	1500	2000
Hours of patient contact / month	4(h)*5(d)*4(w)=80 hr/month	5(h)*6(d)*4(w)=120 hr/month	4(h)*5(d)*4(w)=80 hr/month
Cost per hour of patient contact	18.75 LE	12.5 LE	25 LE

h:hour, d:day, w:week

Outputs:

Outputs included cost and effectiveness outcomes for each treatment arm, and Average Cost-Effectiveness Ratio (ACER) comparing medication versus behavioural therapy versus combined therapy .Total direct costs were estimated by summing direct costs across all study period. Three months weight Quality Adjusted Life Years (QALYs) were estimated as the sum of the weighted time spent for the 3-months study period, using the utility score of health status due to intervention (CGI-S) for each group. To obtain 3-months QALY we calculated average total health gain utility after treatment for each group for a year then divided by 4.Finally, ACER was estimated as the ratio between cost and effectiveness and was expressed as cost per QALY.

$$\text{Average Cost Effectiveness Ratio (ACER)} = \frac{\text{health care cost (\$)}}{\text{clinical outcome (not in \$)}}$$

Sensitivity analysis:

To test the stability of our results to variation in the input parameters, we performed various one-way sensitivity analyses, as recommended by Consolidated Health Economic Evaluation Reporting Standards (CHEERS): ISPOR Task force report [39]. We tested the robustness of the study towards study variables with one-way sensitivity analyses on costs, and utility value. Health services costs and utility values of each group were varied by setting the upper and lower bounds of the 95% confidence intervals (CIs) reported in the study .All of these analyses were performed using Microsoft Excel 2010.

RESULTS AND DISCUSSIONS

The present study included 64 child (84.375% boys) ranging in age between 6 and 12 years (mean 8.159, SD 1.3978) these participants had an IQ ≥70 to reduce the confounding impact of low IQ on 3 months performance evaluation. ANOVA showed no statistically significant difference between base line characteristics among the three groups of patients thus 3 groups were comparable before treatment (table 4).

Table 4: Baseline characteristics of the three studied groups

Characteristics	Group I	Group II	Group III	*P*-value*
Gender, N (%)	*N=20*	N=21	N=23	>0.05[a]
• Male,	17 (85%)	17 (81%)	20 (87%)	
• Female	3 (15%)	4 (19%)	3 (13%)	
Age, mean (S.E)	8.365 (0.2992)	7.848 (0.253)	8.265 (0.3417)	>0.05[a]
IQ ,mean (S.E)	96.7 (0.7)	95.1 (3.197)	90.17 (2.534)	>0.05[a]
Weight, mean (S.E)	31.65 (3.598)	25 (1.434)	28.23 (2.24)	>0.05[a]
CGI-S	5.40 (0.184)	5.15 (0.221)	5.522 (.59311)	>0.05[a]
Utility baseline	*0.51475 (0.02659)*	0.52147 (0.0205)	.51135 (0.018593)	>0.05[a]
Socioeconomic status, n (%)				
Below average:				
Average:	2 (4.76%)	1 (5%)	2 (13.0435%)	
Above average:	12 (57.14%)	10 (50%)	14 (60.87%)	>0.05[a]
High:	7 (33.33%)	8 (40%)	5 (21.74%)	
	1 (4.76%)	1 (5%)	1 (4.35%)	
CPRS-R,Score (±SD)				
DSM Inattention	76.35 (7.842)	74.33 (8.941)	74.57 (7.809)	>0.05[a]
DSM Hyperactivity	74.55 (7.395)	74.81 (9.108)	76.17 (7.930)	>0.05[a]
DSM total	76.20 (4.895)	74.52 (8.364)	76.48 (7.160)	>0.05[a]
CGI-I mean (±SD)	2.30 (0.92338)	3 (0.85840)	2 (0.95346)	0.003
Health gain mean(±SD)	0.1590 (0.05739)	0.1225(0.07447)	0.1696(0.0439)	0.03[b]

Group I: medication only group, group II: behavioral therapy group, group III: combined treatment group, IQ: intelligence quotient, CGI-S: clinical global impression severity, CGI-I clinical global impression-improvement, N: number of patients, CPRS-R: conners parent rating scale revised, DSM: diagnostic and statistical manual, SE: standard error, SD: standard deviation,*One-way ANOVA test, a: non significant, b: significant.

Table 5 shows the use of health service resources and costs during the three months of follow-up in the study. Total costs of care per patient for medication group versus behavioral versus combined group at 3 months was 620.49 LE, 532.41 LE , 1033.95 LE,

Table 5: Resources and cost data used in the base-case economic analysis

Variable mean cost (±SD,SE)		Group I N 20	Group II N 23	Group III N 21
Medication cost (Atomoxetine 25 mg)	Mean ±S.D S.E	529.2000, (175.88345, 39.32874)	493.4087 (174.3741 , 36.35952)	_
Session s cost	Mean ±S.D S.E	_	448.9130 (40.04845, 8.35068)	452.0548 (42.31857, 9.23467)
Nurse cost	Mean ±S.D S.E	16.2900 (3.09114, .69120)	6.5929 (0.92494 , .20184)	16.0803 (3.63773, 0.75852)
Psychiatrist cost	Mean ±S.D S.E	75.0020 (5.73081, 1.28145)	75.5452 (5.92918, 1.23632)	73.7619 6.82114 1.48850
Total cost	Mean ±S.D S.E	620.4920 174.81002 39.08871	1033.9472 168.51639 35.13810	532.4095 43.30479 9.44988

Group I: medication only group, group II: behavioral therapy group, group III: combined treatment group, SE: standard error, SD: standard deviation, N:number of patients.

Combined therapy was associated with the highest Average Cost Effective Ratio with ACER of 6158.25 LE per QALY, medication therapy was 3734.97 LE per QALY. While ACER of behavioral therapy was 3476.83 LE per QALY. This means that, according to base case results, Behavioral therapy is the most cost effective treatment option among those assessed, followed by medication treatment as second choice, combined therapy comes as third choice. All results of the base-case analysis are presented in Table 6.

Table 6: Average Cost-Effectiveness analysis comparing pharmacological versus psychological versus combined treatment for children with ADHD over 3 months

	total costs (mean)	3Mon QALY (mean)	ACER (per patient)
Average cost /effectiveness ratio in medication group	620.49	0.16613	3734.97
Average cost /effectiveness ratio in behavioral group	532.41	0.1531	3476.83
Average cost/effectiveness ratio in combined group	1033.95	0.1679	6158.25

According to base-case analysis, combined therapy was associated with the greatest health benefits and highest costs. While behavioral therapy was associated with the least health benefits and lowest costs . both are trade off options depends on the decision maker choices .Three months QALY was obtained via dividing mean health gain utility value after treatment for each group by 4 (multiplied by 12 months, then divided by 3 months). Treatment with medication

therapy and combined therapy was associated with 0.734 and 1.45 additional QALYs gained, when compared to behavioural treatment, respectively.

Sensitivity analysis results:

One-way sensitivity analyses (Figures:1,2,3) were conducted to identify the key parameters with the greatest impact on the ACER. This analysis indicated that the utility values of the states had the largest impact on the results. In our base-case analysis, we used the cost for Ministry of Health mandatory Tariff. In a sensitivity analysis using uncertainty 95% CI ranges estimated from cost ranges, in this sensitivity analysis, the results did not change the conclusion that would be drawn from the analysis resulted in no effect on treatment decision.

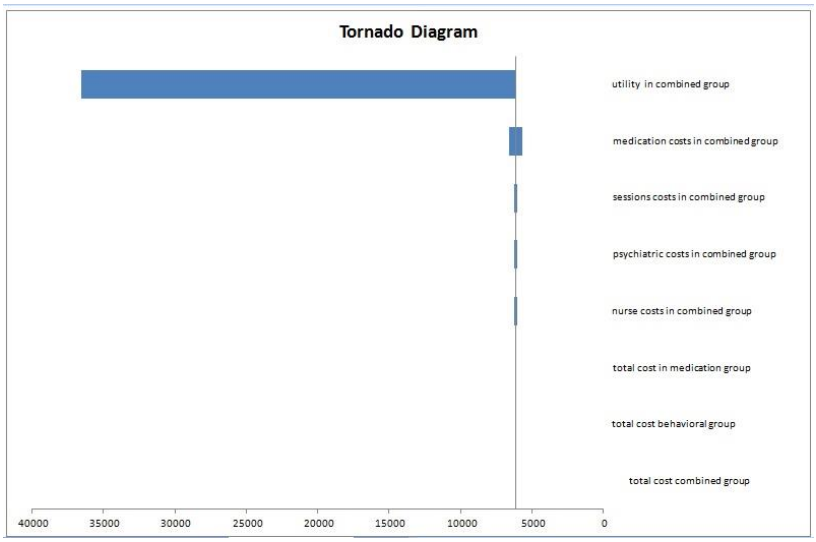

Figure 1. Univariate sensitivity analysis for combined group. The base-case cost-effectiveness ratio is 6158.246418 LE /QALY

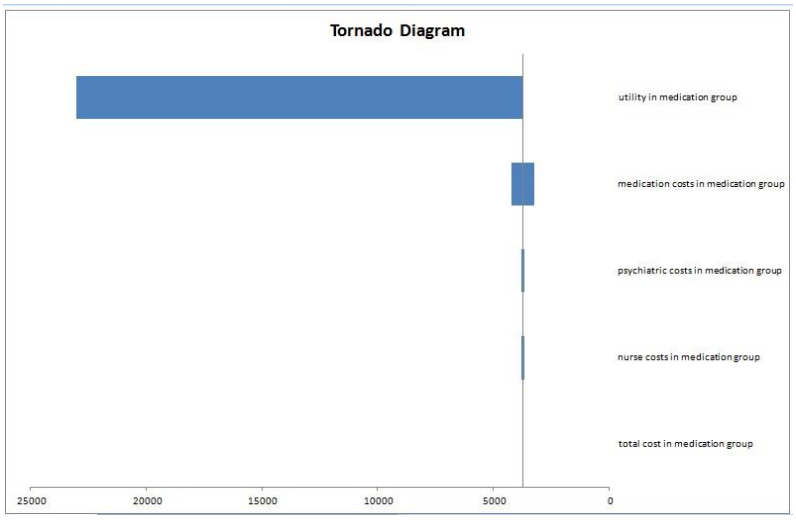

Figure 2. Univariate sensitivity analysis for medication only group. The base-case cost-effectiveness ratio is 3734.975551 LE/QALY

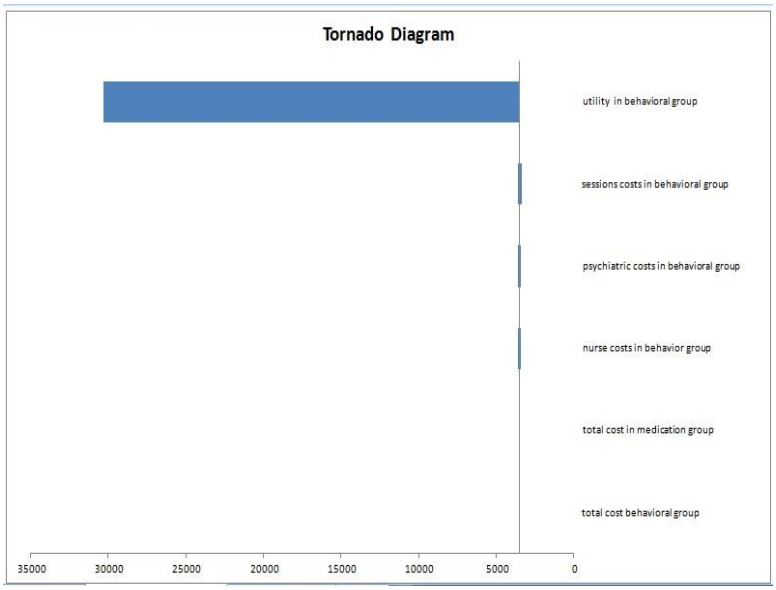

Figure 3.Univariate sensitivity analysis for behavioral therapy only group. The base-case cost-effectiveness ratio is 3476.82697 LE/QALY.

DISCUSSION:

This study sought to apply pharmacoeconomic techniques to the process of informing how to select a cost effective treatment for children with ADHD from the perspective of Egyptian Ministry of Health and Population to help allocating health sector limited resources in the most efficient way to improve health care services in Egypt [11]. Atomoxetine, considered a new treatment option in the Egyptian market, was compared to behavioral therapy, and combined treatment. Results from our study may better inform decision makers about the value of Atomoxetine for children with ADHD, and assess potential cost implications as well. As ADHD is a complex neuro-developmental constellation of problems rather than a single disorder, with core symptoms of inattention, hyperactivity and impulsivity and other more general symptoms such as poor school performance and poor social functioning. It has been suggested that there might be unique patterns of effects created by different treatments (e.g. drug interventions versus behavioral therapy BT) and a single outcome measure might not be sufficiently sensitive [36]. Although measures that are used for reporting outcomes in a disaggregated way may be useful from a clinical perspective, the use of these instruments has limitations from a decision making perspective. It is not possible to use these measures to calculate the net impact on Health Related Quality Of Life HRQoL [36]. When assessing the cost-effectiveness of an intervention, the use of such disparate measures may lead to conflicting results depending on the instrument or subscale used. One way to overcome this problem is to use a preference-based index of HRQoL [36]. Quality of life measures such as utility valuation are able to capture this variable nature in a way

that traditional ADHD efficacy measures cannot [40], that is why we choose to use clinical global impression CGI to obtain utility values as effectiveness measure in our study. In our study we measured Quality of life as a final outcome measure with other intermediate outcomes such as hyperactivity, and inattention subscales scores in Conners' rating scale, but in this paper we are discussing the final outcome. Combined treatment was associated with higher costs and better outcomes, translated into increased 3 months-QALY, when compared to either psychological or pharmacological treatment, according to our base case results, Behavioral therapy is the most cost effective treatment option followed by medication ,followed by combined treatment. Limitations of our study include. First, the trial excluded patients who have any current co-morbid psychiatric diagnosis .However the effectiveness may be affected by patient co-morbidities. Therefore, the study findings may not be generalizable to children with co morbidity.(co morbidities is very common with ADHD but this will include difficult fragmentation of heterogenous costs and effectiveness evaluation). Second, this study was conducted from Egyptian Ministry of Health payer perspective and did not include indirect cost estimates associated with parent and caregiver work loss, additional educational resources, and crime and delinquency (as this is beyond the scope of our study and needs financial and organization co operation among different foundational efforts). It is recognized that, it could be argued that a longer time frame may have been desirable to account for longer-term differences in costs and adverse effects of treatment. However 3 months were the accepted time horizon by NICE and the health technology assessment HTA R&D programme , plus the real world experience showed that at school semester the cases are best compliant to medication and behavioral therapy to allow better follow up data). Our literature search identified these economic studies that compared the cost effectiveness of pharmacological, psychological and combination therapies in children with ADHD, no studies directly evaluated Atomoxetine with behavioral interventions. Studies support our results in superiority of combined treatment, although not presenting it as the most cost effective alternative. Most of the studies presented medication as the most cost effective however medication evaluated was methylphenidate rather than Atomoxetine, methylphenidate is the most commonly used medication in clinical practice; because it is the first line of treatment and more economic ,no study reported psychological therapy as cost effective alternatives. In Lord and Paisley (2000) [42] cost effectiveness analysis combination therapy, consisting of methylphenidate plus behavioural therapy was compared with behavioural therapy alone for children with ADHD in the UK. From National Health Service (NHS) perspective .The clinical-effectiveness data was extracted from the Multimodal Treatment

Study of Children with ADHD MTA study (MTA Co-operative Group 1999a; 2004a; 2007)[43-45] . Costs of drug acquisition and pharmacotherapist costs were included. Results of the analysis reported that ICER of combination therapy versus behavioural therapy alone was £1,596 per SMD in the SNAP-IV Score. Limitation of the study included the use of the change in SNAP-IV scores as the primary outcome measure, which could not capture the HRQoL of children with ADHD. [14] Schlander and colleagues [46-48] evaluated the relative cost effectiveness of combined treatment and medication management in the MTA study .Combined treatment resulted in normalization (improvement)of higher proportions of children compared to medication management in all sub-groups of children examined. The author concluded that neither intensive behavioural therapy nor combined treatment are likely to be cost effective for children with ADHD from the perspective of the NHS [14], this result is consistent with conclusion reported in other published studies about the cost effectiveness of behavioural and combined therapies. Medication management was the most cost-effective option compared with intensive behavioural therapy and combined treatment. A sub-analysis [49] compared the cost effectiveness of combination strategies included behavioural therapy plus dexamfetamine as first line, atomoxetine as second line and MR methylphenidate as third line.Versus medication strategy consisting of dexamfetamine as first line, IR methylphenidate as second line and third-line atomoxetine. The ICER of the combined versus medication strategy was £1,241,570/QALY; according to this study results combination strategies were not cost effective from the perspective of the NHS. Other two studies [50-51] analyzed the cost effectiveness of the alternatives used in the Multimodal Treatment Study of Children with ADHD MTA study (MTA Co-operative Group 1999a; 2004a; 2007)[43-45]. Results of this analysis reported superior effectiveness of combined treatment, while medication was likely to be the most cost-effective option for children with ADHD, specially for those without co morbidities. According to Foster and colleagues (2007) [51], The most cost effective opt for pure ADHD, medication management was certainly the most cost-effective option at all levels of willingness-to-pay WTP; but for policy makers willing to pay more to avert future costs such as special education and juvenile justice costs, intensive behavioural treatment alone or combined with medication management (depending on the comorbidity) was likely to be the most cost-effective treatment. Zupancic and colleagues (1998) [52], assessed the cost effectiveness of methylphenidate, dexamfetamine, pemoline, psychological/behavioural therapy and combination therapy (consisting of psychological/behavioural therapy and methylphenidate) in comparison with no treatment from

the perspective of a third-party payer in Canada. The economic analysis demonstrated that methylphenidate dominated both psychological/behavioural therapy and combination therapy. To summarise, The results of the Assessment Group model suggest that methylphenidate, dexamfetamine and atomoxetine are all cost-effective treatments for ADHD. However, given the limited data used to inform response and withdrawal rates and the small differences in benefits between different treatments, different costs of both medication and psychotherapy among the studies, it is not possible to compare different drug strategies. All economic analysis adopted different approaches to the estimation of treatment effectiveness and associated utility values.[52-53]. We find according to base-case analysis, combined therapy resulted in greatest health benefits but at the same time it was the most expensive treatment option. Behavioral therapy was the least effective and cheapest option. both are trade off options depends on the decision maker choices.

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