Pharmacoeconomics:Open Access
ISSN: 2472-1042

Tockhorn et al., Pharmacoeconomics 2015, 1:1

Research Article Open Access

Atomoxetine for the Treatment of Adults with Attention Deficit Hyperactivity Disorder: A Cost-Utility Analysis in Spain

Antje Tockhorn[1], Foula Televantou[1], Kristina Karlsdotter[1] and Tatiana Dilla[2*]

[1]*Eli Lilly and Company Limited, Windlesham, UK*
[2]*Lilly S.A., Alcobendas (Madrid), Spain*

Abstract

Background: Attention-deficit hyperactivity disorder (ADHD) frequently persists into adulthood and leads to a significant burden of illness. Many adults with ADHD suffer from comorbid conditions such as substance and alcohol use disorders and anxiety. Atomoxetine is the only drug therapy approved in Spain for the treatment of adult ADHD. This study estimates the cost-utility of atomoxetine compared with no treatment in adults with ADHD in Spain and in two specific subgroups: patients with comorbid anxiety or comorbid alcohol abuse.

Method: A simple, state-transition Markov model with three health-states (treatment initiation, response and no-response) was developed. The model estimated the incremental cost per quality-adjusted life year (QALY). Treatment effectiveness and discontinuation rates were estimated from nine atomoxetine clinical trials. Utilities were estimated from a vignette study. Costs and outcomes were estimated over a one-year period from the perspective of the Spanish National Healthcare System.

Results: The incremental cost per QALY gained with atomoxetine versus no treatment was €23,645 in the general ADHD population, €20,860 in patients with comorbid anxiety, and €24,675 in the comorbid alcohol abuse population. These values were below the willingness-to-pay threshold of €30,000 per QALY considered acceptable in Spain. The model was most sensitive to changes in the utility value of patients in the no-response health state. With the exception of some of the utility values, a positive net monetary benefit value was maintained following variations in all model parameters.

Conclusion: Atomoxetine represents a cost-effective option compared with no treatment in adults with ADHD in Spain, including those with comorbid anxiety and alcohol abuse.

Keywords: Atomoxetine; Cost-effective; ADHD; Adults; Spain; Comorbidities

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is characterised by symptoms of hyperactivity, inattention and impulsiveness. In the past, it was thought to affect only children and adolescents, but studies over the past three decades have shown that it frequently persists into adulthood [1-8]. A meta-analysis of follow-up studies has suggested that two thirds of children with ADHD continue to have symptoms as adults, with approximately 15% experiencing the full disorder and 40-60% experiencing partial remission (Faraone et al., 2006). Furthermore, many people reach adulthood before being diagnosed with ADHD for the first time [9,10].

The prevalence of adult ADHD in Europe is estimated at between 1% and 7%, depending upon diagnostic criteria [11-15]. The prevalence of ADHD among patients attending routine psychiatric outpatient clinics in Europe, using Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria, has been recently estimated at 15.8% (DSM-IV) and 17.4% (DSM-V), based on a European observational study of 1,986 patients [9,10].

In Spain, the estimated prevalence varies by more than 10-fold. The World Mental Health survey conducted by the World Health Organization estimated the prevalence of adult ADHD in Spain at 1.2% [12]. A study of primary care records found that only 0.04% of patients were recorded as suffering from adult ADHD [16]. However, a cross-sectional study in which adult patients who attended primary care for any reason were screened for ADHD found a prevalence of 12.5% [17].

Symptoms of ADHD in adults are different to those in children, which may explain the low levels of diagnosis. In adults, ADHD is more likely to present as inner restlessness, inability to relax or remain still, impatience, impulsive behaviour, disorganisation and mood swings [18]. These symptoms adversely affect daily life and functioning, leading to a significant burden of illness. Multiple studies have shown that adult ADHD is associated with underachievement, difficulties in relationships, accidents, criminality and substance misuse [19-24]. Furthermore, recent studies have shown that between 57% and 75% of adults with ADHD have comorbid psychiatric conditions [25-27], with differences between men and women in the type of comorbidity observed [28]. In Spain, the observational CAT (Comorbidities in Adults with ADHD, *Comorbilidad en Adultos con Trastorno por Déficit de Atención e Hiperactividad [TDAH]*) study has shown that 66% of patients with adult ADHD have comorbidities [25].

Treatment of adult ADHD is focused on managing the core symptoms, reducing functional impairment and improving quality

***Corresponding author:** Tatiana Dilla, Eli Lilly Spain, Av. de la Industria, 30, 28108 Alcobendas, Madrid, Spain, Tel: +343491663533; E-mail: dilla_tatiana@lilly.com

Received November 21, 2015; **Accepted** December 21, 2015; **Published** December 28, 2015

Citation: Tockhorn A, Televantou F, Karlsdotter K, Dilla T (2015) Atomoxetine for the Treatment of Adults with Attention Deficit Hyperactivity Disorder: A Cost-Utility Analysis in Spain. Pharmacoeconomics 1: 104.

of life (QoL). Treatment efficacy is usually measured as clinical response defined on rating scales of core symptoms and effects on global functioning [29]. In Spain, atomoxetine is the only drug therapy approved for the treatment of adult ADHD. It is indicated in children of 6 years and older, in adolescents, and in adults as part of a comprehensive treatment programme [30]. Treatment must be initiated by a specialist in the treatment of ADHD [30]. Diagnosis should be made according to current DSM criteria or the guidelines in the international classification of diseases (ICD) [30].

Given the increasing pressures on health care budgets, it is necessary to assess health interventions not only in terms of their safety and efficacy but also in terms of their cost-effectiveness. The objective of the present study was to estimate the cost-utility of atomoxetine compared with no treatment in the treatment of adult ADHD in Spain and in two specific subgroups: patients with comorbid anxiety or comorbid alcohol abuse, from the perspective of the Spanish National Healthcare System.

Method

Model structure

The model was a simple, state-transition Markov model. The model incorporated three health states: treatment initiation, response, and no-response (absorbing state). Patients transitioned between states depending upon the presence or absence of treatment response. The cycle length was set to one month throughout the simulation to capture changes in health states and associated costs; this cycle length also reflects the time usually taken to assess response to treatment. The model base case considered a time horizon of one year, which was deemed an appropriate length of time to capture the benefits of ADHD treatment and was in line with other published ADHD models [31-33]. Furthermore, because ADHD is not expected to impact upon life expectancy, a longer period was not considered necessary. No treatment options other than atomoxetine are available in Spain for these patients, and therefore placebo was used in the model as a proxy for no active treatment.

All patients entered the model at the treatment initiation health state at diagnosis and were assigned to receive atomoxetine or no treatment. They remained in this health state for a maximum of three cycles. At the end of the first and second cycles, patients who responded to treatment during that cycle transitioned to the response state; patients who did not respond remained in the initiation state; and patients who experienced an adverse event requiring discontinuation transitioned to the no-response state. At the end of the third cycle, patients who responded to treatment during that cycle transitioned to the response state; all other patients transitioned to the no-response state. No further entry to the response state was allowed following the completion of the three initiation cycles. From cycle four onwards, patients transitioned out of the response state into the no-response state, based on rates of treatment discontinuation due to adverse events, loss of response/efficacy or discontinuation for any other reason. Given the one-year time horizon, no discounting was used.

The model estimated costs in Euros (€) (2014), quality adjusted life years (QALYs) and the incremental cost-utility ratio (ICER; €/QALY). The ICER was calculated using the following formula:

$$\text{ICER} = \frac{\text{Costs atomoxetine} - \text{Costs no treatment}}{\text{QALYs atomoxetine} - \text{QALYs no treatment}}$$

Results were compared with the willingness-to-pay (WTP) threshold of €30,000 per QALY considered acceptable in Spain [34].

Model parameters

Patient population: The population included patients aged 18 to 65 years with moderate to severe ADHD diagnosed in adulthood. Characteristics of the population in the model were based on nine placebo-controlled clinical trials of atomoxetine [35-44]. Treatments for ADHD are not associated with an increased risk of death, and therefore background mortality in the model reflected that of the Spanish population of the same age as the model cohort.

Treatment effectiveness: A post-hoc analysis of response in the nine placebo-controlled trials of atomoxetine was conducted for the economic model [35-44]. The definition of response captured changes in both symptoms and overall functioning, as recommended by the European Medicines Agency [45].

Symptoms of ADHD were measured in the clinical trials using the Conners' Adult ADHD Rating Scale-Investigator Rated: Screening Version (CAARS-IV: SV) Total ADHD Symptom Score and/or the Adult ADHD Investigator Symptom Rating Scale (AISRS) Total Score. Both scores measure the same 18 symptoms of ADHD defined by DSM-IV, and have been shown to be highly correlated in the atomoxetine clinical trials [35]. Global functioning was measured using the Clinical Global Impressions-Attention-Deficit/Hyperactivity Disorder-Severity Scale (CGI-ADHD-S) (CGI-ADHD-O in the study in the comorbid alcohol population [42].

Response was determined based on a composite of the CAARS-IV: SV or AISRS scores and the CGI-ADHD-S score. The model used a dichotomous variable of response or no-response. Response was defined as a ≥ 30% reduction from baseline in the CAARS-IV: SV or AISRS scores as well as a CGI-ADHD-S score of ≤ 3. No-response was defined as failure to meet these criteria. As included studies had various visit durations, the date of each patient's clinical observation was used and Last Observation Carried Forward was used at each monthly interval to characterize the patient as responder or no-responder.

Treatment discontinuations: Discontinuation rates were based on a post-hoc Kaplan-Meier analysis of the nine placebo-controlled atomoxetine trials. Due to the prolonged onset of the effect of atomoxetine, it was assumed that in the model cycles 1 to 3 patients could only discontinue because of adverse events. From cycle 4 onwards, they could discontinue because of adverse events, loss of efficacy or any other reason observed in the clinical trials.

Unit costs and resource use: Pharmacy costs were obtained from the database of the General Spanish Council of Pharmacists [46] and treatment monitoring costs were based on published tariffs in Spain [47]. Drug costs were derived from public prices, adjusted with 7.5% mandatory rebate. Costs were updated for 2014 if required. Patients were assumed to receive atomoxetine 40 mg once daily for 1 week, followed by a maintenance dose of 80 mg once daily, in line with the Summary of Product Characteristics [30]. Costs of atomoxetine and healthcare visits are shown in Table 1. Patients were assumed to have healthcare visits only with specialist physicians during all model states. The number of visits per month assumed in the model is shown in Table 2.

Health-state utilities: Non-treatment specific utilities associated with each health state in the model were populated using estimates from a vignette study conducted in the UK setting [48]. Utility values are shown in Table 2. In the model, the utility of a responder receiving

no treatment was assumed to be equal to the mean of the utility of a responder receiving treatment (0.82) and the utility at initiation (0.68), i.e., 0.75. This is an assumption, because in clinical trial settings, utility gains associated with no treatment (placebo) may result from the increased frequency of health care consultations. In the non-response health state, utility scores were assumed to be the same for both atomoxetine and no treatment.

No disutility was attributed to adverse events, as most events that occurred during the clinical trials were mild to moderate in intensity and resolved following treatment cessation. This is in line with other economic models in ADHD [49]. Furthermore, utility values were the same for the general ADHD, comorbid anxiety and comorbid alcohol abuse populations.

Subgroup analyses: Subgroup analyses in populations with comorbid anxiety and alcohol abuse were conducted. Drug and treatment monitoring costs, unit costs and health-state utility values were the same as used for the analysis of the general ADHD population (Tables 1 and 2). The number of healthcare visits per month was assumed to be the same for the comorbid anxiety population as for the general ADHD population, but differed for the comorbid alcohol abuse population (Table 2).

Treatment response and discontinuation rates for each analysis population were obtained from each single study evaluating atomoxetine in patients with comorbid social anxiety disorder [36] or patients with comorbid alcohol abuse [49].

The duration of the trial in patients with comorbid anxiety was too short to allow estimation of discontinuation rates beyond 120 days. Therefore, probabilities were recomputed based on the observed ratio of time to discontinuation over 120 to 150 days and 150 to 180 days in the general ADHD population. Data up to 210 days (end of model simulation) were extrapolated based on observed data for the 90 to 180 day period.

Response rates in the comorbid alcohol abuse trial were available only up to 60 days and therefore the 90 day probability of response in this population was estimated by applying the rate of change in response between 60 days and 90 days observed in the general ADHD population. Discontinuation rates due to adverse events were obtained from the comorbid alcohol abuse trial. Discontinuation rates due to loss of efficacy or reasons other than loss of efficacy or adverse events could not be estimated from this trial, so rates from the general ADHD population were used.

Sensitivity analyses: Deterministic one-way sensitivity analyses were performed to explore the robustness of the model to changes in the value of key model parameters, for the general ADHD population and for the subgroups, using the lower and upper boundaries of the ranges shown in Tables 1 and 2. In addition, an alternative data source for utility values and an alternative definition for treatment response were applied. The alternative utility values were derived from EQ-5D questionnaire results from LYDO, a randomised, placebo-controlled maintenance trial of atomoxetine [41]. The alternative definition of treatment response was based on the CAARS/AISRS scale only. Net monetary benefit (NMB) tornado diagrams were generated.

Second order probabilistic sensitivity analyses were conducted, for the general ADHD population and for the subgroups, using 5,000 simulations to estimate the impact of uncertainty in all model parameters on the probability of atomoxetine being cost-effective; 5,000 simulations ensured that the probabilistic analysis outputs were stable.

Table 1: Costs of atomoxetine and treatment monitoring assumed in the model.

	Cost (€)	Range of uncertainty (lower and upper boundaries)[1]
Atomoxetine costs		
40 mg tablet	3.47	2.60, 4.34
80 mg tablet	3.86	2.90, 4.83
Treatment monitoring mean costs per visit		
Specialist visit (initial visit)	109.75	82.31, 137.19
Specialist visit (follow-up)	46.43	34.82, 58.04

[1]The range of the lower and upper boundaries was obtained by calculating ± 25% of the original value

Drug costs from the General Spanish Council of Pharmacists (General Spanish Council of Pharmacists, 2013); monitoring costs from published tariffs in Spain (eSalud Spanish Costs Database (Oblikue)). Costs were updated to 2014 if required. Costs were the same for the general ADHD, comorbid anxiety and comorbid alcohol abuse populations.

Table 2: Input variables: Resource use and health utilities.

Resource use: Healthcare visits	Mean number of visits per month	Range of uncertainty (lower and upper boundaries)[1]
General ADHD and comorbid anxiety populations		
Treatment initiation health state		
Specialist visit (month 1)	1.33	1.00, 1.66
Specialist visit (months 2-3)	0.33	0.25, 0.42
Response health state		
Visits by patients receiving atomoxetine[2]	0.33	0.25, 0.42
Visits by patients receiving no treatment[3]	0.17	-0.13, 0.21
No-response health state[2]	0.33	0.25, 0.42
Comorbid alcohol abuse population		
Treatment initiation health state		
Specialist visit (month 1)	2.00	1.50, 2.50
Specialist visit (months 2-3)	1.50	1.13, 1.88
Response health state		
Visits by patients receiving atomoxetine[4]	0.58	0.44, 0.73
Visits by patients receiving no treatment[5]	0.36	0.27, 0.45
No-response health state[4]	0.58	0.44, 0.73
Health state utilities	**Mean utility value**	
Initiation	0.68	0.64, 0.73
Response (atomoxetine)	0.82	0.80, 0.85
Non-response (atomoxetine)	0.67	0.62, 0.71
Response (no treatment)[6]	0.75	0.68, 0.82

[1]The range of the lower and upper boundaries was obtained by calculating ±25% of the original value
[2]One visit every 3 months
[3]One visit every 6 months
[4]One visit within the first 3 months with one visit every 4 months thereafter
[5]One visit assumed within the first 3 months with one visit every 6 months thereafter
[6]The utility of a responder receiving no treatment was assumed to be equal to the mean of the utility of a responder receiving treatment and the utility at initiation

Cost-effectiveness scatter plots and cost-effectiveness acceptability curves across various WTP thresholds were produced. The NMB was calculated as:

$NMB=(QALY_{atomoxetine}-QALY_{placebo}) * WTP (Cost_{atomoxetine}-Cost_{placebo})$

Results

General ADHD population

The base case analysis estimated that treating a patient with ADHD with atomoxetine would cost €809 per year compared with €283 with no treatment (Table 3). Because of the higher response rate in patients receiving treatment, a QALY gain of 0.022 with atomoxetine was estimated per year, resulting in an ICER of €23,645 per QALY (Table 3).

The tornado diagram of the results of the one-way sensitivity analysis shows the 10 parameters with the most impact on the NMB (Figure 1A). It shows that the model is most sensitive to changes in the utility value of patients in the non-response state for both atomoxetine and no treatment. It indicated moderate sensitivity to the utility data source and to changes in the utility value of patients in the response state. However, with the exception of utility values for response and no response from the vignette study [48] as well as the source of the utilities, a positive NMB was maintained following variations in all model parameters (Figure 1A).

The cost-effectiveness scatter plot generated by the probabilistic sensitivity analysis showed that most of the points (85%) fell within the top right quadrant and 15% of points falling into the top left quadrant of the scatterplot, indicating that atomoxetine had higher costs and QALYs in more than half of the model iterations (Figure 2A). The spread of results probably resulted from the wide confidence intervals around clinical response and utility values, as well as the sensitivity of the model to changes in utility values. The cost-effectiveness acceptability curve showed a 58% probability of atomoxetine being cost-effective at a WTP threshold of €30,000 per QALY (Figure 3A).

Subgroup analyses

In the subgroup of patients with comorbid anxiety, there was an incremental cost of €512 with atomoxetine, with a QALY gain of 0.025 per year (Table 3). Atomoxetine continued to be cost-effective in this population, with an ICER of €20,860 per QALY. Corresponding values for the alcohol abuse population were a €513 incremental cost with atomoxetine, 0.021 QALY gain per year and an ICER of €24,675 per QALY (Table 3).

The tornado diagrams of the results of the one-way sensitivity analyses show the 10 parameters with the most impact on the NMB (Figures 1B and 1C). As with the general ADHD population, the models for the comorbid anxiety and alcohol abuse populations were sensitive to the utility values assigned to patients in the no-response state for both atomoxetine and no treatment.

The probabilistic sensitivity analyses also showed similar results to the general population; there was a 63% and 58% probability of atomoxetine being cost-effective at a WTP threshold of €30,000 per QALY in the comorbid anxiety population and alcohol abuse population, respectively (Figures 3B and 3C).

Table 3: Costs, QALYs and ICER estimated by the model.

	Atomoxetine	No treatment	Incremental
General ADHD population			
Total cost (€)	808.76	282.60	526.16
Drug acquisition	513.92	-	513.92
Treatment monitoring	294.84	282.60	12.24
QALYs	0.702	0.680	0.022
ICER (€/QALY)			23,645.33
Comorbid anxiety population			
Total cost (€)	798.25	286.61	511.64
Drug acquisition	503.29	-	503.29
Treatment monitoring	294.96	286.61	8.35
QALYs	0.701	0.676	0.025
ICER (€/QALY)			20,860.32
Comorbid alcohol abuse population			
Total cost (€)	998.63	485.45	513.18
Drug acquisition	503.77	-	503.77
Treatment monitoring	494. 87	485.45	9. 42
QALYs	0.700	0.679	0.021
ICER (€/QALY)			24,675.24

Discussion

Atomoxetine is the only treatment licensed in Spain for the treatment of adults with ADHD. The model showed that atomoxetine is likely to be cost-effective versus no treatment (placebo) in this population, based on the assumptions made. Although atomoxetine is self-evidently more costly than no treatment, a much higher proportion of patients are considered to have a clinical response, leading to QALY gains. The incremental cost per QALY gain was €23,645 in the general ADHD population, €20,860 in the comorbid anxiety population, and €24,675 in the comorbid alcohol abuse population, all of which are well within the WTP threshold of €30,000 per QALY considered acceptable in Spain [34].

One-way sensitivity analyses indicated that the model is sensitive to utility values assigned to patients in the no-response state. Over time, patients in the model accumulate in the no-response state as they discontinue therapy because of adverse events or loss of efficacy, and therefore parameter values assigned to this state have a substantial impact on model results. Probabilistic sensitivity analyses indicated a 58% probability of atomoxetine being cost-effective at a WTP threshold of €30,000 per QALY in the general ADHD population. Atomoxetine was as likely to be cost-effective in patients with comorbid anxiety or alcohol abuse, with probabilities of 63% and 58%, respectively.

There is consistent evidence that pharmacotherapy is cost-effective compared with no treatment or behavioural therapy in children with ADHD [33]. The cost-utility of atomoxetine compared with no treatment in Spain has been demonstrated in children with ADHD [50]. The incremental cost per QALY gained was €23,820 in children who had previously failed on stimulant treatment and €23,323 in children in whom stimulants were contraindicated [50]. However, few data are available on the cost-utility of ADHD treatment in adults. A German health technology assessment concluded that early treatment of adult ADHD is recommended for health economic as well as medical reasons because of the impact of the disorder on daily life, the high risk of developing comorbid mental illnesses and the costs to society [51].

Comorbidity is a significant problem in adult ADHD [25-28]. In the CAT study of ADHD comorbidities in adults in Spain, 39% of patients with ADHD had comorbid substance use disorder, 23% had comorbid anxiety and 18% had comorbid mood disorders [25]. More than 90% of

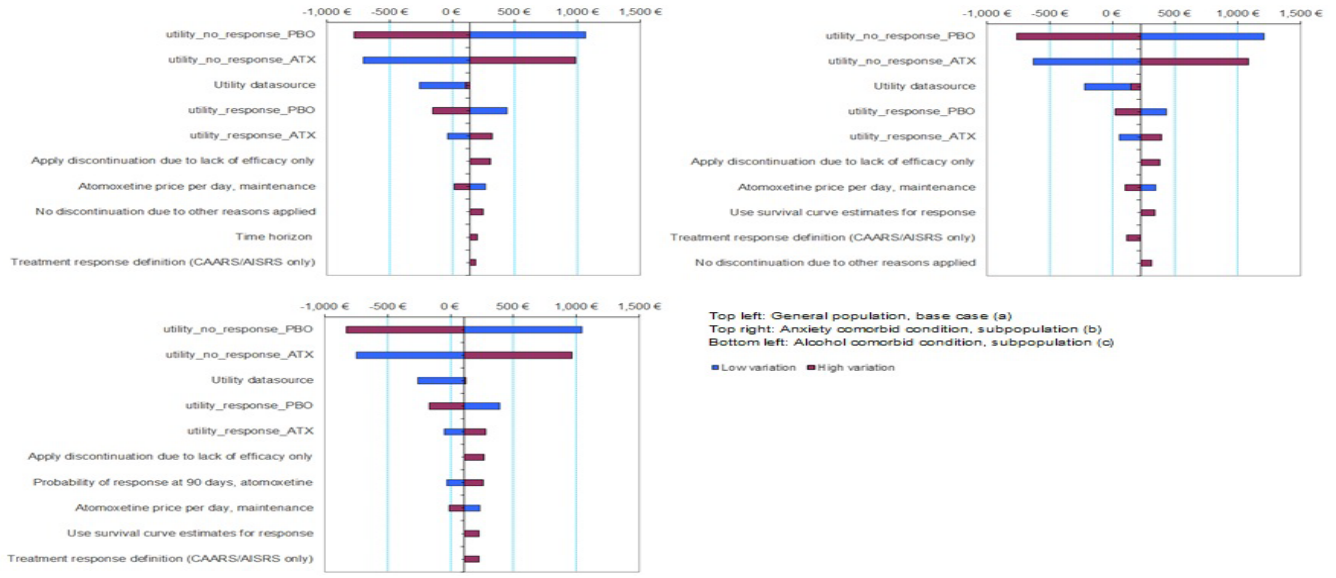

Figure 1: Tornado diagram: Net monetary benefit.

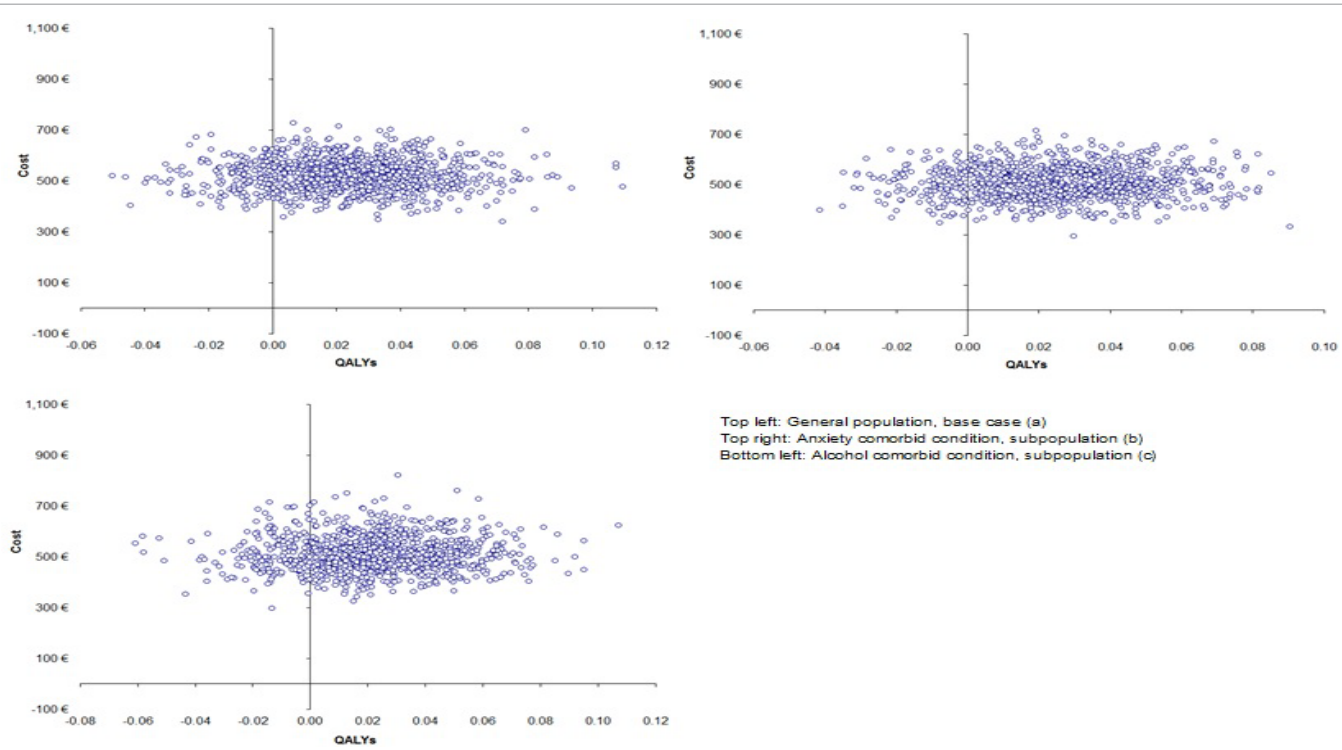

Figure 2: Cost-effectiveness scatter plot.

these patients received methylphenidate, despite this drug not having a licence in Spain for the treatment of adults with ADHD. Patients with comorbid ADHD and substance use disorder are particularly difficult to treat [52]. A meta-analysis has failed to show a reduction in ADHD symptoms with methylphenidate in patients with comorbid substance use disorder [53], although one randomised trial has shown moderate efficacy [54]. In contrast, atomoxetine has shown to be effective in adults with comorbid ADHD and alcohol use disorder [42]. The finding that atomoxetine is cost-effective in patients with comorbid conditions strengthens the case for its use in these populations.

The model had several limitations. Given that no pharmaceutical treatment is licensed for ADHD in adults in Spain, the comparator was assumed to be no pharmaceutical treatment using placebo as a proxy. A non-medical therapy option like cognitive behavioural therapy was not considered as a comparator. Spanish clinical guidelines defining standard of care in adult patients with ADHD do not exist. Conservatively, it assumed that no QoL benefit is achieved during the

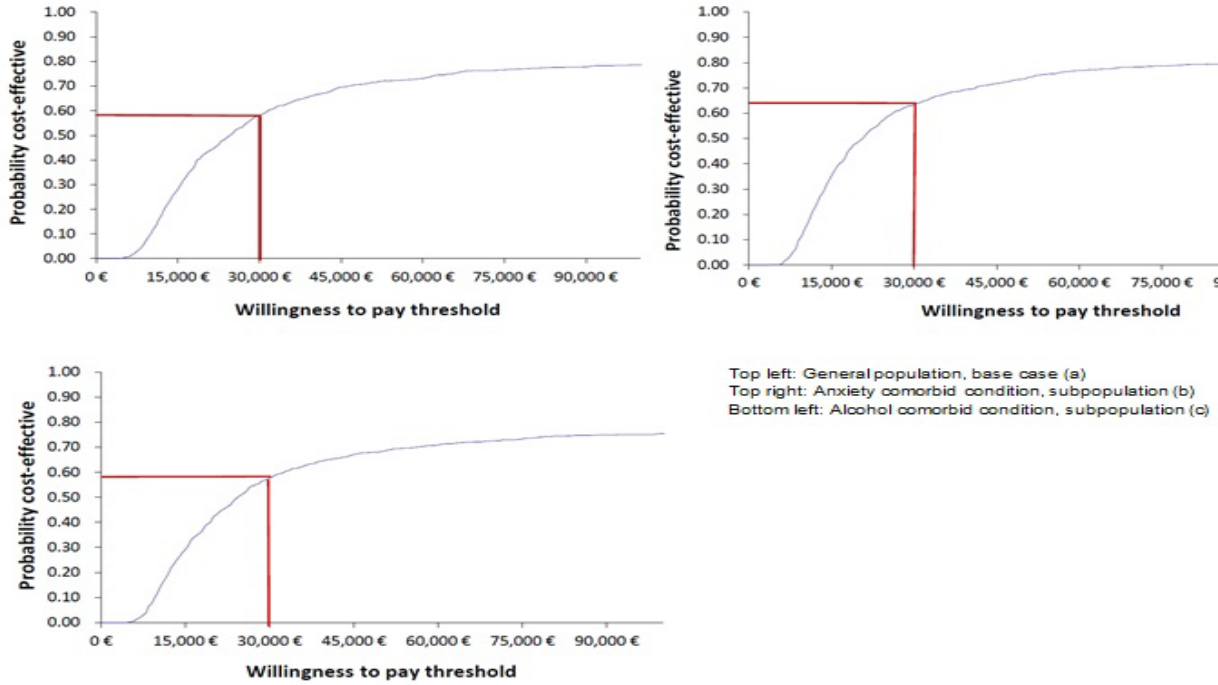

Figure 3: Cost-effectiveness acceptability curve.

initial titration period. Although comorbid conditions might reduce patients' quality of life, equal utility values were assumed for the general population and the subgroup populations. It was also conservatively assumed that the number of healthcare visits per month was the same as the general ADHD population for the comorbid anxiety population.

Another structural assumption is that patients can only move to the no-response state during the first three cycles as a result of discontinuation due to adverse events. Movement to the no-response state for other reasons is not allowed in order to accommodate the fact that up to 12 weeks of treatment may be needed before efficacy is achieved. The model assumes that patients who experience intolerable adverse events will discontinue, and that the symptoms of the adverse event will cease following discontinuation. For this reason, adverse events are not associated with an additional utility decrement in the model, in line with other economic models in ADHD [49].

In addition, compliance with treatment is likely to be higher in clinical trials than in clinical practice as patients are monitored more closely in trials. Conversely, the relatively high response to placebo observed in the trials is unlikely to be generalisable to patients receiving no treatment in clinical practice.

Lastly, the model was sensitive to changes in the utility values as well as to the utility data source used.

In conclusion, considering a WTP threshold of €30,000 per QALY gained in the Spanish setting, atomoxetine represents a cost-effective option compared with no treatment in adults with ADHD.

Acknowledgement

Allen Nyhuis and Marie-Ange Paget contributed as statisticians in the development of the economic model. Ginger Haynes contributed to the overall design and development of the economic model.

Yumi Asukai and Nathaniel Henry contributed to the original model development.

References

1. Gittelman R, Mannuzza S, Shenker R, Bonagura N (1985) Hyperactive boys almost grown up. I. psychiatric status. Arch Gen Psychiatry 42: 937-947.
2. Lara C, Fayyad J, de Graaf R, Kessler RC, Aguilar-Gaxiola S, et al. (2009) Childhood predictors of adult attention-deficit/hyperactivity disorder: Results from the world health organization world mental health survey initiative. Biol Psychiatry 65: 46-54.
3. Lie N (1992) Follow-ups of children with attention deficit hyperactivity disorder (ADHD) Review of literature. Acta Psychiatr Scand Suppl 368: 1-40.
4. Mannuzza S, Klein RG, Addalli KA (1991) Young adult mental status of hyperactive boys and their brothers: A prospective follow-up study. J Am Acad Child Adolesc Psychiatry 30: 743-751.
5. Mannuzza S, Klein RG, Bessler A, Malloy P, LaPadula M (1993) Adult outcome of hyperactive boys. educational achievement, occupational rank, and psychiatric status. Arch Gen Psychiatry 50: 565-576.
6. Mannuzza S, Klein RG, Moulton JL (2003) Persistence of attention-Deficit/Hyperactivity disorder into adulthood: What have we learned from the prospective follow-up studies? J Atten Disord 7: 93-100.
7. Rasmussen P, Gillberg C (2000) Natural outcome of ADHD with developmental coordination disorder at age 22 years: A controlled, longitudinal, community-based study. J Am Acad Child Adolesc Psychiatry 39: 1424-1431.
8. Weiss G, Hechtman L, Milroy T, Perlman T (1985) Psychiatric status of hyperactives as adults: A controlled prospective 15-year follow-up of 63 hyperactive children. J Am Acad Child Psychiatry 24: 211-220.
9. Faraone SV, Spencer TJ, Montano CB, Biederman J (2004) Attention-deficit/hyperactivity disorder in adults: A survey of current practice in psychiatry and primary care. Arch Intern Med 164: 1221-1226.
10. Gibbins C, Weiss M (2007) Clinical recommendations in current practice guidelines for diagnosis and treatment of ADHD in adults. Curr Psychiatry Rep 9: 420-426.
11. Bitter I, Simon V, Balint S, Meszaros A, Czobor P (2010) How do different diagnostic criteria, age and gender affect the prevalence of attention deficit hyperactivity disorder in adults? An epidemiological study in a hungarian community sample. Eur Arch Psychiatry Clin Neurosci 260: 287-296.

12. Fayyad J, De Graaf R, Kessler R, Alonso J, Angermeyer M, et al. (2007) Cross-national prevalence and correlates of adult attention-deficit hyperactivity disorder. Br J Psychiatry 190: 402-409.

13. Kooij JJ, Buitelaar JK, van den Oord EJ, Furer JW, Rijnders CA, et al. (2005) Internal and external validity of attention-deficit hyperactivity disorder in a population-based sample of adults. Psychol Med 35: 817-827.

14. Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA (2007) The worldwide prevalence of ADHD: A systematic review and metaregression analysis. Am J Psychiatry 164: 942-948.

15. Simon V, Czobor P, Balint S, Meszaros A, Bitter I (2009) Prevalence and correlates of adult attention-deficit hyperactivity disorder: Meta-analysis. Br J Psychiatry 194: 204-211.

16. Aragones E, Lluis Pinol J, Ramos-Quiroga JA, Lopez-Cortacans G, Caballero A, et al. (2010) Prevalence in adults of attention deficit hyperactivity disorder using the medical records of primary care. Rev Esp Salud Publica 84: 417-422.

17. Aragones E, Canisa A, Caballero A, Pinol-Moreso JL (2013) Screening for attention deficit hyperactivity disorder in adult patients in primary care. Rev Neurol 56: 449-455.

18. Kooij SJ, Bejerot S, Blackwell A, Caci H, Casas-Brugue M, et al. (2010) European consensus statement on diagnosis and treatment of adult ADHD: The european network adult ADHD. BMC Psychiatry 10: 67.

19. Biederman J, Petty CR, Fried R, Kaiser R, Dolan CR, et al. (2008) Educational and occupational underattainment in adults with attention-deficit/hyperactivity disorder: A controlled study. J Clin Psychiatry 69: 1217-1222.

20. de Graaf R, Kessler RC, Fayyad J, ten Have M, Alonso J, et al. (2008) The prevalence and effects of adult attention-deficit/hyperactivity disorder (ADHD) on the performance of workers: Results from the WHO world mental health survey initiative. Occup Environ Med 65: 835-842.

21. Eakin L, Minde K, Hechtman L, Ochs E, Krane E, et al. (2004) The marital and family functioning of adults with ADHD and their spouses. J Atten Disord 8: 1-10.

22. Mannuzza S, Klein RG, Moulton JL (2008) Lifetime criminality among boys with attention deficit hyperactivity disorder: A prospective follow-up study into adulthood using official arrest records. Psychiatry Res 160: 237-246.

23. Ohlmeier MD, Peters K, Kordon A, Seifert J, Wildt BT, et al. (2007) Nicotine and alcohol dependence in patients with comorbid attention-deficit/hyperactivity disorder (ADHD). Alcohol Alcohol 42: 539-543.

24. Swensen A, Birnbaum HG, Ben Hamadi R, Greenberg P, Cremieux PY, et al. (2004) Incidence and costs of accidents among attention-deficit/hyperactivity disorder patients. J Adolesc Health 35: 346.e1-346.e9.

25. Pineiro D B, Balanza MV, Garcia GP, Soler LB (2014) Psychiatric comorbidity at the time of diagnosis in adults with ADHD: The CAT study. J Atten Disord.

26. Soendergaard HM, Thomsen PH, Pedersen E, Pedersen P, Poulsen AE, et al. (2014) Associations of age, gender, and subtypes with ADHD symptoms and related comorbidity in a danish sample of clinically referred adults. J Atten Disord.

27. Van Emmerik van O K, van de Glind G, Koeter MW, Allsop S, Auriacombe M, et al. (2014) Psychiatric comorbidity in treatment-seeking substance use disorder patients with and without attention deficit hyperactivity disorder: Results of the IASP study. Addiction 109: 262-272.

28. Groß-Lesch S, Dempfle A, Reichert S, Jans T, Geissler J, et al. (2013) Sex- and subtype-related differences in the comorbidity of adult ADHDs. Journal of Attention Disorders.

29. Rosler M, Casas M, Konofal E, Buitelaar J (2010) Attention deficit hyperactivity disorder in adults. World J Biol Psychiatry 11: 684-698.

30. Medicamentos AEd (2013) Strattera 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg or 100 mg capsulas duras.

31. Cottrell S, Tilden D, Robinson P, Bae J, Arellano J, et al. (2008) A modeled economic evaluation comparing atomoxetine with stimulant therapy in the treatment of children with attention-deficit/hyperactivity disorder in the united kingdom. Value Health 11: 376-388.

32. Vanoverbeke N, Annemans L, Ingham M, Adriaenssen I (2003) A cost analysis of the management of attention-deficit/hyperactivity disorder (ADHD) in children in the UK. Journal of Medical Economics 6: 79-94.

33. Wu EQ, Hodgkins P, Ben-Hamadi R, Setyawan J, Xie J, et al. (2012) Cost effectiveness of pharmacotherapies for attention-deficit hyperactivity disorder: A systematic literature review. CNS Drugs 26: 581-600.

34. Sacristan JA, Oliva J, Del Llano J, Prieto L, Pinto JL (2002) What is an efficient health technology in spain? Gac Sanit 16: 334-343.

35. Adler LA, Spencer T, Brown TE, Holdnack J, Saylor K, et al. (2009) Once-daily atomoxetine for adult attention-deficit/hyperactivity disorder: A 6-month, double-blind trial. J Clin Psychopharmacol 29: 44-50.

36. Adler LA, Liebowitz M, Kronenberger W, Qiao M, Rubin R, et al. (2009) Atomoxetine treatment in adults with attention-deficit/hyperactivity disorder and comorbid social anxiety disorder. Depress Anxiety 26: 212-221.

37. Adler LA, Spencer TJ, Levine LR, Ramsey JL, Tamura R, et al. (2008) Functional outcomes in the treatment of adults with ADHD. J Atten Disord 11: 720-727.

38. Adler LA, Spencer TJ, Milton DR, Moore RJ, Michelson D (2005) Long-term, open-label study of the safety and efficacy of atomoxetine in adults with attention-deficit/hyperactivity disorder: An interim analysis. J Clin Psychiatry 66: 294-299.

39. Goto T, Hirata Y, Takita Y, Trzepacz PT, Allen AJ, et al. (2013) Efficacy and safety of atomoxetine hydrochloride in asian adults with ADHD: A multinational 10-week randomized double-blind placebo-controlled asian study. J Atten Disord.

40. Michelson D, Adler L, Spencer T, Reimherr FW, West SA, et al. (2003) Atomoxetine in adults with ADHD: Two randomized, placebo-controlled studies. Biol Psychiatry 53: 112-120.

41. Upadhyaya H, Ramos-Quiroga JA, Adler LA, Williams D, Tanaka Y, et al. (2013) Maintenance of response after open-label treatment with atomoxetine hydrochloride in international european and non-european adult outpatients with attention-deficit/hyperactivity disorder: A placebo-controlled, randomised withdrawal study. Eur J Psychiat 27: 185-205.

42. Wilens TE, Adler LA, Weiss MD, Michelson D, Ramsey JL, et al. (2008) Atomoxetine treatment of adults with ADHD and comorbid alcohol use disorders. Drug Alcohol Depend 96: 145-154.

43. Young JL, Sarkis E, Qiao M, Wietecha L (2011) Once-daily treatment with atomoxetine in adults with attention-deficit/hyperactivity disorder: A 24-week, randomized, double-blind, placebo-controlled trial. Clin Neuropharmacol 34: 51-60.

44. Durell TM, Adler LA, Williams DW, Deldar A, McGough JJ, et al. (2013) Atomoxetine treatment of attention-deficit/hyperactivity disorder in young adults with assessment of functional outcomes: A randomized, double-blind, placebo-controlled clinical trial. J Clin Psychopharmacol 33: 45-54.

45. European Medicines Agency (2010) Guideline on the clinical investigation of medicinal products for the treatment of attention deficit hyperactivity disorder (ADHD).

46. General Spanish Council of Pharmacists (2013) 40 mg: Nomenclator december 1st.

47. eSalud Spanish Costs Database (Oblikue). (2014) Spanish Costs Database (Oblikue).

48. Matza LS, Devine MK, Haynes VS, Davies EW, Kostelec JM, et al. (2014) Health state utilities associated with adult attention-deficit/hyperactivity disorder. Patient Prefer Adherence 8: 997-1006.

49. King S, Griffin S, Hodges Z, Weatherly H, Asseburg C, et al. (2006) A systematic review and economic model of the effectiveness and cost-effectiveness of methylphenidate, dexamfetamine and atomoxetine for the treatment of attention deficit hyperactivity disorder in children and adolescents. Health Technol Assess 10: iii-iv, xiii-146.

50. Hong J, Dilla T, Arellano J (2009) A modelled economic evaluation comparing atomoxetine with methylphenidate in the treatment of children with attention-deficit/hyperactivity disorder in spain. BMC Psychiatry 9: 15.

51. Benkert D, Krause KH, Wasem J, Aidelsburger P (2010) Effectiveness of pharmaceutical therapy of ADHD (attention-Deficit/Hyperactivity disorder) in adults - health technology assessment. GMS Health Technol Assess 6: Doc13.

52. Van Emmerik-van Oortmerssen K, Vedel E, Koeter MW, de Bruijn K, Dekker JJ, et al. (2013) Investigating the efficacy of integrated cognitive behavioral therapy for adult treatment seeking substance use disorder patients with comorbid ADHD: Study protocol of a randomized controlled trial. BMC Psychiatry 13: 132.

53. Castells X, Ramos-Quiroga JA, Rigau D, Bosch R, Nogueira M, et al. (2011) Efficacy of methylphenidate for adults with attention-deficit hyperactivity disorder: A meta-regression analysis. CNS Drugs 25: 157-169.

54. Schubiner H, Saules KK, Arfken CL, Johanson CE, Schuster CR, et al. (2002) Double-blind placebo-controlled trial of methylphenidate in the treatment of adult ADHD patients with comorbid cocaine dependence. Exp Clin Psychopharmacol 10: 286-294.