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A cost-effectiveness analysis of off-label atypical antipsychotic treatment in children and adolescents with ADHD who have failed stimulant therapy

Minji Sohn^{1,3}, Jeffery Talbert¹, Daniela C. Moga^{1,2}, and Karen Blumenschein¹

¹College of Pharmacy, University of Kentucky, 789 South Limestone Street, Lexington, KY 40536, USA

²Department of Epidemiology, College of Public Health, University of Kentucky, 111 Washington Avenue, Lexington, KY 40536, USA

³Department of Pharmaceutical Sciences, College of Pharmacy, Ferris State University, 220 Ferris Drive, Big Rapids, MI 49307, USA

Abstract

The objectives of this study are: (1) to estimate the expected health outcomes of atypical antipsychotics (AAPs) and other non-stimulant attention-deficit/hyperactivity disorder (ADHD) medications and (2) to evaluate the cost-effectiveness of AAPs compared to other non-stimulant ADHD medications. We used decision analysis to compare three alternatives for treating children and adolescents with ADHD who failed initial stimulant treatment: (1) AAPs, (2) a selective norepinephrine reuptake inhibitor (atomoxetine), and (3) selective α 2-adrenergic agonists (clonidine and guanfacine). Probability estimates and quality-adjusted life year (QALY) weights were derived from a literature review. Cost-effectiveness was estimated using the expected health outcomes derived from the decision analysis and expected costs from the literature. The study was conducted from the third-party payer perspective, and the study period was 1 year. One-way deterministic sensitivity analysis and a Monte Carlo simulation were performed. Over the course of 1 year of ADHD pharmacotherapy, the highest QALY was for clonidine/guanfacine (expected QALY = 0.95) followed by atomoxetine (expected QALY = 0.94). Atypical antipsychotics yielded the lowest health outcome with an expected QALY of 0.84. In the cost-effectiveness analysis, the AAP strategy was dominated as it was less effective and more costly than other two strategies. Compared to clonidine/guanfacine, AAPs provided lower QALYs (0.11 QALY lost) at an additional cost of \$2186 on average. Compared to atomoxetine, AAPs resulted in 0.10 QALYs lost at an additional cost of \$2186. In this decision analysis model, AAPs provide lower expected health outcomes than other ADHD medications in children and adolescents who failed prior stimulant therapy. Furthermore, AAPs were not a cost-effective option.

Correspondence to: Minji Sohn.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Human and animals rights Our study uses publicly available aggregate data drawn from published journal articles. Our study does not meet the definition of human subjects' research and therefore does not require IRB review.

Informed consent For this type of study, formal consent is not required.

Keywords

Children; Adolescents; Cost-effectiveness; Decision tree; Antipsychotics; Stimulant

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurobehavioral disorder of childhood, characterized by having trouble paying attention, not being able to control impulsive behaviors, and being overly active (Subcommittee on Attention-Deficit/Hyperactivity D 2011). Those with ADHD may experience academic underachievement, troublesome interpersonal relationship development, and low self-esteem. While medication therapy and/or behavior therapy are recommended for ADHD treatment, medication therapy has been reported as the most cost-effective choice (Jensen et al. 2005). Medication therapy usually initiates with stimulants such as dextroamphetamine or methylphenidate. Although the symptoms are successfully managed with stimulants in most ADHD patients for the short term (6–10 weeks) (Barbarese et al. 2007; Olfson 2004; Remkova and Kratochvilova 2002), an alternative medication regimen is often considered due to adverse side effects, tolerance development or lack of symptom improvement (Sikirica et al. 2012). A selective norepinephrine reuptake inhibitor (atomoxetine) and selective α_2 -adrenergic agonists (clonidine, guanfacine) are non-stimulant ADHD medications approved by the FDA, and they are recommended as an alternative to stimulants (Subcommittee on Attention-Deficit/Hyperactivity D 2011).

A growing number of children and adolescents, including ADHD patients, are prescribed atypical antipsychotics (AAPs) in the USA (Cooper et al. 2006; Weiss et al. 2009; Pathak et al. 2010). Pathak et al. (2010) identified disease categories associated with AAP use in a state Medicaid program during 2000–2005 and reported ADHD as the most common disease. However, the use of AAPs in ADHD treatment is off-label and not yet justified with evidence. Findings about the clinical effectiveness of AAPs in ADHD are mixed with different conclusions (Aman et al. 2004; Armenteros et al. 2007; Tramontina et al. 2009). Moreover, several adverse side effects are reported as being associated with AAPs, including weight gain (Kelly et al. 1998; Martin et al. 2000; Correll et al. 2009), type II diabetes (Andrade et al. 2011; Buse et al. 2003; Bobo et al. 2013), and QTc interval prolongation (Hough et al. 2011; Correll et al. 2011). Therefore, the expected health outcomes based on clinical drug effectiveness and the risk of adverse effects need to be estimated for AAPs before considering them as a stimulant alternative for treating ADHD. This is also true for other non-stimulant medications as they have risks of several adverse effects [e.g., high blood pressure (Wernicke et al. 2003) and/or suicidal ideation (Bangs et al. 2008) in atomoxetine users, and bradycardia (Jain et al. 2011; Daviss et al. 2008) in clonidine or guanfacine users]. A comprehensive assessment of the risks and benefits will allow healthcare providers and patients to compare the expected health outcomes between strategies and take that into account when making decisions about ADHD treatment.

In addition to the expected health outcome, decision making within health care is also affected by costs. Simultaneously evaluating the combination of health outcomes and costs,

which is referred to as cost-effectiveness, is a critical element when choosing appropriate therapy among multiple strategies.

Therefore, the aims of this paper are: (1) to estimate the expected health outcomes of AAPs and other non-stimulant ADHD medications based on trade-offs between clinical effectiveness and adverse effects and (2) to evaluate cost-effectiveness of AAPs compared to other non-stimulant ADHD medications. Both aims target children and adolescents with ADHD who have failed stimulants.

Materials and methods

A cost-effectiveness analysis using a decision tree model was conducted from the US third-party payer perspective. The analysis is intended to address whether atypical antipsychotics (AAPs) would be a cost-effective therapy for children and adolescents with ADHD, compared to other alternatives to stimulants. The data source of the study comes from the literature. Literature review and data collection were completed in January 2014.

The decision tree

Most patients with ADHD who choose to receive medication therapy begin treatment with a stimulant. However, due to either lack of effectiveness or tolerance development, a subset of patients cannot be treated with stimulants. This situation is the focus of our analysis. In other words, the starting point of the decision tree is where the patient seeks an alternative treatment strategy as a replacement for stimulants, with three medication choices: (1) AAPs (aripiprazole, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone), (2) a selective norepinephrine reuptake inhibitor (atomoxetine), or (3) alpha-2 adrenergic agonists (clonidine, guanfacine) (Fig. 1).

The square box at the start of the decision tree is a decision node and represents the decision to be made by the prescriber and patient. The branches emanating from the decision node represent the range of possible pathways that could result from different choices. Each pathway consists of a series of branches that leads to particular events that might be experienced by a patient. In this study, those events are ADHD symptoms, weight gain, type II diabetes, suicidal ideation, and cardiovascular events such as QTc interval prolongation, high blood pressure, or bradycardia. Uncertain events are defined by circular nodes (chance nodes). The endpoint of the decision tree is 1 year of treatment. In total, 28 different pathways are possible. In this model, the expected health outcomes are estimated using quality-adjusted life years (QALYs) that are weighed on the basis of the probabilities of clinical drug effectiveness and side effects.

Estimating probabilities and quality-adjusted life years (QALYs)

Probability estimates were derived from the literature review (Table 1). If multiple studies exist for one estimate, the weighted average was calculated (Naglie et al. 1997). The “Supplementary Appendix” provides the conversion process used to create standardized probabilities that have the minimum value of 0 and the maximum value of 1.

For the baseline probability estimate of AAPs' effectiveness in ADHD, three randomized controlled trials (RCT) were used (Aman et al. 2004; Armenteros et al. 2007; Tramontina et al. 2009). Although these studies are restricted to risperidone (Aman et al. 2004; Armenteros et al. 2007) and aripiprazole (Tramontina et al. 2009), we assumed that other AAP agents will have a similar effectiveness because they share a similar mechanism of action.

The adverse side effects associated with AAPs including weight gain, type II diabetes, and QTc interval prolongation were examined. The baseline probability of weight gain was obtained from three cohort studies in which AAP users were compared with nonusers (Kelly et al. 1998; Martin et al. 2000; Correll et al. 2009). For type II diabetes, we based our assumptions on two observational studies (Andrade et al. 2011; Bobo et al. 2013). For AAP-associated cardiovascular events, we obtained the baseline probability of QTc interval prolongation by averaging the findings of a RCT conducted by Hough et al. (2011) and a case-control study conducted by Correll et al. (2011).

We obtained the drug effectiveness estimate of atomoxetine from RCTs (Gau et al. 2007; Kelsey et al. 2004; Kratochvil et al. 2011; Martenyi et al. 2010; Takahashi et al. 2009). The average estimate was 0.62 with a small variation. There is a black-box warning on atomoxetine concerning suicidal ideation, and the baseline probability of experiencing suicidal ideation in pediatric patients was estimated to be 0.0037 from a meta-analysis conducted by Bangs et al. (2008). As another adverse side effect of atomoxetine, the baseline probability of having increased diastolic blood pressure was estimated from a RCT conducted by Wernicke et al. (2003).

The baseline probability of the effectiveness of clonidine or guanfacine (hereafter referred to as clonidine/guanfacine) was obtained from three RCTs (Jain et al. 2011; Biederman et al. 2008; Sallee et al. 2012). Similar to atomoxetine studies, the average estimate was 0.63 with a small variation. One of the major adverse side effects with these medications, bradycardia, was examined in two RCTs, and the average estimate was used as the baseline probability (Jain et al. 2011; Daviss et al. 2008).

In order to calculate QALYs for each pathway in the decision tree as the health outcome, we derived QALY weights from a literature review (Table 2). Papers that were chosen to estimate QALY weights for ADHD, overweight/obese, diabetes, and cardiovascular events (QTc interval elongation, increased diastolic blood pressure, and bradycardia) were consistent in using PedsQL™ 4.0 (Pediatric Quality of Life inventory™ version 4.0) as the measurement instrument (Varni and Burwinkle 2006; Williams et al. 2005; Varni et al. 2003; Uzark et al. 2008). The PedsQL is a scale designed to measure quality of life in the pediatric population. However, to our knowledge, the QALY weights for suicidal ideation in the pediatric population have not been published, and therefore, we chose a study conducted by Goldney et al., in which a QALY weight was estimated in those aged 15 and over using the Assessment of Quality of Life (AQoL) instrument (Goldney et al. 2001).

Using QALY weights derived from the literature, QALYs over 1 year of ADHD treatment were estimated. Health outcomes beyond this time were not estimated. Also, it was assumed that health benefits and adverse side effects seen within ~6 weeks after initial treatment will

persist for a year as medication treatment continues. For AAP-associated weight gain, because significant weight gain was not observed in 6-week trial (Aman et al. 2004) but observed in 12-week trial (Correll et al. 2009), we assumed that the notable weight gain would take effect approximately between 6 weeks and 3 months after initiating AAP treatment and persist throughout the treatment period. For AAP-associated type II diabetes, it was assumed to occur within 6 months after initiation of therapy, as reported in several pediatric treatment trials (Koller et al. 2001, 2004; Sohn et al. 2015).

We were not able to find studies that measured health-related quality of life specifically associated with QTc interval prolongation, high blood pressure, and bradycardia in the pediatric population. Instead, we used a study conducted by Uzrak et al. (2008) in which quality of life scores were stratified by disease severity. They categorized disease severity as follows: (1) mild cardiovascular disease (CVD) requiring no therapy or effectively treated nonoperatively (catheter therapy); (2) moderate CVD requiring no therapy or surgically corrected (curative); (3) surgically treated CVD (1 procedure) with significant residua or need for additional surgery; and (4) complex or severe CVD, uncorrectable or palliated (includes single ventricle). We took the average score of severity 1 and 2 as the baseline estimate of QTc interval prolongation, high blood pressure, and bradycardia, because those conditions may not require any medical procedure in some cases, but they are risk factors for other heart diseases.

Cost estimation

Expected costs were derived from a retrospective cohort study conducted by Sikirica et al. (2012). In the study, children and adolescents with ADHD who received non-stimulant therapy were followed for one or more years and total healthcare costs were estimated from the third-party payer perspective. Total healthcare costs included all-cause medical costs (i.e., hospitalizations, ER visits, outpatient visits) and all-cause prescription drug costs. The average total healthcare costs were compared between AAP users and other ADHD medication users. In order to control for potential selection bias, Sikirica et al. matched the two groups using patient demographics, geographic region, year of therapy initiation, stimulant use history, comorbidity, all-cause and mental health-related medical care utilization and pharmacy costs during the six-month pre-index period. They excluded patients who had any medical claims associated with conditions that are frequently treated with AAPs (schizophrenia, bipolar disorder, etc.) to increase the likelihood that patients received AAPs for ADHD and not other indications. The results indicated that the average annual total healthcare cost for AAP users was \$6934, while it was \$4748 for other ADHD medication users (estimated in 2010 dollars, $P < 0.001$). Breakdown of cost categories is available in the original article by Sikirica et al. For other ADHD medication users, we assumed that the expected costs of atomoxetine and guanfacine/clonidine would not be significantly different because they have close estimates for the average monthly drug costs (\$239 vs. \$212, respectively) (ADHD 2012), drug effectiveness (0.63 vs. 0.63, respectively), and health outcomes (0.94 vs. 0.95, respectively).

Sensitivity analyses

Multiple sensitivity analyses were conducted to evaluate the robustness of our model. First, we conducted the one-way deterministic sensitivity analysis for estimating expected QALYs. In the analysis, the expected QALYs were examined as one variable varied across the plausible range (Table 3), while holding other variables constant. Second, a Monte Carlo probabilistic sensitivity analysis was performed to examine the cost-effectiveness of the three strategies in 50,000 simulations. The beta distribution was used for probabilities and QALYs, and the gamma distribution was used for costs.

Results

Base case analysis

Over 1 year of ADHD medication treatment, the highest QALY was estimated for clonidine/guanfacine (expected QALYs 0.95), followed by atomoxetine (expected QALYs 0.94) (Table 3, left). Atypical antipsychotics yielded the lowest health outcome with the expected QALY of 0.84.

In the cost-effectiveness analysis, the strategy of AAPs was “dominated” as it was less effective and more costly than other two strategies. Compared to clonidine/guanfacine, AAPs provided a lower QALY (0.11 QALY lost) at an additional cost of \$2186 on average. Compared to atomoxetine, AAPs resulted in 0.10 QALY lost at an additional cost of \$2186.

One-way sensitivity analyses for expected health outcomes

One-way deterministic sensitivity analyses indicated that our finding from the base case analysis was robust in all variables. Also, we identified variables with the most influence on incremental QALYs from the analyses. The result of comparing AAPs to clonidine/guanfacine is shown in a tornado diagram (Fig. 2). The QALYs for having untreated ADHD (i.e., medication is not effective) had the most impact on the change in health outcomes. The QALYs for having overweight/obesity were also shown to have a comparably large impact. Among probabilities, the probability of AAP effectiveness was the most influential variable, followed by the probability of having AAP-associated type II diabetes. The comparison between AAPs and atomoxetine leads to the same conclusions.

Probabilistic sensitivity analyses for cost-effectiveness

The simulated cost-effectiveness derived from the Monte Carlo probabilistic sensitivity analysis is presented with a scatter plot in Fig. 3. The closer a point is to the right-bottom corner of the chart, the more cost-effective it is. It is observed that the cost-effectiveness points of clonidine/guanfacine and atomoxetine are more concentrated around the right-bottom corner of the chart than AAPs. The cost-effectiveness points of AAPs are spread over a larger area, indicating the higher frequency of being less cost-effective than other strategies.

The average costs and expected QALYs from the base case analysis were compared to the ones generated from the probabilistic sensitivity analysis (Table 3, right). The average cost-effectiveness ratio is smaller in the probabilistic sensitivity analysis compared to the base

case analysis for AAPs (Table 3, left), while it is larger in the probabilistic sensitivity for other strategies. However, the conclusion about AAPs being the dominated strategy is consistent in both analyses.

Discussion

The aims of the study were to: (1) estimate expected QALYs for non-stimulant medications in children and adolescents with ADHD who have failed stimulants and (2) examine whether atypical antipsychotics (AAPs) should be recommended for children and adolescents with ADHD as a cost-effective strategy after failing stimulant therapy, compared to other alternatives. Our decision analysis showed that AAPs lead to lower expected QALYs than other strategies. Also, AAPs were not a favored choice for the stimulant-failed ADHD pediatric population with respect to cost-effectiveness and should not be recommended over other strategies. This is depicted on the cost-effectiveness plane, as drawn in Fig. 4, where point A represents AAP pharmacotherapy. The incremental ratio, compared to other strategies (O), is OA. The “northwest” quadrant of the cost-effectiveness plane for which cost is increasing and quality is decreasing (“dominated”) is where AAP pharmacotherapy is located. It is generally uncontroversial to reject such strategies, and therefore, we did not present an incremental cost-effectiveness ratio (ICER), although it is typically shown in many cost-effective analyses.

In our decision tree model, the option of “no treatment” was not included because we assumed that the decision about whether a patient will receive the pharmacotherapy or not occurs before they initiate stimulant treatment. Once stimulant therapy has failed, the patient would seek alternative medications to treat ADHD based on the prior decision to treat with medications. However, it is possible that the patient and his/her prescriber could consider no treatment when they make a decision after stimulant failure. If this is the case, the conclusions of this paper may not be applicable.

The findings of this paper are best implemented in treating children and adolescents with ADHD who do not have comorbid mental disorders for which AAPs are frequently prescribed, such as schizophrenia, bipolar disorder, or autism spectrum disorders. The estimated effectiveness of medications in our decision model is from clinical trials measuring drug effectiveness in ADHD only. Therefore, the results could be different when another comorbid mental disorder is present.

Also, we used the QALY of overweight/obesity and the probability of weight gain when estimating the expected health outcomes in the analyses. However, one should note that weight gain may not necessarily result in overweight or obesity. Considering our tornado diagram identifying the QALYs of overweight/obesity as the second most influential variable on the change in health outcome (Fig. 3), the expected health outcomes in AAPs could have been underestimated.

When implementing the conclusions of this paper, our assumption that the healthcare costs of atomoxetine treatment are not significantly different from those of clonidine/guanfacine should be considered as a study limitation. For example, although our analyses suggested

that the most cost-effective choice was clonidine/guanfacine over atomoxetine, the conclusion could be changed depending on the costs associated with each strategy, as the price differs by manufacturers (brand name drugs vs. generic drugs) and the formulation of the drug (extended release vs. immediate release). The rank of cost-effectiveness could be easily affected by the costs, because the expected health outcomes of clonidine/guanfacine and atomoxetine are similar (expected QALYs 0.95 vs. 0.94, respectively). The primary aim of the study was to evaluate the cost-effectiveness of AAP compared to other alternatives, and the decision between the two non-AAP medications requires further specification.

Another study limitation was the inclusion of type I diabetes when estimating QALY weights for AAP-associated side effects. We based our assumption about QALY weights for type II diabetes on the study conducted by Varni et al., in which the quality of life for both type I and type II diabetes pediatric patients was assessed. It is possible that the quality of life for type I diabetes patients is inherently different from type II diabetes patients, and the QALY weight estimated by Varni et al. may not reflect the true value for type II diabetes.

Clearly, the side effects associated with each strategy are not limited to the ones in the decision model. Some side effects associated with taking medications such as headache, nausea, vomiting, fatigue, and dizziness, were omitted because they are likely to be present in all strategies and the effect of those conditions would be canceled out during the analyses.

Lastly, the intention of our study is to provide a cost-effectiveness viewpoint in approaching ADHD pharmacotherapy. The findings of the study cannot serve as sole evidence when making decisions about ADHD treatment. For example, benefit–cost analysis may lead to a substantially different ranking of alternatives than cost-effectiveness analysis. While cost-effectiveness analysis look for cost-saving alternatives per unit of outcome generated, benefit–cost analysis focuses more on options that have the highest magnitude of net benefits. Despite the limitations described above, and the inherent limitations associated with cost-effectiveness analysis, our findings provide quantitative confirmation that treating ADHD with AAPs delivers lower patient outcomes (as measured by QALYs) at an increased cost when compared to clonidine/guanfacine.

Supplementary appendix

This section provides supplementary material for the primary paper, including a more detailed presentation of several methodological points. They should be read in conjunction with the primary paper.

Standardizing probabilities from different forms presented in literature

Probabilities of events in our decision tree were obtained in various forms from the literature. One of the typical ways of presenting the effectiveness/safety of a drug in a randomized control trial (RCT) is to use a two-by-two table. Also, many RCTs report effect size, which is calculated as the difference between the treatment group mean and the control group mean divided by pooled standard deviation [i.e., effect size = (treatment mean—control mean)/pooled SD]. However, these are rarely used in observational studies. For example, studies that assessed antipsychotic agent-associated weight gain reported the

average change in body weights with standard deviation. In order to convert the different forms of probabilities into a standardized probability that takes 0 as the lowest possible value and 1 as the highest possible value, we used following methods.

1. Calculating the standardized probability from two-by-two table (ADHD 2012).

The effectiveness/safety of a drug can be expressed using two-by-two table in a RCT. For example, following table is based on the result of RCT conducted by Daviss et al. (2008).

	Bradycardia	No Bradycardia
Clonidine-treated ($n = 31$)	7	24
Placebo ($n = 30$)	1	29

They reported that the probability of having bradycardia in clonidine-treated children was 22.6 % ($7/31 \times 100 = 22.6\%$), and the probability of having bradycardia in placebo group was 3.3 % ($1/30 \times 100 = 3.3\%$). The probability of clonidine-associated bradycardia is calculated as the proportionate increase in the probability of bradycardia resulting from clonidine treatment, which is equal to $0.854 = (0.226 - 0.033)/0.226$.

2. Calculating the standardized probability from effect size (Tickle-Degnen 2001).

The effect size is defined as the difference between the mean outcomes for treatment and control groups in standard deviation units. Tickle-Degnen (2001) argues that because the effect size is a standard normal deviate, we can assume a normal distribution to describe the variation of individuals' responses around the average outcomes (Tickle-Degnen 2001). For example, if the effect size is 0.65 as shown in the guanfacine RCT study conducted by Sallee et al. (2012), the probability of effectiveness is simply the area under the standard normal curve at 0.65, which is equal to 0.627.

3. Calculating the standardized probability from the change in body weight.

The effect size of a drug with respect to weight gain is calculated based on the reported body weight changes of the treatment and control groups. Once the effect size is estimated, the standardized probability is obtained using the standard normal table (Tickle-Degnen 2001).

4. Calculating the standardized probability from hazard ratio (Chinn 2000).

The hazard ratio is equivalent to the odds that a patient in the treatment group reaches the endpoint first (Chinn 2000). For example, the probability of developing type II diabetes first can be derived from the odds of developing type II diabetes first, which is the probability of developing type II diabetes first divided by the probability of not developing first:

$$\text{Hazard ratio (HR)} = \text{odds} = P/(1-P);$$

$$P = \text{HR}/(1 + \text{HR})$$

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Fig. 1.
Decision tree model

Fig. 2.
Tornado diagram at AAPs versus clonidine/guanfacine

Fig. 3.
Cost-effectiveness scatter plot

Fig. 4.
Cost-effectiveness plane

Table 1

Probability estimates

Variable	Baseline	Variation range		References
		Low	High	
<i>Atypical antipsychotic</i>				
Effectiveness	0.22	0	0.65	Aman et al. (2004), Armenteros et al. (2007), Tramontina et al. (2009)
Weight gain	0.7	0.65	0.8	Kelly et al. (1998), Martin et al. (2000), Correll et al. (2009)
Type II diabetes	0.38	0	0.84	Andrade et al. (2011), Bobo et al. (2013)
QTc interval prolongation <i>Atomoxetine</i>	0.53	0	0.97	Hough et al. (2011), Correll et al. (2011)
Effectiveness	0.63	0.6	0.64	Gau et al. (2007), Kelsey et al. (2004), Kratochvil et al. (2011), Martenyi et al. (2010), Takahashi et al. (2009)
Increased blood pressure	0.56	0	0.88	Wernicke et al. (2003)
Suicidal ideation <i>Clonidine/guanfacine</i>	0.0037	0.0007	0.0044	Bangs et al. (2008)
Effectiveness	0.63	0.6	0.65	Jain et al. (2011), Biederman et al. (2008), Sallee et al. (2012)
Bradycardia	0.59	0.17	0.85	Jain et al. (2011), Daviss et al. (2008)

Table 2

Utility estimates

Variable	Baseline	Variation range		References
		Low	High	
Untreated ADHD	0.8673	0.5583	1	Varni and Burwinkle (2006)
Overweight/obese	0.9249	0.74485	1	Williams et al. (2005)
Diabetes	0.9847	0.92855	1	Varni et al. (2003)
QTc interval prolongation	0.9913	0.727	1	Uzark et al. (2008)
High blood pressure	0.9913	0.727	1	Uzark et al. (2008)
Bradycardia	0.9913	0.727	1	Uzark et al. (2008)
Suicidal ideation	0.6156	0.4194	0.8118	Goldney et al. (2001)

Table 3

Estimated average costs and QALYs

	Base case			Probabilistic sensitivity analysis		
	Total cost	QALY	Cost/QALY	Total cost (SD)	QALY (SD)	Cost/QALY
Atypical antipsychotics (AAPs)	\$6934	0.84	\$8254.76 (Dominated)	\$6906 (\$8625)	0.84 (0.08)	\$8221.43 (dominated)
Atomoxetine	\$4748	0.94	\$5051.06	\$4778 (\$5865)	0.94 (0.04)	\$5082.98
Clonidine/guanfacine	\$4748	0.95	\$4997.89	\$4778 (\$5865)	0.95 (0.04)	\$5029.47