ECONOMIC EVALUATION

Cost-Effectiveness Analysis of Aripiprazole Augmentation Treatment of Patients with Major Depressive Disorder Compared to Olanzapine and Quetiapine Augmentation in Turkey: A Microsimulation Approach

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ABSTRACT

Objectives: Major depressive disorder (MDD) is a chronic illness associated with a major burden on quality of life (QOL) and health care resources. Aripiprazole augmentation to antidepressant treatment was recently approved for patients with MDD responding insufficiently to antidepressant treatment in Turkey. The objective was to estimate the cost-effectiveness of aripiprazole augmentation in this indication compared with olanzapine and quetiapine augmentation from a payer perspective. Methods: A lifetime economic model was built simulating transitions of patients with MDD between major depressive episodes (MDEs) and remission. During MDEs, patients were treated with adjunctive aripiprazole, quetiapine, or olanzapine. Patients who did not respond switched to subsequent treatment lines. Comparative effectiveness between adjunctive aripiprazole, quetiapine, and olanzapine was estimated by using an indirect comparison. Resource utilization and costs were obtained from Turkish studies. Results: Over a lifetime horizon, patients treated with aripiprazole spent less time in MDEs than did patients treated with quetiapine (~11 weeks) and olanzapine (~7 weeks). On average, patients treated with aripiprazole showed improvement in QOL compared with patients treated with quetiapine (+0.054 quality-adjusted life-years [QALYs]) and olanzapine (+0.039 QALYs) combined with cost saving of 593 Turkish lira (TL) versus quetiapine and 485 TL versus olanzapine. The probability that adjunctive aripiprazole would be cost-effective among the three strategies ranged between 74% and 75% for willingness-to-pay values between 0 TL and 100,000 TL per QALY gained. Conclusions: This is the first lifetime health-economic model in Turkey that takes patient heterogeneity into account when assessing QOL and costs of different adjunctive strategies in MDD. The results indicate that adjunctive treatment with aripiprazole provides health benefits at lower costs in patients with MDD when compared with quetiapine and olanzapine augmentation. Keywords: antipsychotics, aripiprazole, cost-effectiveness analysis, depression, discrete probability distribution, major depressive disorder, olanzapine, quetiapine, simulation model, Turkey.

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Introduction

Mood disorders represent a major health problem. Depression is a frequent and severe illness with a substantial impact on personal and familial suffering. Several surveys such as the National Comorbidity Survey Replication in the United States have shown a lifetime prevalence of mood disorders of more than 20% in adults [1]. Most of this prevalence was associated with major depression, which had a lifetime prevalence of 16.6%. In the World Health Organization’s World Mental Health Survey Initiative, the projected lifetime prevalence of any mood disorder was 31.4% in the United States [2]. In the European Study of the Epidemiology of Mental Disorders, 13% of the individuals reported a history of major depression, with a 12-month prevalence of 4% [3]. In Turkey, the prevalence of depression was estimated to be 21% in 2004 [4]. Depression is a highly recurrent disease; 80% of the patients with a history of two episodes will have another recurrence during their lifetime [5]. Because of the high risk of suicide (6.3% annually [6]), depression can be a life-threatening illness.

According to the World Health Organization, major depression is currently ranked as the leading cause of disability in middle- and high-income countries. At an international level, 4.1% of the total global burden of disease is due to major depression [7]. Depression, being an important source of impaired health-related quality of life (HRQOL) of patients [8,9], was also the fourth leading cause of disease burden in Turkey [4]. Depression primarily impacts the usual activities, pain and discomfort, and anxiety and depression domains on the EuroQol five-dimensional questionnaire [10]. Reported utility values for depressive episodes were between 0.09 and 0.47 [10–14]. Total cost for depression was estimated at $267 million in Turkey in 2004, primarily related to hospital-based treatment (93%) [15].

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Today, the ultimate goal in the treatment of major depression is remission, that is, a full symptomatic recovery with a return to premorbid functioning. Indeed, partial remission is associated with a greater risk of relapse and recurrence, decreased quality of life, a poorer psychosocial functioning, a higher mortality risk, and increased cost of illness. A Swedish study has shown that patients who are not in remission use 1.6 times more medical resources than do those in remission [15].

In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, less than 30% of the patients reached remission with first-step antidepressant treatment within 14 weeks of starting treatment [17,18]. Another recent study performed in primary care also reported very low remission rates with antidepressant treatment: 28.3% according to the clinicians and 17.1% according to the patients [19]. For these insufficient responders to antidepressant treatment, one may consider increasing the dose or switching to another antidepressant, depending on the level of initial response. Alternatively, the treatment of patients with an insufficient response to an antidepressant may be augmented with an atypical antipsychotic. Turkey was the first country in Europe to approve aripiprazole augmentation for the treatment of major depressive episodes in patients who showed inadequate response after at least one antidepressant treatment [20]. For reimbursement decisions, it is important to consider the value for money of this strategy compared with other alternatives. Quetiapine augmentation is also approved for this indication in Turkey [20], and olanzapine augmentation is off-label (it is not officially approved in Turkey but has a US license as combination with fluoxetine [http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020592s060s061l,021086s038s039lbl.pdf]). The short-term use of these regimens has been compared in a recent cost-effectiveness analysis in the United States [21]. A Turkish cost-effectiveness assessment, however, is still missing. As such, this article aimed to assess the cost-effectiveness of aripiprazole augmentation compared with that of quetiapine and olanzapine augmentation for the treatment of major depressive disorder (MDD) in Turkey from a payer perspective.

Methods

Model Structure

A patient-level simulation model was built structuring the evidence on clinical and economic outcomes of treating patients suffering from MDD with antidepressant or with atypical antipsychotic augmentation with quetiapine and adjunctive olanzapine. The model was built in Microsoft Excel and Visual Basic for applications. A total of 50,000 patients were simulated to reach stable results. A microsimulation approach was deemed most appropriate in this indication, due to the heterogeneity of the patient population and the strong association between a patient’s history and his or her future disease course. To represent this with a Markov model would require too many health states. A schematic overview of the simulation model structure is presented in Figure 1, representing the modeled health states and possible transitions. The depressive episode is the initial health state of a patient. Duration was simulated to determine the time at which a patient would move to the remission state. Once there, the time until a next depressive episode was simulated, specifying the length of stay in remission. If that period was longer than 9 months, a patient spent the remaining time in the “between episodes” state, incurred fewer costs and experienced further quality of life improvements. Back in the depressive episode state, the procedure was repeated until a patient died. Time of death was simulated at model entrance (based on age and gender) and could be shortened if a patient committed suicide, which was possible only during a depressive episode. During each depressive episode it was simulated whether a patient had committed suicide. It was assumed that this would take place in the middle of the episode. Further model details are provided in the following sections.

Patient Population Simulated

The characteristics of the patients that were simulated at model entrance resemble the populations enrolled in the double-blind randomization phases of the three clinical trials assessing the efficacy of aripiprazole augmentation [22–24]. The patients in these trials suffered from a major depressive episode and had an insufficient response to at least two prior antidepressant therapies prior to trial entry. Their characteristics and the distributions used for simulating them in the model are provided in Table 1.

Clinical Data

The time a patient spent in the depressive episode state depended on the remission rate of the therapy. Remission rates with aripiprazole augmentation were based on the three clinical trials assessing the efficacy of aripiprazole as adjunctive therapy in MDD [22–24]. During a 6-week treatment period, 28.8% of the patients reached remission (see Table 2). A Bernoulli distribution with a probability of 0.288 was used in the model to simulate whether a patient would respond to aripiprazole augmentation within 6 weeks. This discrete probability distribution takes a value of 1 (response) with a probability of 28.8% and a value of 0 (no response) with a probability of 71.2%. A remitting patient would move to the remission state after 6 weeks. Patients not reaching remission after 6 weeks remained in the depressive state and were switched to a subsequent treatment line (see Fig. 2). Comparative 6-week remission rates of the other adjunctive strategies were based on a formal indirect comparison due to a lack of direct comparable data in this indication. To estimate the efficacy of other adjunctive strategies, a systematic review was conducted identifying head-to-head or placebo controlled studies (PCSs) of antidepressant augmentation with aripiprazole.

Table 1 – Baseline patient characteristics [13–15] and corresponding distributions used for simulating.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean ± SD</th>
<th>Distribution</th>
<th>Parameter (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>45.1 ± 4.4</td>
<td>Normal</td>
<td>μ = 45.1, σ = 4.4</td>
</tr>
<tr>
<td>Gender (% males)</td>
<td>68.0</td>
<td>Bernoulli</td>
<td>P = 0.68</td>
</tr>
<tr>
<td>Number of prior episodes</td>
<td>6 ± 5.2</td>
<td>Geometric</td>
<td>P = 0.17</td>
</tr>
</tbody>
</table>

Fig. 1 – Schematic model representation.
quetiapine, olanzapine, lithium, and triiodothyronine in a treatment-resistant depression adult population. A literature search was conducted in MEDLINE covering studies published between January 1980 and June 2010. Three PCSs for aripiprazole [22–24], two PCSs for adjunctive quetiapine [25,26], three PCSs for adjunctive olanzapine [27–29], one PCS for lithium [30], and one PCS for T3 [31] were identified. Remission rates of the active treatments and the control group were extracted. Study characteristics and remission numbers are summarized in Table 3. Subsequently, a fixed effects Bayesian meta-analysis using non-informative priors implemented in WinBUGS [32] was conducted on the remission rates to obtain indirect odds ratios of each treatment compared with aripiprazole [33]. The indirect odds ratios were applied to the aripiprazole remission rate to obtain indirect odds ratios of each treatment compared with aripiprazole [33]. The indirect odds ratios were applied to the aripiprazole remission rate to obtain indirect odds ratios of each treatment compared with aripiprazole [33]. The indirect odds ratios were applied to the aripiprazole remission rate to obtain indirect odds ratios of each treatment compared with aripiprazole [33]. The indirect odds ratios were applied to the aripiprazole remission rate to obtain indirect odds ratios of each treatment compared with aripiprazole [33]. The indirect odds ratios were applied to the aripiprazole remission rate to obtain indirect odds ratios of each treatment compared with aripiprazole [33]. The indirect odds ratios were applied to the aripiprazole remission rate to obtain indirect odds ratios of each treatment compared with aripiprazole [33]. The indirect odds ratios were applied to the aripiprazole remission rate to obtain indirect odds ratios of each treatment compared with aripiprazole [33]. The indirect odds ratios were applied to the aripiprazole remission rate to obtain indirect odds ratios of each treatment compared with aripiprazole [33]. The indirect odds ratios were applied to the aripiprazole remission rate to obtain indirect odds ratios of each treatment compared with aripiprazole [33]. The indirect odds ratios were applied to the aripiprazole remission rate to obtain indirect odds ratios of each treatment compared with aripiprazole [33]. The indirect odds ratios were applied to the aripiprazole remission rate to obtain indirect odds ratios of each treatment compared with aripiprazole [33]. The indirect odds ratios were applied to the aripiprazole remission rate to obtain indirect odds ratios of each treatment compared with aripiprazole [33]. The indirect odds ratios were applied to the aripiprazole remission rate to obtain indirect odds ratios of each treatment compared with aripiprazole [33]. The indirect odds ratios were applied to the aripiprazole remission rate to obtain indirect odds ratios of each treatment compared with aripiprazole [33].

A patient failing three consecutive adjunctive therapies was assumed to receive so-called best supportive care (BSC). In reality, at this stage, medical professionals will try different therapies including different treatment combinations. It is difficult to formally implement all these different treatment options in a health economic model structure because of the complexity of decisions and lack of published data to substantiate corresponding efficacy. Therefore, BSC grouped all these treatment alternatives into one for which efficacy was based on the STAR*D trial, thereby mimicking real-life practice [34]. It was anticipated that this simplification would not affect incremental results. STAR*D found that 13% of the patients responded to treatment within 9.2 weeks. This was implemented in the model by drawing a duration on BSC from an exponential distribution with a weekly hazard rate of 0.015 (−ln(1 – 0.13)/9.2).

A patient who developed a new major depressive episode received the same treatment as he or she had previously responded to. No efficacy data are available for patients with a prior response to adjunctive treatment. However, it is highly likely that this subgroup of patients will have an increased probability of remission, reflected by assuming a 6-week probability of remission of 90%. This value was applied to all therapies except for BSC, for which the duration was drawn from the same exponential distribution as for the first treatment episode. The impact of the remission probability value for prior responders was tested in a sensitivity analysis.

The assumed risk of developing a new major depressive episode reflected the naturalistic data observed by Solomon et al. [35]. They followed 318 patients suffering from MDD over a period of 10 years and found a decrease in mean time until the next major depressive episode with an increase in the amount of prior episodes. Weibull curves were fitted on their data (see Fig. 3), and time until the next major depressive episode was simulated from the appropriate distribution reflecting the number of prior episodes a patient had experienced. Weibull curves were selected on the basis of a least square difference between fit and actual data. Patients in the remission and time between episodes health states continued their antidepressant but stopped their augmentation strategy. To date, there is no evidence surrounding the impact of long-term atypical augmentation on the risk of developing a depressive episode.

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**Table 2 – Health economic model input parameters.**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Remission probability (%) at 6 wk</th>
<th>Utility values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole augmentation</td>
<td>28.8 (25.0–33.0)</td>
<td>Depressive episode 0.46 (0.34–0.58)</td>
</tr>
<tr>
<td>Quetiapine augmentation</td>
<td>24.5 (16.7–32.2)</td>
<td>Remission 0.81 (0.76–0.86)</td>
</tr>
<tr>
<td>Olanzapine fluoxetine combination</td>
<td>25.4 (18.2–33.2)</td>
<td>Between episodes 0.86 (0.84–0.88)</td>
</tr>
<tr>
<td>Lithium augmentation</td>
<td>16.0 (1.00–44.6)</td>
<td></td>
</tr>
<tr>
<td>Triiodothyronine augmentation</td>
<td>67.9 (14.5–89.8)</td>
<td></td>
</tr>
<tr>
<td>Best supportive care (yearly hazard)</td>
<td>0.78</td>
<td></td>
</tr>
</tbody>
</table>

Remission probability prior responders: 90.0 (50.0–99.0)

Costs ($/TL$)

- Aripiprazole augmentation: 221 (108–327)
- Quetiapine augmentation: 200 (87–306)
- Olanzapine fluoxetine combination: 210 (96, 316)
- Lithium augmentation: 188 (74–294)
- Triiodothyronine augmentation: 187 (74–293)
- Best supportive care: 187 (61–307)
- Suicide attempt cost: 1269 (801–1763)

Note. 95% Confidence intervals reported between parentheses. All parameters showing confidence intervals in this table were varied in the probabilistic sensitivity analysis.

TL, Turkish lira.

*Please note that the purchasing power parity between Turkey and the United States is 1.0 (2010 figure, http://stats.oecd.org).*

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**Fig. 2 – Treatment sequence strategies.** T3, triiodothyronine.
Table 3 – Characteristics of studies used in indirect comparison.

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration (wk)</th>
<th>Country</th>
<th>Participants</th>
<th>Methods</th>
<th>Remission definition</th>
<th>Placebo</th>
<th>Active arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>6</td>
<td>US</td>
<td>Age: 18-65 y; MDE according to DSM-IV-TR; HAM-D-17 score ≥ 18 at end of the screening phase; 1–3 historical ADTs of &gt; 6 wk</td>
<td>7-28-d screening phase; 8-wk prospective treatment phase with open-label ADT plus single-blind adjunctive placebo. Patients with incomplete response continued ADT and entered the randomization phase.</td>
<td>≥ 50% decrease in MADRS score + MADRS score ≤ 10</td>
<td>172</td>
<td>27</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>6</td>
<td>US</td>
<td>Same as above</td>
<td>Same as above</td>
<td>Same as above</td>
<td>184</td>
<td>28</td>
</tr>
<tr>
<td>Marcus et al. [24]</td>
<td>6</td>
<td>US</td>
<td>Same as above</td>
<td>Same as above</td>
<td>Same as above</td>
<td>169</td>
<td>32</td>
</tr>
<tr>
<td>Berman et al. [23]</td>
<td>6</td>
<td>US</td>
<td>Same as above</td>
<td>Same as above</td>
<td>same as above</td>
<td>29</td>
<td>5</td>
</tr>
<tr>
<td>Intyre et al. [26]</td>
<td>8</td>
<td>CA</td>
<td>Age: 18-65 y; MDE according to DSM-IV; HAM-D-17 score ≥ 18. One historical ADT of ≥ 6 wk.</td>
<td>Patients treated for current episode with single AD at therapeutic dose for ≥ 6 wk and meeting study criteria for residual depressive and comorbid anxiety symptoms were randomized.</td>
<td>HAM-D-17 score ≤ 7</td>
<td>29</td>
<td>5</td>
</tr>
<tr>
<td>Bauer et al. [25]</td>
<td>6</td>
<td>AU, CA, EU, and ZA</td>
<td>Outpatients; age: 18-65 y; MDD according to DSM-IV-TR; HAM-D-17 score ≥ 20; HAM-D item 1 ≥ 2. One historical ADT of ≥ 6 wk.</td>
<td>Eligible patients with an inadequate response to an ADT during their current episode were randomized to 6- wk double-blind quetiapine extended release or placebo adjunctive to ongoing ADT.</td>
<td>MADRS score ≤ 10</td>
<td>160</td>
<td>50</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>8</td>
<td>US and CA</td>
<td>Age: 18-65 y; DSM-IV unipolar, nonpsychotic MDD; MADRS score ≥ 20 at the beginning and the end of the screening phase. One historical ADT (SSRI ≥ 4 wk at a therapeutic dose).</td>
<td>2-7-d screening/washout phase; 7-wk lead-in phase of nortriptyline to demonstrate treatment failure to a TCA, 8-wk randomized, double-blind phase: olanzapine/fluoxetine combination, olanzapine, fluoxetine, or nortriptyline</td>
<td>2 consecutive MADRS total scores of ≤ 8</td>
<td>142</td>
<td>19</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Population Size</td>
<td>Age</td>
<td>DSM-IV/DSM-III-R</td>
<td>ADT Duration</td>
<td>ADT Dose</td>
<td>Screening Phase</td>
</tr>
<tr>
<td>-------------------------------</td>
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<td>--------------</td>
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<td>----------------</td>
</tr>
<tr>
<td>Corya et al. [29]</td>
<td>Various</td>
<td>12</td>
<td>≥18</td>
<td>MDD, single or recurrent, unipolar, without psychotic features; CGI-S score ≥ 4</td>
<td>One historical ADT (SSRI ≥ 6 wk at a therapeutic dose)</td>
<td>2-7-d screening phase; 7-wk open-label venlafaxine lead-in phase; patients with &lt; 30% improvement on MADRS score proceeded to 5-9-d double-blind taper phase before the randomization phase.</td>
<td>2 consecutive MADRS total scores of ≤ 8</td>
</tr>
<tr>
<td>Thase et al. [28]*</td>
<td>US and CA</td>
<td>8</td>
<td>18-65</td>
<td>MDD, recurrent, without psychotic features; HAM-D-17 score ≥ 22</td>
<td>One historical ADT ≥ 6 wk</td>
<td>3-14-d screening phase; 8-wk open-label lead-in phase to establish fluoxetine resistance; patients with &lt; 25% decrease in HAM-D-17 score and HAM-D-17 score ≥ 18 and ≤ 15% decrease between week 7 and 8 of lead-in entered</td>
<td>MADRS score ≤ 10 at end point</td>
</tr>
<tr>
<td>Thase et al. [28]*</td>
<td>US and CA</td>
<td>8</td>
<td>Same as above</td>
<td>Same as above</td>
<td>Same as above</td>
<td>Same as above</td>
<td>101</td>
</tr>
<tr>
<td>Lithium Nierenberg et al. [30]</td>
<td>US</td>
<td>6</td>
<td>18-70</td>
<td>MDD, HAM-D-17 score ≥ 18; 1-5 historical adequate AD courses. One prospective ADT failed</td>
<td>1-5 adequate AD courses failed; 6-wk prospective open-label nortriptyline</td>
<td>≥ 50% decrease in HAM-D-17</td>
<td>17</td>
</tr>
<tr>
<td>T3 Joffe et al. [31]</td>
<td>CA</td>
<td>2</td>
<td>Mean age 37.4 y; RDC unipolar, nonpsychotic MD; HAM-D score ≥ 16 after 5 wk of desipramine or imipramine</td>
<td>Subjects were randomly assigned to receive 2-wk liothyronine, lithium, or placebo in addition to desipramine or imipramine</td>
<td>≥ 50% decrease and HAM-D score ≤ 7</td>
<td>16</td>
<td>2</td>
</tr>
</tbody>
</table>

AD, antidepressant; ADT, antidepressant trial/therapy; AU, Australia; CA, Canada; CGI-S, Clinical Global Impression – Severity; Dur., duration; DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revised; EU, Europe; HAM-D-17, Hamilton rating scale for depression; MADRS, Montgomery Åsberg Depression Rating Scale; MD, major depression; MDD, major depressive disorder; MDE, major depressive episode; N, patient population size; n, number of remitted patients; RDC, Research Diagnostic Criteria; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant, US, United States; ZA, South Africa.

*Two identical studies reported in one article.
Time of death was simulated at model entry on the basis of general mortality statistics in Turkey taken from the World Health Organization (http://apps.who.int/whosis/database/life_tables/life_tables.cfm, accessed April 2010). The risk of suicide during major depressive episodes was based on information from Bernal et al. [36] who found a 3.91-fold (95% confidence interval 2.74–5.6) higher suicide risk for patients with MDD relative to the general population. According to Devrimci-Ozguven and Seyil [37], suicide risk in the general Turkish population was 112.11 per 100,000 inhabitants in 2001. This gives an estimated suicide attempt probability (rate) of 0.4% (0.044) per year for patients with MDD in Turkey. A constant hazard rate was assumed for determining the probability of attempting suicide, based on the patient's actual depressive episode duration. The model imputed an 8.3% probability that an attempted suicide resulted in death, which was based on Bilici et al. [38] who found 2.6 completed suicides out of 31.5 attempts per 100,000 person-years.

Utility Weights
No specific utility values for Turkish patients with MDD were available at the time of this research. A Swedish study by Sobocki et al. [10,16], however, reported utility values for patients with moderate depression (Clinical Global Impression – Severity score of 4) and remission, based on a naturalistic longitudinal observational study of 447 patients in primary care. Utilities were derived from patients’ EuroQol five-dimensional questionnaire health status questionnaires, applying UK national tariff in the absence of specific social tariffs for Sweden at the time of their study [10]. Utility values were applied to the depressive episode and remission health states in the model. It was assumed that the quality of life of patients in the between episodes health state resembled the quality of life in the general population [39] (see also Table 2).

Cost Data
Drug prices were extracted from the Turkish Ministry of Health, Directorate of Pharmaceuticals Official Web Page on February 2, 2010 [40], and adjusted for mandatory discounts to obtain reimbursed prices. It was assumed that all patients would incur the same background antidepressant cost during the entire model horizon. Background antidepressant costs were calculated as a weighted average cost of the antidepressants used at randomization in the clinical trials of aripiprazole augmentation [22–24]. Augmentation treatment costs were incurred during depressive episodes. Health care resource use during a depressive episode is generally higher than during remission periods. Turkish-specific data about resource use is available only for patients with MDD in general without stratification between both states [41]. A Swedish study, however, has shown that patients in a depressive episode and a remission episode have 1.24 and 0.8 times the medical resource consumption of an average patient with MDD, respectively [16]. The number of psychiatrist visits and the average number of hospitalization days were obtained from Karamustafalioglu et al. [41] and multiplied with corresponding Turkish unit costs [42] to obtain health care resource costs for an average patient with MDD. The ratios from Sobocki et al. [16] were multiplied with this number to obtain depressive and remission cost estimates for Turkey. Costs during the between episodes state were assumed to reflect only the antidepressant use. The cost of suicide attempts was based on Karamustafalioglu et al. [41], including only the costs of care received. Total weekly costs per health state and adjunctive treatment are outlined in Table 2. Please note that remission cost and between episode cost are identical for all treatments because there is no differentiation in treatment costs opposed to the depressive episode phase. Costs and quality-adjusted life-years (QALYs) were discounted with 3.5% per annum.

Probabilistic Sensitivity Analysis
As with all health-economic models, the input parameters are subject to uncertainty. To describe the influence of the uncertainty in model parameters on the incremental model outcomes, a probabilistic sensitivity analysis (PSA) was conducted. The joint uncertainty surrounding incremental costs and effects following from the uncertainty around all model input parameters was addressed by generating 1000 random sets of input parameters, using probability distributions for each parameter that reflect its

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Fig. 3 – Time until next episode per number of prior episodes. Data points are from Solomon et al. [35]. Lines represent Weibul survival curve fits.
uncertainty. Model outputs were subsequently recorded. The 95% confidence intervals for each parameter are presented in Table 2. A major source of the uncertainty in incremental model outcomes is the uncertainty surrounding the difference in remission rates between adjunctive aripiprazole and adjunctive quetiapine and olanzapine as represented by their respective odds ratios. The uncertainty surrounding these inputs was based on the joint posterior distribution obtained from the indirect comparison. The corresponding uncertainty surrounding the remission rates of adjunctive quetiapine and olanzapine is presented in Table 2. Utility values were varied by using beta distributions, and the costs inputs were varied by using gamma distributions. A scatter plot was generated, showing the 1000 combinations of incremental costs and effects generated from the PSA. Corresponding cost-effectiveness acceptability curves were drawn, showing the probability that adjunctive aripiprazole augmentation is cost-effective compared with adjunctive quetiapine and olanzapine at various levels of willingness to pay (WTP) per QALY gained.

Results

Base Case

Results for the comparison of adjunctive aripiprazole with adjunctive quetiapine and adjunctive olanzapine are presented in Table 4. Costs are presented in Turkish lira (TL), which has a purchasing power parity of 1.0 compared with the US dollar (2010 figure, http://stats.oecd.org). The average life expectancy of a patient in the model is 31.6 years, with an average starting age of 45 years, implying that patients, on average, live to be 76 years old. The minor difference in life expectancy between the different treatment sequences is explained by a difference in completed suicides. Aripiprazole augmentation has fewer attempted and thereby fewer committed suicides compared with adjunctive quetiapine and olanzapine. This difference is explained by the lesser time spent in major depressive episodes with aripiprazole, during which patients are exposed to the risk of suicide (11 and 7 weeks less compared with quetiapine and olanzapine augmentation). Because of a higher remission rate with adjunctive aripiprazole, on average, patients treated with adjunctive aripiprazole spend less time in the depression state than do those treated with adjunctive quetiapine and olanzapine. Because the depressive episode is associated with diminished quality of life, patients starting with aripiprazole augmentation gain 0.054 and 0.039 QALYs on average than do those starting with quetiapine augmentation and olanzapine augmentation, respectively.

A major cost driver in the model is hospitalization costs, which comprise approximately 71% of total costs. Because patients in the depressive episode are more likely to be hospitalized and patients in the aripiprazole augmentation arm spend less time in that episode, hospitalization costs are saved compared with quetiapine augmentation (712 TL) and olanzapine augmentation (554 TL). A similar pattern is observed for psychiatrist visit costs (savings of 240 TL and 174 TL, respectively). Augmentation costs for the aripiprazole augmentation arm are higher than for quetiapine and olanzapine augmentation arms due to the higher drug acquisition costs for aripiprazole. Because of the savings on hospitalization and psychiatrist visit costs, however, aripiprazole augmentation saves, on average, 593 TL and 485 TL per patient than do quetiapine and olanzapine augmentation, respectively.

Dominance of aripiprazole augmentation was independent of the remission probability value for prior responders.

Table 4 – Health economic model results.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Aripiprazole augmentation</th>
<th>Quetiapine augmentation</th>
<th>Olanzapine-augmentation</th>
<th>Difference aripiprazole with quetiapine</th>
<th>Difference aripiprazole with olanzapine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life expectancy (y)</td>
<td>31.62</td>
<td>31.61</td>
<td>31.62</td>
<td>0.012</td>
<td>0.010</td>
</tr>
<tr>
<td>Time spent in depressive episodes (y)</td>
<td>9.44</td>
<td>9.64</td>
<td>9.58</td>
<td>−0.21</td>
<td>−0.14</td>
</tr>
<tr>
<td>Time spent in remission (y)</td>
<td>8.88</td>
<td>8.81</td>
<td>8.83</td>
<td>0.08</td>
<td>0.06</td>
</tr>
<tr>
<td>Time spent between episodes (y)</td>
<td>13.31</td>
<td>13.17</td>
<td>13.22</td>
<td>0.14</td>
<td>0.09</td>
</tr>
<tr>
<td>Percentage of patients attempting suicide</td>
<td>4.30</td>
<td>4.30</td>
<td>4.33</td>
<td>−0.01</td>
<td>−0.04</td>
</tr>
<tr>
<td>Percentage of patients completing suicide</td>
<td>0.30</td>
<td>0.33</td>
<td>0.34</td>
<td>−0.03</td>
<td>−0.04</td>
</tr>
<tr>
<td>QALYs (discounted)</td>
<td>13.62</td>
<td>13.56</td>
<td>13.58</td>
<td>0.054 (−0.038 to 0.213)</td>
<td>0.039 (−0.048 to 0.171)</td>
</tr>
<tr>
<td>Total costs ($/TL)</td>
<td>84,800</td>
<td>85,393</td>
<td>85,285</td>
<td>−593 (−3780 to 619)</td>
<td>−485 (−3132 to 757)</td>
</tr>
<tr>
<td>Antidepressant</td>
<td>3,840</td>
<td>3,839</td>
<td>3,841</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Augmentation</td>
<td>580</td>
<td>222</td>
<td>367</td>
<td>359</td>
<td>212</td>
</tr>
<tr>
<td>Psychiatrist visits</td>
<td>20,265</td>
<td>20,504</td>
<td>20,439</td>
<td>−240</td>
<td>−174</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>60,086</td>
<td>60,798</td>
<td>60,604</td>
<td>−712</td>
<td>−554</td>
</tr>
<tr>
<td>Suicide</td>
<td>29</td>
<td>29</td>
<td>29</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

QALY, quality-adjusted life-years; TL, Turkish lira.

*Please note that the purchasing power parity between Turkey and the United States is 1.0 (2010 figure, http://stats.oecd.org). Numbers in the table may not add up because of rounding errors.
Probabilistic Sensitivity Analysis

The scatter plot illustrated in Figure 4 represents the joint uncertainty surrounding incremental QALYs and incremental costs for both comparisons, based on 1000 Monte Carlo simulations. This is a result of the combined uncertainty surrounding all model parameters, including efficacy, quality of life, and cost inputs. Scatter points in the lower right quadrant represent instances in which aripiprazole augmentation improves quality of life and saves costs. This occurs in 85% and 86% of the cases for the comparison with quetiapine and olanzapine, respectively. The top left quadrant represents instances in which aripiprazole augmentation decreases quality of life and is more expensive. This occurs in 13% of the cases for both comparisons. The uncertainty surrounding results is mainly driven by the uncertainty around the remission probabilities for aripiprazole, quetiapine, and olanzapine augmentation.

Figure 5 presents the cost-effectiveness acceptability curves for the three treatment strategies showing the probability that each of them is cost-effective at various WTP thresholds. If one is interested only in health gains at no additional costs, aripiprazole augmentation has a probability of being cost-effective of 74%, whereas quetiapine and olanzapine each have a probability of 13% to be cost-effective. The acceptability lines remain relatively stable at various WTP levels. This is because only 2% of the scatter points for both comparisons are in the northeast and southwest quadrants, where an actual trade-off is made between costs and health gains.
incremental QALYs and incremental costs. As such, at WTP values ranging from 0 to 100,000 TL per QALY gained, the probability that aripiprazole is cost-effective among all three strategies varies between 74% and 75%.

Discussion

The objective of this research was to assess the cost-effectiveness of adjunctive aripiprazole treatment compared with adjunctive quetiapine and olanzapine in treatment in patients with MDD who had an insufficient response to antidepressant treatment in Turkey.

A patient-level simulation model was developed simulating the chronic and deteriorating course of the disease, as well as the sequence of treatment steps.

The model results showed that adjunctive aripiprazole is dominant compared with quetiapine and olanzapine. Patients starting with adjunctive aripiprazole spend 11 weeks and 7 weeks less in major depressive episodes than do patients starting with quetiapine and olanzapine, respectively. This translates to 0.054 and 0.039 QALY gains, respectively. Despite the higher drug acquisition cost, on average, the total cost for a patient starting with adjunctive aripiprazole is 593 TL and 485 TL less than those for a patient starting with adjunctive quetiapine and olanzapine, respectively. These savings are mainly explained by less hospitalization costs and fewer psychiatrist visits. The increased remission rate of adjunctive aripiprazole compared with quetiapine and olanzapine underlies the health gains and cost savings. The difference in remission rates between adjunctive aripiprazole, quetiapine, and olanzapine were obtained from an indirect comparison, combining the available evidence reported in the published literature by using 10 identified PCSs [22–31]. The influence of the uncertainty in the estimated differences in remission rates between the three adjunctive atypical antipsychotic treatments resulting from this indirect comparison was incorporated in a PSA. In addition, the uncertainty surrounding the other model inputs was incorporated in the PSA. The probability that adjunctive aripiprazole would be cost-effective among the three strategies ranged between 74% and 75% for WTP values between 0 TL and 100,000 TL per QALY gained.

To ensure that the model resembled Turkish clinical practice, resource use, unit cost, and mortality data were based on Turkish sources. To the best of our knowledge, no lifetime cost-effectiveness models in this indication have been published. Previously published cost-effectiveness models in MDD are limited. Only two lifetime horizon models have been published so far, both by Revicki et al. in 1995 and 1997 [43,44]. Economic guidelines by the National Institute for Health and Clinical Excellence [45] and Drummond and Jefferson [46] recommend a lifetime model horizon in the case of chronic illnesses such as depression. Also, the deteriorating course of depression should ideally be captured in the model. This is, however, possible only when the model is able to take the history of a patient into account. Until now, the only published model in which patients could experience multiple recurrences was a Markov model published by Sobocki et al. in 2006 [47].

A recent cost-effectiveness analysis in the United States also compared adjunctive aripiprazole, quetiapine, and olanzapine for acute treatment of MDD [21]. It was concluded that the cost per additional responder was lower for aripiprazole than for quetiapine or olanzapine/fluoxetine [21]. In the present analysis, aripiprazole is not only more effective but also cost saving. This difference is likely due to the short horizon length of the US analysis (6 weeks only) that cannot capture future cost savings.

Limitations

Because of a lack of Turkish evidence, Swedish-specific utility values were used. Different utility values, however, would impact only the magnitude of QALYs gained. As such, the base-case and PSA conclusions are independent of country-specific utilities. Clinical trial data were largely based on US populations; however, it is not expected that these would be different in a Turkish population.

The only data available for adjunctive aripiprazole in MDD consider the treatment of acute depressive episodes for a duration of 6 weeks. This is also the case for the comparators. The impact on relapse prevention of adjunctive aripiprazole is yet to be investigated. As such, the differences in outcomes between the three adjunctive atypical antipsychotic treatments are solely based on the differences observed during the acute depressive episode treatment. When additional data about relapse prevention become available, however, the model can be adjusted to incorporate this.

The relative efficacies of the three treatments are major drivers of uncertainty in the incremental outcomes. Preferably, these should be based on direct comparable data; however, such trials have not been conducted so far, which is why an indirect comparison of PCSs was used for this research. If direct comparable evidence would become available in the future, this can be imputed in the model.

Adverse events are not included in the model. This is because augmentation treatment is given only for a short period of time and most important side effects for these drugs will develop when taking the drug for a longer duration. Aripiprazole augmentation treatment is associated with akathisia. This side effect was not implemented in the model. This is because akathisia will be present only in the 6 weeks of treatment and will therefore have a minor influence on the total model outcomes. However, side effects commonly associated with quetiapine and olanzapine (such as extrapyramidal syndrome, weight gain, and diabetes) are also not incorporated. Because of the relatively short amount of time in which the drugs are given in the model and the already high disability of the disease itself, it is expected that incorporating side effects would have only a minor influence on model outcomes and omitting them is expected to be a conservative approach for aripiprazole.

Costs associated with monitoring tests during atypical antipsychotic use were not incorporated. Because monitoring would be required for all three atypical augmentation regimes compared, this would not affect incremental costs.

When implementing long-term data on the effects of aripiprazole augmentation in the model, side effects should be taken into account. In the long run, the chronic use of antipsychotic medication is a risk factor for developing diabetes mellitus type 2 and extensive weight gain. There is evidence, however, substantiating that aripiprazole is an exception and will have less impact on these side effects than, for example, quetiapine or olanzapine.

Indirect costs associated with work productivity losses, which are not uncommon in patients with MDD, are not considered by the Turkish payer, which is why these were excluded from the analysis. Including indirect costs, however, would likely result in further cost savings for aripiprazole augmentation. Less time is spent in depressive episodes with this treatment, during which patients have a higher chance of incurring work productivity losses than during phases of remission.

Conclusions

The cost-effectiveness model described here showed that aripiprazole augmentation dominates quetiapine augmentation and olanzapine augmentation. Taking into account the uncertainty in all model input parameters, the probability that adjunctive aripiprazole would be cost-effective among the three strategies
ranged between 74% and 75% for WTP values between 0 TL and 100,000 TL per QALY gained. Although atypical antipsychotics have the same reimbursement status for augmentation treatment of MDD in Turkey, these economic findings may help inform clinicians in their choice of antipsychotic augmentation.

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