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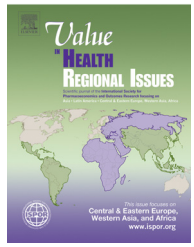

ECONOMIC EVALUATION

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.

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].

Conflicts of interest: The authors have indicated that they have no conflicts of interest with regard to the content of this article.

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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 [16].

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 used 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/2011/020592s060s061,021086s038s039lbl.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 adjunctive aripiprazole compared with adjunctive 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.

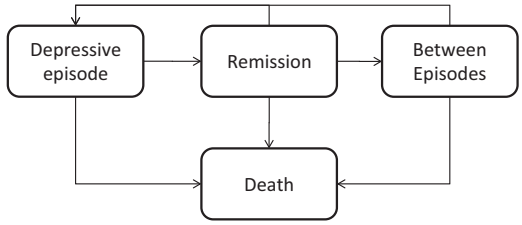

Fig. 1 – Schematic model representation.

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.

Characteristic	Mean ± SD	Distribution	Parameter (s)
Age (y)	45.1 ± 4.4	Normal	$\mu = 45.1$, $\sigma = 4.4$
Gender (% males)	68.0	Bernoulli	$P = 0.68$
Number of prior episodes	6 ± 5.2	Geometric	$P = 0.17$