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Artículo original

Cost-effectiveness evaluation of olanzapine/fluoxetine 6/25 mg combination in the management of depressive episodes associated with bipolar disorders

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ABSTRACT

Bipolar disorder (BD) is a chronic mental disorder characterized by the presence of a major depressive episode in patients with a histor y of at least one episode of mania or hypomania. According to the diagnostic and statistical manual of mental disorders fourth edition (DSM-IV), BD is divided into type I and type II bipolar disorder, cyclothymia and bipolar disorder not other wise specified. This affective disorder is one of the most frequently found mental diseases worldwide. Its high prevalence constitutes a real public health problem due to the high risk of suicide (17-19%) during the depressive phase which is associated with high morbidity. This suicide rate is 15 to 20 times greater than the rates reported for the general population. Different pharmacological alternatives have been evaluated for the treatment of the acute depressive phase of type I bipolar disorder, including lamotrigina (LTG), litheum (LI), quetiapine (QTP) and a fixed combination of 6mg of olanzapine plus 25mg of fluoxetine (OFC, 6/25mg). Although most of these alternatives are the treatment of choice for a majority of published treatment guidelines, some have not been approved by Mexican Ministr y of Health (SSA) in Mexico or by the Food and Drug Administration (FDA) in the United States. The present analysis was performed with the aim of evaluating the cost-effectiveness relationship of OFC compared to LTG, LI and QTP in the management of depressive episodes associated with type I bipolar disorder. For this analysis, a decision-tree chart was designed based on the international treatment algorithms. For the economic analysis, we made an adaptation of the CANMAT treatment guidelines algorithm that proposes OFC or LTG, LI and QTP monotherapies as first line treatments. The efficacy of each treatment was obtained from the values reported by Vieta 2010 in a meta-analysis of randomized, double-blind, placebo controlled trials that used a ≥ 50% reduction on the Montgomer y-Asberg Depression Rating Scale (MADRS) compared to baseline scores as primar y outcome. The results suggest that the use of OFC in one capsule is a cost-effective alternative when compared to LTG and LI and a dominant alternative when compared to QTP during a 38-week period if hospitalization costs are not considered (first treatment strategy). Patients not showing an adequate treatment response were placed in the second treatment strategy group, which includes hospitalization costs during 17 days in the 46-week period. For the second strategy, OFC proved to be a dominant option when compared to LTG, LI and QTP.

Key word: bipolar disorders, depressive episodes, olanzapine/fluoxetine, cost-effectiveness.

Evaluación del costo-efectividad de la combinación de olanzapina / fluoxetina 6/25 mg en el manejo de los episodios depresivos asociados con el trastorno bipolar

RESUMEN

El trastorno bipolar (TB) es un trastorno mental intermitente y crónico, caracterizado por presencia de un episodio de depresión mayor en pacientes con antecedentes de al menos un episodio de manía o hipomanía. De acuerdo con el manual

diagnóstico y estadístico de los trastornos mentales - 4ta edición (DSM-IV), se subdivide en trastorno bipolar tipo I, tipo II, ciclotimía y trastornos no específicados. El trastorno bipolar es uno de los trastornos mentales crónicos más frecuentes en el mundo. Su prevalencia lo convierte en un problema de gran importancia relacionado con la salud pública, siendo durante la fase depresiva cuando la morbilidad aumenta, debido al riesgo de suicidio (17 a 19%), que es 15 a 20 veces mayor que el reportado en población general. Diferentes alternativas cuya eficacia se ha evaluado para el tratamiento de la fase aguda de episodios depresivos asociados con el trastorno bipolar tipo I incluyen: lamotrigina (LMO), litio (LIT), quetiapina (QTP) y la combinación de olanzapina/fluoxetina (6/25mg [OFC]). Sin embargo, a pesar de ser alternativas de primera elección en la mayoría de las guías de tratamiento publicadas, algunos de estos medicamentos no han sido aprobados por la Secretaría de Salud en México o la FDA en Estados Unidos de Norteamérica, para el tratamiento del TB. Con base en lo anterior, se llevó a cabo el presente análisis. *Objetivo:* evaluar la relación costo-efectividad del uso de la combinación olanzapina/fluoxetina 6/25 mg en el manejo de la fase depresiva del trastorno bipolar tipo I *vs* litio, lamotrigina y quetiapina. *Material y métodos:* para realizar el análisis se construyó un árbol de decisión a partir de los algoritmos internacionales de tratamiento publicados. Para el análisis económico, se realizó una adaptación del algoritmo de la guía canadiense (CANMAT), que propone monoterapia con lamotrigina, la combinación fija de olanzapina/fluoxetina (6/25mg), o litio como alternativas de primera elección, incluyendo quetiapina. La efectividad de las alternativas de tratamiento se obtuvo del meta-análisis de Vieta 2010, que incluye estudios clínicos aleatorios, de diseño doble ciego, controlados con placebo, que evaluaron la efectividad de los comparadores incluidos en el presente trabajo, tomando en cuenta una reducción ≥ 50% en la escala de depresión de Montgomery Asberg (MADRS) con respecto a la clasificación basal. En los diferentes análisis realizados se demuestra que la combinación fija olanzapina/fluoxetina constituye una alternativa costo-efectiva *vs* el uso de litio, lamotrigina y quetiapina en el tratamiento de la fase depresiva del trastorno bipolar, sin considerar costos de hospitalización en un horizonte temporal de 38 semanas. Los resultados del presente estudio sugieren que el uso de la combinación fija de olanzapina/fluoxetina en una cápsula, representa una alternativa costo-efectiva con respecto a litio y lamotrigina, y una alternativa dominante con respecto a quetiapina, durante un periodo de tratamiento de 38 semanas, ésto sin considerar los costos por hospitalización. En aquellos casos, en los que los pacientes no respondieron de manera adecuada al segundo esquema de tratamiento, haciéndose necesaria la hospitalización, se observa que el uso de la combinación fija de olanzapina/fluoxetina es una alternativa dominante con respecto al uso de quetiapina, litio y lamotrigina (menor costo y mayor efectividad), en un periodo de tratamiento de 46 semanas.

Palabras clave: trastorno bipolar, epsodios depresivos, olanzapina/fluoxetina, costo-efectividad.

Bipolar disorder (BD), is a chronic mental disorder characterized by the presence of a major depressive episode in patients with history of at least one episode of mania or hypomania[1].

According to the American Psychiatric Association (APA), BD is classified as an affective disorder. These disorders are characterized by a deregulation of mood, behavior and affection. According to DSM-IV criteria, BD is divided into type I and type II bipolar disorder, cyclothymia and bipolar disorder not otherwise specified[2].

BD is one of the most frequent mental disorders worl dwide, with a growing prevalence that represents an important problem for public health systems. The estimated prevalence of type I and type II bipolar disorder in US adults ranges from 0.4 to 3.7%[3,4]. In Mexico, a national epidemiologic survey for mental disorders was performed in the year 2003. This survey reported a prevalence of 1.3 ± 0.2% for BD, with a higher prevalence for the male population (1.6 ± 0.3%) than for the female population (1.1 ± 0.2%)[5]. The age of BD onset varies, ranging from childhood to adolescence and adulthood, and this disease may last for lifetime[6-8].

The etiology of BD is unknown; however, it is believed that BD could have a genetic basis as a consequence of multiple biologic abnormalities influenced by environmental factors. Given these characteristics, diagnosis is extraordinarily complicated: a person with BD may be evaluated by three to four physicians and spend around eight years searching the most adequate treatment before proper diagnosis is made[9].

Bipolar spectrum disorders implicate the presence (or history) of manic, hypomanic or mixed episodes, usually accompanied by the presence (or history) of episodes of major depression[10]. Although BD is an episodic disorder, its frequency and severity may increase with time. Morbidity increases during the depressive phase, representing a suicide risk of 17-19% which is 15-20 times greater than the risk reported for the general population[11-17]. BD is a debilitating disorder that requires maintenance therapy to reduce the functional disability and socioeconomic burden caused by recurrent mood episodes. Evidence indicates that

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the lifetime costs of BD exceed those of major depression. Although both manic and depressive symptoms and their treatment contribute to these costs, depressive symptomatology is associated with higher economic burden, greater disability and substantially higher mortality rates than mania[18].

The DSM-IV criteria establish the same symptoms for depressive disorder and depression associated with BD. However, there are significant differences in the presentation and development of both disorders[2]. Compared to unipolar depression, bipolar depression is associated to more emotional instability, longer psychomotor delay and longer periods of sleep during the depressive episode. There is also a smaller weight loss for bipolar depression patients compared to unipolar depression patients[10].

The presence of depressive episodes may have negative long-term implications and consequences. In the first place, once exposed to a major depressive episode, the patient's emotional stability and capability to successfully handle stressful situations are reduced[19]. The second hypothesis is the possibly permanent modification of functional structures in the brain that are involved in the pathophysiology of depressive episodes. The idea of a modification on neuroplasticity with the subsequent effect on adaptive capability to stressful situations is a hypothesis that should be taken into account, although there is not enough empirical data to support it. However, it is an observational fact that the presence of a depressive episode on a patient's background increases the risk of general morbidity and mortality due to suicidal conduct[19].

The main types of medication used to manage BD symptomatology include mood stabilizers, antipsychotics and antidepressants. Approximately 82% of BD patients receive medication, with an average of 2.3 to 3.87 agents per patient[1,2]. The use of antipsychotics and benzodiazepines is of particular importance since they are present in up to 80% of treatment strategies[3].

Currently there are several therapeutic options available (mood stabilizers, antipsychotics and antidepressants); however, an adequate treatment selection is not easy to tailor for each particular patient considering that the strategy must include acute phase and maintenance treatments[20]. Herein lies the need of performing a full economic evaluation that may provide useful information to define safe/effective treatment strategies and provide health care providers with more elements of certainty for their decision making process. Consequently, health institutions and patients may avoid unnecessary costs.

Treatment options that have shown efficacy in the treatment of depressive episodes associated with type I bipolar disorder include lamotrigine (LGT), litheum (LI), quetiapine (QTP) and the fixed combination of 6 mg of olanzapine plus 25mg of fluoxetine (OFC, 6/25mg). Although these alternatives are mentioned as first line treatments for bipolar depression in most treatment guidelines, some of them have not been approved for use in Mexico by the Ministry of Health (SS) or in the United States by the Food and Drug Administration (FDA)[21].

METHODS

With the information and background mentioned above, the objective of the present study was to evaluate the use of OFC 6/25mg as treatment of choice compared to LTG 200mg, LI 1200mg and QTP 300mg for the management of depressive episodes associated with type I bipolar depression from the Public Health Care Perspective. A cost-effectiveness economic evaluation of OFC 6/25mg for the management of patients with depressive episodes associated with BD was performed.

Competing strategies

The following agents were compared:

I. Fixed combination of olanzapine and fluoxetine (OFC 6/25 mg): oral administration of 6 mg of olanzapine and 25 mg of fluoxetine, fixed combination in one capsule per day.

II. Lamotrigine (LTG): oral administration of a daily dosage of 25 mg per day. After 2 weeks of treatment patients doubled the dose to 50 mg per day. In the fourth week, oral administration patients titrated their dose to 100 mg per day. In the following weeks patients increased the dose to 200 mg per day.

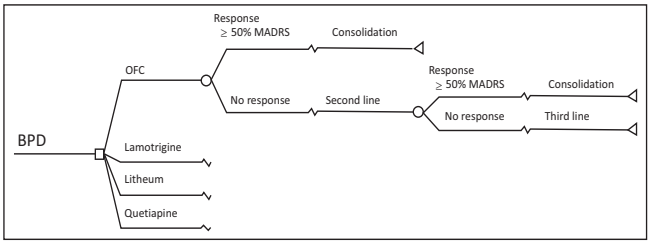
III. Quetiapine (QTP): oral administration of 150 mg twice daily.

IV. Litheum (LI): oral administration of 1200 mg per day.

Model description

The model used for the present analysis was a decision tree (figure 1) a tool that shows and displays the calculation of the possible consequences within the evaluated temporal horizon. Following recommendations of the guidelines for conducting economic evaluations of health interventions in Mexico no discount rate was considered as the time horizon considered was 38 and 46 weeks (less than a year)[22]. Considering that hospitalization

stay costs have a great impact on total cost, two horizons were considered: a 38-week analysis that does not account for hospitalization costs, and a 46-week horizon that considers 17 day hospitalization stay as a possible consequence. Figure 1 outlines the possible outcomes regarded in the model. The analysis was conducted in Excel®.



Response: A ≥50% reduction in the Montgomery-Asperg rating scale (MADRS). DB: Bipolar Disorder; OFC: Olanzapine/fluoxetine Combination (6/25 mg). The model describes the possible outcomes for OFC, however, all other treatments have the same pathway.

Figure 1. Structure of the analyzed decision tree.

An adaptation of the Canadian guidelines (CANMAT) was performed and validated by a group of Mexican experts in order to reflect daily practice[23-25]. These guidelines recommend the use of OFC, LTG, LI or QTP as first line treatments. If an adequate response is not achieved, the guidelines recommend titration of the initial monotherapy with a Selective Serotonin Reuptake Inhibitor (SSRI) plus LI. If an adequate treatment response is still not achieved with the second option, it is recommended as third line treatment the subsequent hospitalization of the patient with an olanzapine +imipramine and LI regimen with or without electroconvulsive therapy (ECT). Regarding the time required to define if treatment response is adequate or not, *Brown, et al* (2006); established that a 7-week period is appropriate for the acute phase evaluation. In case of achieving an adequate treatment response (≥ 50% reduction on MADRS score), treatment must be continued for an additional 24-week period. In case of inadequate treatment response, the health care provider must proceed to the subsequent treatment steps of the algorithm[17].

The treatment success or failure was evaluated within the 7 weeks of treatment for the 38-week and within 8 weeks for the 46-week period. The odds of treatment success or failure were determined by the effectiveness of the selected therapy. An adequate response was defined as a ≥ 50% reduction on MADRS score (compared with baseline values). The model consists of 6 possible outcomes in which the patient may have an adequate treatment response (≥ 50% reduction on MADRS score) or not, according to published articles. Those patients not achieving an adequate response with first line treatments required a second line that was given for 8 weeks (awaiting response) and a 24-week maintenance period. Finally if the patient did not respond to treatment, hospitalization stay for a period of 17 days as third line treatment option in the 46-week scenario was considered. Due to the lack of evidence of efficacy on combined treatment strategies, this model assumes that if the patient did not have an adequate response, the first line effectiveness is the same when combined with another agent as second-line alternative.

Efficacy data

In order to obtain all data and bibliographic material related to this study, a literature search was performed using international scientific and medical databases and journals: Imbiomed, PubMed, the Cochrane Library, Economic Evaluations Database, ISPOR, The New England Journal of Medicine, Doyma and Net Society at Psychiatrist, ScienceDirect. The mentioned databases and journals were the main source of information to identify general epidemiological, clinical and therapeutic aspects related to bipolar depression. The title/*items* and keywords used were: «*bipolar depression, bipolar disorder, lamotrigine, olanzapine, fluoxetine, imipramine, quetiapine, litheum, guideline, algorithm, cost, cost-effectiveness, effectiveness, MADRS, depression, economic, double blind, trial, placebo-controlled*».

The efficacy of the analyzed treatment alternatives was obtained from a meta-analysis by Vieta *et al* [21]. This analysis included randomized, placebo controlled clinical trials that evaluated the efficacy of several treatment options of bipolar depression (including the options used for the present analysis: OFC, LTG, LI and QTP).

This meta-analysis[21] included 9 clinical trials that studied the treatment of the depressive phase associated with BD with OFC, LTG, LI or QTP. The primary efficacy outcome for these clinical trials was a ≥ 50% reduction

Table 1. Relative Risk (RR) of getting a ≥50% on MADRS score compared to placebo.

Comparator	=50% MADRS	
	RR	P
Olanzapine – fluoxetine	1.84 (1.44-2.36)	<0.0001
Litheum	1.12 (0.92-1.37)	0.271
Lamotrigine	1.14 (1.00-1.30)	0.043
Quetiapine	1.37 (1.24-1.51)	<0.0001
Placebo	1.00	-

RR: Relative Risk. MADRS: Montgomery-Åsberg Depression Rating Scale (MADRS)

in MADRS score, compared with baseline values. Using meta-analysis tools, the heterogeneity of the studies was evaluated and a Relative Risk (RR) was calculated along with the proportion of patients that would attain a ≥ 50% reduction on MADRS score, compared to baseline (table 1).

The RR of attaining treatment response compared to placebo shows significant improvement for OFC ($p<0.0001$), QTP ($p<0.0001$) and LTG ($p=0.043$), but not for LI ($p=0.271$). However, it must be noted that RR is a relative measure of the effect size that indicates the number of times a treatment tends to achieve a ≥ 50% reduction in MADRS score, compared to placebo[26]. Consequently, it is necessary to consider the rate of response reported for placebo as the point of reference for the rates of treatment response correspondent to the analyzed agents and thus, such data may serve as input for the decision tree. For example, if the placebo controlled group presents a 44.2% treatment response rate, then the adjusted treatment response rate for LTG (RR = 1.14) is 50.3% (table 2).

Table 2. Treatment-response rates (≥50% MADRS).

Comparator	Response rate
6 mg olanzapine+ 25 mg fluoxetine fixed combination (OFC)	81.20%
Litheum (LI)[+]	49.40%
Lamotrigine (LTG)[+]	50.30%
Quetiapine (QTP)[+]	60.50%
Placebo^	44.20%

^Taken from *Vieta E. et al, 2010.* [+]Estimated values from the data published by *Vieta E. et al, 2010.*

A bivariate analysis of sensitivity was performed (cost-effectiveness). The first consisted of a randomized modification of the efficacy measures that were used in the decision tree and the costs of treatment failure to generate 1,000 hypothetical possible outcomes. A normal distribution and a proportional standard deviation of 10% for the efficacy of each comparator were assumed along with a Weibull distribution to simulate treatment failure associated costs (for both second and third line options). Additionally, the simulation considered two scenarios to evaluate the decision tree: up to 38 weeks of treatment with the second line option, and up to 46 weeks of treatment with the third line option.

Response: a ≥ 50% reduction in the Montgomery-Asperg rating scale (MADRS). DB: bipolar disorder; OFC: olanzapine/fluoxetine combination (6/25 mg). The model describes the possible outcomes for OFC, however, all other treatments have the same pathway.

Resources and associated costs

Total medical costs during the acute phase of the depressive episode associated with BD are expressed in 2012 Mexican currency (pesos) and were obtained from the relationship of resource input and services required for the completion of the treatment algorithm. The total cost is integrated by the costs generated from the algorithm: diagnosis, acute phase management (7 weeks) with each treatment from the first choice alternatives, maintenance phase (24 weeks) for each selected treatment, and the costs of hospitalization. Treatment and procedure costs were obtained from a Governmental Electronic System for Purchases (Compranet)[27] and current prices were obtained from the «Instituto Mexicano del Seguro Social (IMSS)» under a Medical Services Coordination Agreement [28], respectively. The costs are grouped according to the different stages of the algorithm: diagnosis, acute phase treatment (7 weeks), maintenance treatment (24 weeks); each per alternative and hospitalization costs (table 3).

Table 3. Direct costs of management of acute depression associated to type i bipolar disorder.

Comparator	1st-line treatment		2nd-line treatment		3rd-line treatment		Total
	Acute Phase 7 Weeks	Maintenance 24 Weeks	Acute Phase 8 Weeks	Maintenance 24 Weeks	Acute Phase 8 Weeks	Maintenance 24 Weeks	
Lamotrigine	$959	$2,914	$1,149	$3,575	$86,710	$3,919	$90,629
Olanzapine/ fluoxetine	$2,965	$9,772	$3,150	$10,433			
Litheum	$954	$2,874	$1,149	$3,575			
Quetiapine	$2,968	$9,779	$3,152	$10,440			

The cost of each stage is described as follows: (i) *Diagnosis:* costs include specialist visit, laboratory tests (blood count, blood chemistry, lipid profile and thyroid profile) and other tests (electroencephalogram and cranial CT); (ii) *First line treatment:* once diagnosis is made, a treatment of choice is selected (OFC, LTG, LI or QTP) and used for a period of 7 weeks as established by *Brown et al*[17] and following the established treatment algorithm. During the acute phase, patients are evaluated after 7 weeks of therapy. If there is an adequate response, a maintenance phase for an additional 24-week period is established; (iii) *Second line treatment:* in case of not achieving an adequate response (≥ 50% reduction on MADRS scores, compared to baseline scores), an antipsychotic pluss an antidepressant or a mood stabilizer is added for an additional 7-week period and a subsequent 24-week maintenance phase in case an adequate response is achieved; (iv) *Third line treatment (hospitalization costs*

only applicable for the 46-week analysis): those patients shown to be refractory to different treatment options are remitted to a hospital where treatment includes olanzapine+imipramine and LI with or without ECT for an additional 8-week period. ECT is not included in the cost analysis because no published information regarding ECT could be found. Finally, cost estimations for each agent do not reflect any relationship with medication effectiveness, since they constitute prescription costs for acute and maintenance phases only.

RESULTS

Two scenarios were analyzed for the expected cost of medical attention: the first scenario evaluated the effectiveness of initial monotherapy, and if first line treatment failed, a second line treatment was considered adding the associated costs without considering hospitalization costs. The second scenario evaluated first and second line options and included the possibility of third line treatment option in case the second line treatment did not provide an adequate clinical response. This second scenario considered a temporal horizon of 46 weeks including 3 weeks hospitalization costs (table 4).

Table 4. Expected treatment costs for each patient, including both scenarios

Comparator	Scenarios	
	38 weeks (Not including hospitalization costs)	46 weeks (Including hospitalization costs)
Olanzapina/fluoxetina (OFC)	$16,536	$19,359
Litheum (LI)	$7,847	$30,093
Lamotrigina (LTG)	$7,856	$29,332
Quetiapina (QTP)	$17,337	$29,857

The results of the cost-effectiveness analysis are presented in table 5. In the 38-week horizon (not considering hospitalization costs), the fixed combination of olanzapine+fluoxetine (OFC) in one capsule was a cost-effective alternative compared to LI and LTG and a dominant choice compared to QTP (e.g. more effective and less costly).

Table 5. Expected costs per patient treated for all treatments evaluated.

Comparator	Expected Cost		Outcome =50% MADRS		Incremental cost-effectiveness quotient	
	38 weeks	46 weeks	RR	Rate of treatment response	38 weeks	46 weeks
Olanzapine-fluoxetine	$16,536	$19,359	1.84	81.2%	-	-
Litheum	$7,847	$30,093	1.12	49.4%	$8,689	Dominated
Lamotrigine	$7,856	$29,332	1.14	50.3%	$ 8,680	Dominated
Quetiapine	$17,337	$29,857	1.37	60.5%	Dominated	Dominated

Dominated: The strategy is more expensive and less effective compared to OFC in one capsule.

Dominated: the strategy is more expensive and less effective compared to OFC in one capsule.

On the other hand, when third line treatment is considered (including hospitalization costs) for non-responders to second line treatment, OFC proved to be a dominant alternative (less expensive, more effective), compared to LI, LTG and QTP during the 46-week period.

As shown in the previous graph, the use of OFC in one capsule for the management of bipolar depression is a dominant alternative (less expensive, more effective), compared to quetiapine and is cost-effective compared to LI and LTG. These results correspond to the first scenario (38-week horizon) where hospitalization costs are not included.

When hospitalization costs were included, those patients without an adequate response to the second line treatment showed dominant results for OFC in one capsule for the management of bipolar depression (less expensive, more effective), compared to QTP, LTG, and LI within a 46-week horizon.

Sensitivity analysis

Figure 2 shows the results for the sensitivity analysis when a 38-week horizon is considered, OFC demonstrated to be a cost-effective option compared to LTG with an incremental cost of $7,001 (CI 95%: $6,911-$7,091) and also provided increased effectiveness of 0.310 (CI 95%: 0.308-0.312). Subsequently, when OFC was compared to LI, OFC represented a cost-effective alternative with an incremental cost of $7,227 (CI 95%: $7,134-$7,321), and increased effectiveness of 0.317 (CI 95%: 0.315-0.319). The results of the analysis also suggest that the use of OFC compared to QTP represent a dominant choice: savings of $8,756 (CI 95%: $8,881-$8,632) with an increased response rate of 0.209 (CI 95%: 0.207-0.211) figure 2.

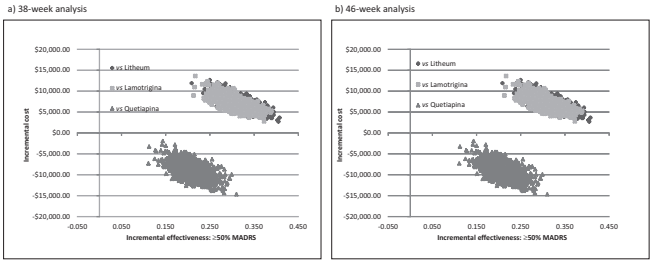


Figure 2. Sensitivity analysis of OFC compared to LTG, LI and QTP.

Deterministic and probabilistic analyses confirmed that OFC is a cost saving therapy for the treatment of bipolar depression compared to LTG, LI and QTP with per-patient savings of $ 25,177 (CI 95%: $ 25,477-$ 24,878); $ 22,116 (CI 95%:$ 22,428-$ 21,805), and $ 24,280 (CI 95%: $ 24,502-$ 24,057), respectively.

The acceptability curve is derived from this incremental cost-effectiveness probabilistic analysis and represents the proportion of paired variables (effectiveness and incremental effectiveness) threshold (willingness to pay). The curve shows the probability that a cost-effective therapy may be considered under certain defined limits. The decision of considering or not OFC treatment as a cost-effective alternative will be determined by the quantity expressed by the expected cost-effectiveness quotient. Such value must be compared to the Gross Domestic Product (GDP) *per capita* to be considered as highly cost-effective (<GDP *per capita*), cost-effective (between 1 and 3 times the GDP *per capita*) or not cost-effective (>3 GDP *per capita*) (figure 3, 4 and 5).

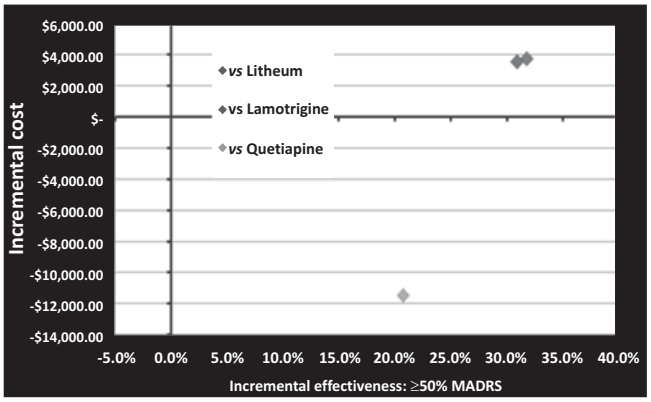


Figure 3. Incremental cost-effectiveness for ofc compared to li, ltg and qtp, considering second line treatment.

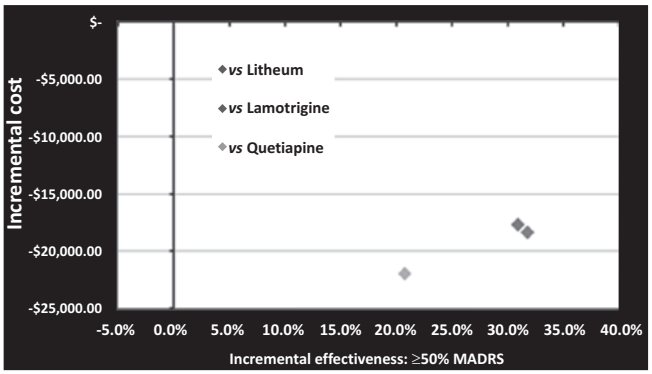


Figure 4. Incremental cost-effectiveness for ofc compared to li, ltg and qtp, considering third line treatment.

The probability of OFC of being cost-effective for the 38-week scenario with a threshold of $30,000.00 MXN (under $8,960.00 U.S dollars GDP *per capita*)[29] compared to LTG, LI and QTP is 0.864 (CI 95%, 0.843-0.885), 0.918 (CI 95%, 0.901-0.935) and cost-saving, respectively. When the 46-week horizon (third line treatment option) is included, OFC is cost-saving compared to the other treatment options.

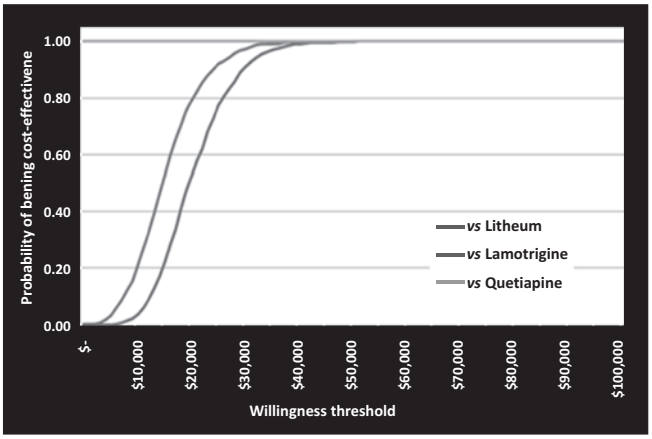


Figure 5. Acceptability curve (38-week horizon).

DISCUSSION

There are no published registries about the prevalence of clinically diagnosed BD in Mexican population. Therefore, the demand of health services for this particular disease is not defined with precision. However, from the available information published by *Weissman* [3]*, Caraveo* [30] *and Medina-Mora* [5] about the prevalence of depression and the results from a diagnostic algorithm developed by an expert panel for this particular analysis, a prevalence for type I bipolar disorder in the general population may be estimated between 0.4% and 1.6%. These rates are consistent with the results from a National Epidemiologic Psychiatric Survey applied in Mexico during the year 2002-2003, which reported a prevalence of 1.3 ± 0.2% for type I bipolar disorder[5].

Although episodes of mania and hypomania define BD, depressive episodes represent a major complication for BD treatment due to the longer duration, higher frequency and patient predisposition for these episodes. Above all, it is during the depressive episode when BD patients show higher suicide rate[31].

The recommended therapeutic strategies for BD must be selected according to the severity, clinical presentation and evolution of each patient, always having remission of the depressive episode as the main goal of treatment. CANMAT guidelines [23-25] recommend the use of QTP monotherapy as first line treatment during the acute phase of bipolar depression and most treatment guidelines do not recommend the use of antidepressant monotherapy due to the risk of inducing mania in BD patients[22].

LTG is also recommended as first line treatment option for the treatment of bipolar depression by the American Psychiatric Association (APA 2007),[32] Oxford University (DPUO 2009)[33]. The Expert Consensus Guideline Series (ECGS 2004)[34] and the Canadian

Network for Mood and Anxiety Treatment Guidelines for the Management of Patients with Bipolar Disorder (CANMAT 2005)[23-25]. Nevertheless LTG is not approved by the Mexican Health Ministry (Secretaría de Salud) nor the FDA in the treatment of the acute phase of bipolar depression. On the other hand, OFC was the first treatment approved by the FDA in the US[21] for the management of acute bipolar depression and up to date it remains as the only alternative for the management of depressive episodes associated with type-I BD, approved by both the Mexican Health Ministry (Secretaría de Salud) and the FDA.

OFC has shown higher efficacy compared to LTG, LI and QTP for the treatment of bipolar depression in different studies that used MADRS scores as primary efficacy outcome measure[21.]

Another important issue to be considered is the efficacy of OFC on the incidence of suicidal thoughts and ideation. Patients treated up to seven weeks with OFC showed a rate of 0.5% for suicidal and self-injurious behavior compared to 3.4% for those treated with LTG (p=0.037). On the other hand, LI reduces the suicide rate in 29%, resulting in a rate of 10.8 attempts for every 1000 patients per year and a 0.7% suicide average per year. The available information about the efficacy of QTP in preventing or increasing suicidal ideation is contradictory. This aspect is a top priority when considering a treatment strategy for this group of patients, which present 20-fold higher risk, compared to the general population[11-17].

In addition to the proven efficacy of OFC in the management of depressive episodes associated with type-I BD (compared to LTG, LI and QTP), the results of this analysis must also be considered from an institutional perspective. At an institutional level, the use of this combination leads to significant savings. Such factors are fundamental for the decision-making process regarding the prescription of OFC as a treatment of choice.

In the present study, OFC in one capsule demonstrated higher cost-effectiveness in the hypothetical evaluated population compared to LTG and LI and was completely dominant when compared to QTP in the 38-week horizon, not considering hospitalization costs. When a third line treatment was considered hospitalization stay was considered in this scenario OFC in one capsule was a dominant alternative (less expensive, more effective), compared to LTG, LI and QTP during a 46-week horizon.

One of the study limitations is that due to the lack of evidence on combined treatment strategies, this model assumes that if the patient did not have an adequate response, the first line effectiveness is the same when combined with another agent as second-line alternative. Other limitation of the study is that quality of life and safety was not evaluated in the model. A longer time-horizon beyond the one considered in the present analysis was not possible to realize, due to the fact that there are no clinical trials that evaluate long-term efficacy outcomes and tolerability for olanzapine and fluoxetine in the treatment of BD.

Corey-Lisle et al (2003); published the results of an article that evaluated the economic impact of the augmentation of olanzapine with fluoxetine for the treatment of depression and treatment-resistance. In this study, a significant reduction of the weekly treatment cost was proven. The number of patient medical visits was reduced in 60.3%, while the number of hospitalization days was reduced in 29.3%. Similarly, medical costs were reduced in 20.3% after treatment initiation with OFC. These data prove that OFC is efficacious in terms of cost and medical resource reduction[35-39].

The combination of both agents in one single capsule presents different advantages from medical, clinical and economical points of view. A single daily dose provides better treatment adherence, comfort and simplicity for the patient, which means easier posology and from the economical point of view, as proven in the present analysis, OFC significantly reduces therapy costs in both ambulatory and hospitalized patients.

The results of the present study outline the efficacy and cost-effectiveness of the olanzapine/fluoxetine 6/25mg combination in one capsule for the treatment of depressive episodes associated with bipolar disorders. Results of the present study suggest that OFC might have clinical and economical advantages over its comparators.

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