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Artículo de revisión

A systematic review of combined olanzapine-fluoxetine as therapy for bipolar depression in adult and adolescent patients

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ABSTRACT

Objective: this systematic review assessed the safety and efficacy of olanzapine-fluoxetine combination (OFC) for treatment of bipolar depression, specifically in studies of 8 to 12 weeks duration in adults (primary objective) and adolescents (secondary objective). *Materials and methods:* trials were identified using MEDLINE, EMBASE, Cochrane Library, Web of Knowledge, LILACS, WHOLIS, NEURO, Latindex, and DIALNET (2000 – July 2014). English and Spanish free-text and MeSH terms were used. Searches were supplemented with identified trials (Clinical Trials.gov) and congress abstracts. Evidence from randomized controlled trials (RCTs), nonrandomized trials, and meta-analyses were considered. *Results:* nine publications reporting 5 RCTs (6 publications), 1 nonrandomized trial, and 2 meta-analyses were included. One RCT was conducted in adolescents and one RCT was conducted in a Latin American population. Studies enrolled from 34 to 833 participants, were conducted for 7 to 8 weeks and up to 6 months, and varied in methodological quality and reporting. The efficacy of OFC (depression rating scales, response and remission rates) was greater compared with olanzapine monotherapy, lamotrigine monotherapy, and placebo. OFC was well tolerated in adults and adolescents. However, there was a greater frequency of weight gain, somnolence, nausea, diarrhea, and elevated metabolic parameters in participants receiving OFC versus active comparators or placebo. *Conclusions:* this systematic review presents findings that OFC is effective and generally well tolerated for acute treatment of bipolar depression in adults and adolescents. Existing evidence suggests that the efficacy and safety profile of OFC in patients from Latin America is not different to Caucasian populations.

Key words: bipolar disorder, bipolar depression, olanzapine-fluoxetine combination, symbyax.

Revisión sistemática de la combinación olanzapina-fluoxetina como tratamiento de la depresión bipolar en adolescentes y adultos

RESUMEN

Objetivo: se evaluó la seguridad y eficacia de la combinación olanzapina- fluoxetina (COF) para tratamiento de la depresión bipolar, en especial en estudios clínicos con duración de 8 a 12 semanas, en adultos y adolescentes. *Material y métodos:* los estudios se identificaron en las bases de datos *MEDLINE, EMBASE, Cochrane Library, Web of Knowledge, LILACS, WHOLIS, NEURO, Latindex y DIALNET* (del 2000 a julio 2014). Se utilizaron términos de búsqueda en inglés, español y vocabulario MeSH (Medical subjet headings). Se complementaron con ensayos clínicos identificados *(Clinical Trials.gov)* y resúmenes de congresos. Se consideró la evidencia de estudios controlados aleatorizados (ECA), estudios no aleatorizados y metanálisis. *Resultados:* se recuperaron 9 publicaciones/estudios, incluyendo: 5 ECA (6 publicaciones), un estudio no aleatorizado y 2 metanálisis. Un ECA se llevó a cabo en adolescentes y otro en una población Latinoameéricana. Los estudios enrolaron desde 34 hasta 833 pacientes, con una duración de 7 a 8

semanas y hasta 6 meses, difirieron en cuanto a la calidad metodológica y del reporte. La eficacia de COF (medida con reducción del puntaje de escalas y porcentajes de respuesta y remisión) fue mayor en comparación con la monoterapia con olanzapina, lamotrigina y/o placebo. El tratamiento con COF fue bien tolerado en adultos y adolescentes. Sin embargo, hubo una mayor frecuencia de ganancia de peso, somnolencia, náusea, diarrea y elevados parámetros metabólicos en los pacientes que recibieron COF *vs* los comparadores activos o el placebo. *Conclusiones:* esta revisión muestra que el tratamiento agudo con COF es efectivo y por lo general bien tolerado en adultos y adolescentes con depresión bipolar. La evidencia existente sugiere la ausencia de diferencias en el perfil de eficacia y seguridad de COF entre los pacientes de América Latina y poblaciones caucásicas.

Key words: trastorno bipolar, depresión bipolar, combinación olanzapina-fluoxetina, symbyax.

Bipolar disorder, which is characterized by recurrent episodes of (hypo)mania that alternate or overlap with episodes of depression[1-4], is listed by the World Health Organization as the 12th most disabling condition worldwide, affecting an estimated 22.2 million individuals of all ages[5]. In Latin American countries such as Mexico and Colombia, the lifetime prevalence of bipolar spectrum disorders (1.9% and 2.6%, respectively) is similar to the prevalence in the rest of the world (2.4%)[6]. Most patients with bipolar disorder spend much more time in depressive episodes, including subsyndromal depressive symptoms, than in (hypo)manic or mixed episodes[7]. However, early and adequate treatment can provide not only complete control of symptoms but also improved prognosis[8]. Significantly, patients diagnosed with bipolar disorder during childhood or adolescence are at greater risk for poorer psychiatric, psychosocial, and health-related outcomes, including suicide, than patients diagnosed later in life[9].

The overall treatment recommendations for the management of bipolar depression (BD) differ across published guidelines and principally focus on the adult population[10-16]. In general, the recommended first-line therapies comprise a mood stabilizer (eg, lithium, lamotrigine) or an atypical antipsychotic (eg, olanzapine, quetiapine) as monotherapy or in combination with a selective serotonin reuptake inhibitor[10-14]. In Latin America, recommendations for the treatment of BD tend to mirror guidelines from the United States (US) and Canada, and specifically focus on US Food and Drug Administration (FDA) approved treatment options[17]. In practice, however, clinical treatment strategies in Latin America often diverge from these published guidelines, with clinicians modifying recommended treatments on a case-by-case basis[18]. A recent Latin American study assessing the preferences of clinicians for treatment of bipolar disorder demonstrated that 27.0% choose lamotrigine, 20.5% quetiapine, 19.7% olanzapine-fluoxetine combination (OFC), 14.7% lithium carbonate, and 11.7% *"an undefined antidepressant"*[18]. Despite the relatively high preference for OFC in Latin America, there exists a critical need to more fully understand the role of the antidepressant effect of fluoxetine in BD and the relatively low risk of treatment-emergent mania and rapid cycling, when associated with OFC therapy, particularly where adolescents are concerned[11,19,20].

In 2003, OFC was approved in the US for adults for the acute treatment of depressive episodes associated with bipolar I disorder[21,22]. The antidepressant efficacy of OFC in adults is demonstrated in a dose range of olanzapine 6 to 12 mg/day and fluoxetine 25 to 50 mg/day[23]. In addition, OFC has been approved in the US for use in children and adolescents 10 to 17 years of age for the acute treatment of depressive episodes associated with bipolar disorder. The treatment recommendations for children and adolescents (10 to 17 years of age) are that OFC should be administered once daily, with a recommended target dose in a dose range of olanzapine 3 to 12 mg/day and fluoxetine 25 to 50 mg/day[23]. The clinical trial outcomes within the adolescent study population have not been systematically reviewed to date.

The aim of this systematic review was to retrieve and summarize clinical studies on the use of OFC as therapy for treatment of BD, with a primary emphasis on controlled studies of 8 to 12 weeks duration. This therapeutic window was chosen as it typically represents the minimum time necessary to achieve either response or remission, and for effectively evaluating the risk of treatment-emergent mania[24]. The secondary objective of this review was to examine the evidence for the use of OFC in the treatment of BD in adolescent populations.

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MATERIALS AND METHODS

Search strategy/Study eligibility criteria

One person (not an author) conducted the literature search and screened the titles and abstracts of all publications retrieved using predefined eligibility criteria. MEDLINE via Pubmed, EMBASE, Cochrane Library, Web of Knowledge, Literatura Latinoamericana y del Caribe en Ciencias de la Salud (LILACS), Sistema de Información de la Biblioteca de la OMS (WHOLIS), Artículos sobre neurociencias (NEURO), Latindex, and Difusión de Alertas en la Red (DIALNET) were searched on 9 July 2014. Where possible, search limits included studies conducted in humans and those published between 2000 and 2014. Free-text terms *(English and Spanish)* and medical subject headings (MeSH) were used to search for (combined olanzapine-fluoxetine OR olanzapine-fluoxetine combination OR olanzapine and fluoxetine OR fluoxetine plus olanzapine OR Symbyax) AND (bipolar depression OR depressive disorder-bipolar). The search was supplemented with reference lists of identified trials databases *(Clinical Trials.gov)* and evidence from relevant congress abstracts, including the American Psychiatric Association, the International Society for Bipolar Disorders, and the European College of Neuropsychopharmacology; all of which were electronically searched for bipolar depression AND (olanzapine AND fluoxetine), published between 2000 and 2014. Searches were conducted with truncation symbols and Boolean operators (AND, OR) as needed. The full text of publications identified were rescreened using the same criteria, and reference lists of systematic reviews and other relevant publications were hand screened to identify additional publications for inclusion. All authors reviewed and approved the publications identified for inclusion in the systematic review. One person (not an author) extracted all data from the included publications. Data collected included publication type and year, study design, indication, participant characteristics, and treatment received.

Included studies were those that assessed the use of OFC in any dosing regimen in male or female participants of any age for treatment of BD. Noncomparative studies of OFC and studies comparing OFC with any other active comparator (eg, monotherapy) or placebo were included. For the primary objective, evidence from meta-analyses, systematic reviews, randomized controlled trials (RCTs) and nonrandomized clinical trials were considered for inclusion. For the secondary objective, evidence from observational studies, case studies, and case series were also considered. Evidence from retrospective (post hoc) studies, narrative reviews, letters, editorials, and commentaries were excluded from both objectives. To maximize retrieval of published articles, there were no restrictions on publication type or language.

Efficacy outcome measures

The efficacy outcome measures included in this review were improvement in depressive symptoms measured by objective scales including the Montgomery-Åsberg Depression Rating Scale (MADRS), Hamilton Anxiety Rating Scale (HAM-A), Hamilton Depression Rating Scales (HAM-D17/17R and HAM-D28), 11-item Young Mania Rating Scale (YMRS), Clinical Global Impressions-Severity of Illness (CGI-S), Clinical Global Impressions-Severity of Illness Bipolar version (CGI-BP-S), Clinical Global Impressions Bipolar version-Depressed (CGI-BP-D), Clinical Global Impressions Bipolar version-Mania (CGI-BP-Mania), the Medical Outcomes Study-12 and 36-item short-form health surveys (SF-12 and SF-36), Quality of Life In Depression Scale (QLDS), Children's Depression Rating Scale (CDRS-R), and Quality of Life Questionnaire for Children and Adolescents (KID-KINDL was used for children aged 6 to 11 years, KIDDO-KINDL for adolescents aged 12 to 17 years, and KINDL for parents of patients aged 6 to 17 years). Response and remission rates were also included when recorded. For response and remission rates, the definition used in each study was used.

Safety and tolerability measures

Safety and tolerability measures considered in this review included the type, incidence, and severity of treatment-emergent adverse events, including weight gain, changes in metabolic parameters (eg, plasma lipids and plasma glucose concentrations), hypercholesterolemia, nausea and diarrhea, somnolence, dry mouth, and sedation; rate of treatment-emergent mania; rate of discontinuation due to adverse events; and rate of discontinuation for any reason.

Assessment of data quality

Assessment of the methodological quality of included trials was based on the modified CONSORT statement checklist for bipolar disorder[25]. Items considered in the assessment of quality included the inclusion and exclusion criteria used, outcome measures and minimum differences, method of assignment of participants to treatment (randomization method and blinding procedure), sample size, demographics, clinical characteristics of the study population, the inclusion of

controls, adverse event reporting, and the quality of statistical analyses[25].

Assessment of the methodological quality of included meta-analyses was based on the PRISMA statement guidelines for meta-analyses and systematic reviews[26]. Items considered in this assessment included the quality of the included studies, the principal measures of effect, the method of combining results (statistical testing and confidence intervals), how statistical heterogeneity was assessed, and the assessment of publication bias[26].

RESULTS

Literature search output

A total of 634 potential publications or trials were retrieved from the literature search of MEDLINE via Pubmed, EMBASE, Cochrane Library, Web of Knowledge, LILACS, WHOLIS, NEURO, Latindex, DIALNET, ClinicalTrials.gov, and conference abstracts and were screened for inclusion (figure 1). Three additional publications were identified by hand searching of the reference lists of relevant systematic reviews. After exclusion of duplicate publications between databases, the primary reason for exclusion was that studies were not conducted on OFC therapy. One additional unpublished study with results was identified in the Clinical Trials.gov database; no publications were excluded on the basis of non-English language. Overall, 9 publications or studies including 5 RCTs [6 publications], 1 nonrandomized trial, and 2 meta-analyses met the eligibility criteria for inclusion.

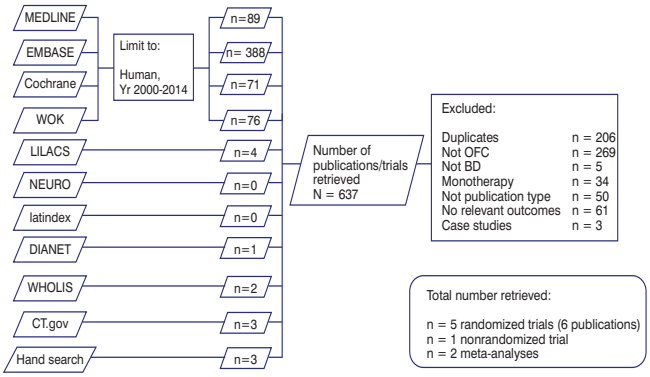

Figure 1. Systematic search and data extraction methodology output flowchart. Abbreviations: BD = bipolar depression, CT.gov = www.clinicaltrials.gov, DIALNET = Difusión de Alertas en la Red, EMBASE = Excerpta Medica database, OFC = olanzapine-fluoxetine combined, LILACS = Literatura Latinoamericana y del Caribe en Ciencias de la Salud, MEDLINE = Medical Literature Analysis and Retrieval System Online, NEURO = Artículos sobre neurociencias, RCT = randomized control trial, WOK = Web of Knowledge, WHOLIS = Sistema de Información de la Biblioteca de la OMS, Yr = year.

Overview of publication characteristics

The publications/studies included in this review fell into 1 of 3 categories: RCTs reporting the efficacy and/or safety of OFC (Table 1), nonrandomized trials (Table 1) supporting the efficacy of OFC (table 1), and meta-analyses supporting the efficacy of OFC. Most were full-text reports that included adult participants and reported on daily administration of OFC over a 7-, 8-, or 12-week period; 2 studies reported on administration of OFC at 6/25, 6/50, or 12/25-50 mg/day, 1 study reported on OFC at 6-12/25-50 mg/day, and 1 study reported on OFC at 5-15/10-40 mg/day. Only one unpublished RCT specific to adolescent participants was identified[27]. One study examined OFC dosing over an extended therapeutic window of 25 weeks[28] and one study was conducted in a Latin American population (Puerto Rico)[29].

Efficacy and safety of olanzapine-fluoxetine combination therapy in adults

A total of 4 RCTs (5 publications) and 1 nonrandomized trial were conducted to assess the efficacy, safety, and tolerability of OFC in adults (≥18 years of age) with bipolar I and II disorder over 8 to 25 weeks study duration (tables 1, 2, and 3):

1. Tohen, *et al*[22] conducted a double-blind, 8-week RCT in which adults with bipolar I depression were randomly assigned to receive placebo, olanzapine 5 to 20 mg/day, or OFC 6/25, 6/50, or 12/50 mg/day. Corya, *et al*[30] conducted a 6-month open-label extension of this study that reported on the efficacy and safety of longer-term treatment with OFC or olanzapine monotherapy. Participants who had been enrolled in the Tohen, *et al*[22] study and entered the open-label extension phase received 1 week of olanzapine monotherapy (5–20 mg/day). At all subsequent visits, participants could choose between olanzapine monotherapy (5–20 mg/day) or OFC (6/25, 6/50, or 12/50 mg/day). Three treatment groups (olanzapine, OFC, or switched) were defined retrospectively according to the medication course taken from Week 1.

2. Brown, *et al*[28, 31] conducted a double-blind, 25-week RCT in which adults with bipolar I depression were randomly assigned to receive OFC (6/25, 6/50, 12/25, or 12/50 mg/day) or lamotrigine titrated to 200 mg/day. Findings from the 7-week acute phase of this study were published separately[31].

3. Tamayo *et al*[29] conducted an open-label, 19-week RCT

in which adults with bipolar depressive episodes were randomly assigned to OFC (daily starting dosage, 12/25 mg/day [range, 6/25 to 12/50 mg]) or olanzapine monotherapy starting at 10 mg/day (range, 5 to 20 mg). In this study, participants were treated with OFC for 7 weeks (Study Phase 1;SP1) following an open-label design before randomization. Participants who responded to treatment with OFC (CGI-BP-D score ≤3, ≥50% reduction in MADRS) were then randomized to either olanzapine or continued with OFC (Study Phase 2; SP2).

4. Amsterdam, *et al*[32] conducted a preliminary, 8-week RCT in which adults with types I and II major depressive episode were randomly assigned to placebo, OFC (5-15/10-40 mg/day), fluoxetine monotherapy (10–30 mg/day), or olanzapine monotherapy (5-20 mg/day). Outcome measures included the *28-item* HAM-D with embedded HAM-D 17, atypical symptom profile 17-item HAM-D 17-R, MADRS and YMRS (table 1). However, this study principally focused on the relative rates of treatment-emergent manic symptoms associated with the treatment groups.

The studies identified varied in methodological quality and reporting (table 1), with studies ranging in size from 34 to 833 randomized participants (table 1). In all studies, the diagnosis of bipolar disorder was based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for bipolar type I or II disorder, with depression based on clinical assessment. The primary inclusion criteria for diagnosis of depression across studies was a required MADRS of ≥20 at screening visit (table 1)[22,28,29,31,32]. Brown *et al*[28, 31] also included CGI-S of ≥4 for depressive symptoms and Amsterdam, *et al*[32] included HAM-D17 ≥18 (table 1).

The discontinuation rate was reported in all studies (table 3). For acute treatment (7–12 weeks), the completion rates for the OFC study arm were similar to or greater than the completion rates for the other study arms, with overall completion rates ranging between 64 and 77% for participants randomized to OFC compared with 65.4% for lamotrigine, 31.6 and 48.4% for olanzapine, and 38.5% for placebo[22,29,31]. For longer duration treatment (25 weeks), the completion rates for the double-blind phase were similar for OFC (33.2%) and lamotrigine (33.7%).

Four of the 5 RCTs were double blinded; however, the method of randomization was rarely reported[22,29,31,32]. The main efficacy outcomes reported included changes in MADRS total scores, HAM-D and A (28, 17-item and 17-R), and YMRS scores. Secondary efficacy measures included CGI-BP-S and D, and quality of life measures, including change in the SF-36 and QLDS. The main safety outcome reported was the frequency of adverse events.

Severity of symptoms and response to treatment

In general, participants enrolled in most studies were primarily Caucasian (except for one study, which was conducted in Puerto Rico[29]), severely depressed, and had few manic symptoms (table 2). There was an overall and significant improvement in MADRS scores in participants on OFC treatment in the first 7 to 8 weeks of treatment, which were maintained for up to 6 months of treatment (table 2).

In the Tohen *et al*[22] study, participants in the OFC group had significantly greater improvement from baseline in MADRS compared with placebo ($P < 0.001$) and olanzapine monotherapy at 8 weeks (table 2). At Week 8, MADRS total scores were lower than at baseline by 11.9, 15.0, and 18.5 points in the placebo, olanzapine, and OFC groups, respectively (table 2). At Week 8, CGI-BP-S total scores were lower than at baseline by 1.2, 1.6, and 2.2 points in the placebo, olanzapine, and OFC groups, respectively (table 2). Remission criteria were met by 24.5% (87/355) of the placebo group, 32.8% (115/351) of the olanzapine group, and 48.8% (40/82) of the OFC group. For participants who started the extension phase[30] in remission (MADRS total score <12), MADRS total scores did not change significantly from baseline to endpoint for the OFC group (0.8 ± 1.25, $P = 0.5$), but increased slightly in those who switched treatment (2.3 ± 1.0, $P = 0.02$). For participants who started the extension phase in nonremission (MADRS total score ≥12), MADRS total scores decreased significantly from baseline in all groups (OFC: -5.7, $P = 0.001$; olanzapine: -11.6, $P = 0.004$; switched: -6.4, $P = 0.015$). The proportions of participants who entered the extension phase in nonremission and achieved remission during the study were similar between groups (OFC: 66.7%, olanzapine: 64.7%, switched: 62.5%).

In the Brown *et al*[28, 31] study, participants in the OFC group had significantly greater improvement from baseline in CGI-S and MADRS compared with lamotrigine at 7 weeks (table 2). However, response rates (≥50% reduction in MADRS) did not differ significantly between the groups (OFC, 68.8% *vs* lamotrigine, 59.7%; $P = 0.073$). Time to response (50% reduction in MADRS total score) was significantly shorter for the OFC group (median days [95% CI] = 17 [14 to 22]) compared with the lamotrigine group (23 [21 to 34]; $P = 0.010$) [31]. At 6 months, the changes from baseline in MADRS and CGI-S total scores remained significantly greater for the OFC group compared with the lamotrigine group (table 2).

Response rates did not significantly differ, when defined as ≥50% reduction in MADRS total score, between lamotrigine and OFC groups; however, when defined as a CGI-S≤3, the OFC group displayed a significantly higher rate of response over the 6-month study period (table 2). Remission rates did not significantly differ between lamotrigine and OFC groups (table 2).

In the Tamayo et al[29] study, participants treated

Table 1. Characteristics of Randomized and Nonrandomized Studies Assessing the Efficacy and/or Safety of Olanzapine-Fluoxetine Combination Therapy for Treatment of Bipolar Depression.

Study/Publication	Study Design (Duration) Treatment Groups	BD Diagnostic Inclusion Criteria	N[a] Mean Age, yr (SD) Female (%)	Primary Outcomes Reported
Tohen et al 2003[22] [Lilly Registry ID 3077a]	RCT, DB, PC (8 week) Groups: Placebo OLZ (5-20 mg/d) OFC (6/25, 6/50, 12/50 mg/d)	DSM-IV for bipolar disorder I, depressed. MADRS =20 At least 1 previous manic or mixed episode requiring treatment	N=833 Age=41.8 (12.5) 63.0%	Changes in MADRS total scores, YMRS, CGI-BP-S, HAM-A Adverse events
Corya 2006[30] [Lilly Registry ID 3077b]	NRT, OLE (6 month extension of Tohen et al 2003) Groups: SP1 (1 week): OLZ (5-20 mg/d) SP2 (6 months): OLZ (5-20 mg/d) or OFC (6/25, 6/50, or 12/50 mg/d)	DSM-IV for bipolar disorder type I. MADRS =20 At least 1 previous manic or mixed episode requiring treatment	Remitters (MADRS total score <12) N=198 Age=41.3 (12.6) 62.1% Nonremitters N=178 Age=44.2 (13.1) 65.2%	Changes in MADRS total scores, YMRS, CGI-BP-D Adverse events
Brown et al 2006, 2009[28, 31] [Lilly Registry ID 7980]	RCT, DB (25 week) RCT, DB (7 week) study arm Groups: LAM (200 mg/d) OFC (6/25, 6/50, 12/25, or 12/50 mg/d)	DSM-IV for bipolar disorder I, depressed. MADRS =20 CGI-S =4 At least 1 previous manic or mixed episode requiring treatment	N=410 Age=37.0 (11.1) 60.0%	Changes in MADRS total scores, YMRS, CGI-S Adverse events
Tamayo et al 2009[29] [Lilly Registry ID 9370]	RCT, OL (19 weeks) Groups: SP1 (7 weeks): OFC (12/25 mg/d) SP2 (12 weeks): OFC (12/25 mg/d) OLZ (10.8 mg/d)	DSM-IV for bipolar disorder type I or II, depressed. MADRS =20	N=114 Age=44.4 (11.9) 58.0%	Changes in MADRS total scores, YMRS, CGI-BP-D, CGI-BP-Mania Adverse events
Amsterdam et al 2005[32]	RCT, DB, PC (8 week) Groups: Placebo OFC (5-15/10-40 mg/d) OLZ (5-20 mg/d) FLUO (10-30 mg/d)	DSM-IV for bipolar disorder type I or II. DSM-IV for MDE. HAM-D 17 =18	N=34 Age=40.0 (11.0) 23.5%	17-item HAM-D, 17-item HAM-D "atypical" symptom profile (HAM-D 17-R), 28-item HAM-D, MADRS, YMRS
Unpublished ClinicalTrials.gov NCT00844857[27]	RCT, DB, PC (8 week) Groups: OFC (3/25 mg/d titrated up to 12/50 mg/d by the end of Week 2, with flexible dosing thereafter (6/25, 6/50, 12/25, or 12/50 mg/d).	DSM-IV-TR for bipolar disorder type I. KINDL - current episode depressed. CDRS-R =40 YMRS =15 YMRS item 1 =2	N=255 Age=14.7(2.3) 49.0%	Changes in CDRS-R Total Score, CGI-BP, KINDL, YMRS, BDRS Adverse events

[a] Number of participants.

Abbreviations: BD = Bipolar depression, BDRS = Bipolar Depression Rating Scale, CDRS-R = Children's Depression Rating Scale, CGI-BP = Clinical Global Impressions of Illness – Bipolar, CGI-BP-D = Clinical Global Impressions of Illness – Bipolar-Depressed, CGI-BP-S = Clinical Global Impressions-Severity of Illness – Bipolar, CGI-S = Clinical Global Impressions-Severity of Illness, DB = double-blind, d = day, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders 4th Edition, DSM-IV-TR = Diagnostic and Statistical Manual of Mental Disorders – Text revision 4th Edition, FLUO = fluoxetine, HAM-A = Hamilton Anxiety Rating Scale, HAM-D = Hamilton Depression Rating Scale, LAM = lamotrigine, MADRS = Montgomery-Asberg Depression Rating Scale, MDE = major depressive episode, NRT = nonrandomized trial, OFC = olanzapine-fluoxetine combination, OL = open-label, OLE = open-label extension, OLZ = olanzapine, PC = placebo-controlled, RCT = randomized controlled trial, SP1 = Study phase 1, SP2 = Study phase 2, YMRS = Young Mania Rating Scale, KINDL = Quality of Life Questionnaire for Children and Adolescents, yr = year.

Table 2. Efficacy Outcomes of Randomized and Nonrandomized Studies of Olanzapine-Fluoxetine Combination for Bipolar Depression.

Publication	Mean Baseline BD Status (SD)	Efficacy Outcomes (Mean[a] Change from Baseline in Total Scores)	Response Rate	Remission Rate	Relapse Rate
Tohen et al 2003[22] [Lilly Registry ID 3077a]		8 weeks	8 weeks	8 weeks	NR
	MADRS: Pla= 31.3 (5.7) OLZ= 32.6 (6.3) OFC= 30.8 (5.0)	MADRS:[b] Pla= -11.9 (-13.4 to -10.4) OLZ= -15.0 (-16.4 to -13.6), P=0.002 (vs Pla) OFC= -18.5 (-21.1 to -16.0) P<0.001 (vs Pla) P=0.01 (vs OLZ)	MADRS=50% Reduction Pla= 30.4% OLZ= 39.0%, P=0.02 (vs Pla) OFC= 56.1%, P<0.001 (vs Pla)	MADRS (Total) =12 Pla= 24.5% OLZ= 32.8%, P=0.02 (vs Pla) OFC= 48.8%, P<0.001 (vs Pla)	
	YMRS: Pla= 4.8 (4.6) OLZ= 5.0 (4.8) OFC= 5.0 (4.8)	YMRS: Pla= -0.1 (0.3) OLZ= -1.4 (0.3), P=0.002 (vs Pla) OFC= -1.9 (0.6), P=0.004 (vs Pla), P=0.38 (vs OLZ)			
	CGI-BP-S: Pla= 4.8 (0.8) OLZ= 4.9 (0.8) OFC= 4.8 (0.7)	CGI-BP-S: Pla= -1.2 (0.1) OLZ= -1.6 (0.1), P=0.004 (vs Pla) OFC= -2.2 (0.2), P<0.001 (vs Pla), P=0.01 (vs OLZ)			
	HAM-A: Pla= 16.7 (0.4) OLZ= 17.1 (0.4) OFC= 15.8 (1.0)	HAM-A: Pla= -3.5 (0.4) OLZ= -5.5 (0.4), P=0.002 (vs Pla) OFC= -7.0 (1.0) P<0.001 (vs Pla) P=0.16 (vs OLZ)			
Corya 2006[30] Lilly Registry ID 3077b]		6 months	6 months	6 months	6 months
	MADRS: [c]Remitters= 6.1 (4.0) [d]Nonremitters= 22.2 (7.5)	MADRS: Remitters (MADRS=12) OFC= 0.8 (1.2), P=0.50 (vs Baseline) OLZ= 0.3 (0.8), P=0.73 (vs Baseline) Switched= 2.3 (1.0), P=0.02 (vs Baseline)	NR	MADRS (Total) =12 OFC= 66.7% OLZ= 64.7% Switched= 62.5%	MADRS (Total) =12 (week 1) =16 (at any other time) OFC= 23.7% OLZ= 11.1% Switched= 50.0%
	YMRS: Remitters= 2.0 (2.6) Nonremitters= 4.2 (3.9)	Nonremitters OFC= -5.7 (1.7), P=0.001 (vs Baseline) OLZ= -11.6 (3.9), P=0.004 (vs Baseline) Switched= -6.4 (2.6), P=0.015 (vs Baseline)			
	CGI-BP: Remitters= 2.0 (1.0) Nonremitters= 4.0 (1.2)	YMRS: Remitters OFC= 1.3 (5.3) OLZ= 1.0 (5.4) Switched= 0.6 (4.9) Nonremitters OFC= 0.8 (5.5) NS OLZ= -0.7 (7.2) NS Switched= -1.1 (4.9), P=0.02 (vs Baseline)			
		CGI-BP: Remitters OFC= -0.3 (1.3) NS OLZ= 0.1 (1.1) NS Switched= 0.4 (1.4) NS Nonremitters OFC= -0.9 (1.4), P<0.001 (vs Baseline) OLZ= -0.9 (1.1), P=0.004 (vs Baseline) Switched= -0.6 (1.4), P=0.005 (vs Baseline)			

Table 2. Efficacy Outcomes of Randomized and Nonrandomized Studies of Olanzapine-Fluoxetine Combination for Bipolar Depression.

Publication	Mean Baseline BD Status (SD)	Efficacy Outcomes (Mean[a] Change from Baseline in Total Scores)	Response Rate	Remission Rate	Relapse Rate
Brown 2006, 2009[28, 31] [Lilly Registry ID 7980]		7 weeks	7 weeks	7 weeks	NR
	MADRS: LAM= 31.35 (5.23) OFC= 30.94 (5.42)	MADRS: LAM= -12.92 (0.50) OFC= -14.91 (0.49), P=0.002 (vs LAM)	MADRS=50% Reduction LAM= 59.7% OFC= 68.8%, P=0.073 (vs LAM)	MADRS (Total) =12 LAM= 49.2% OFC= 56.4%, P=0.158 (vs LAM)	
	YMRS: LAM= 4.64 (3.26) OFC= 5.21 (3.51)	YMRS: LAM= -0.94 (0.18) OFC= -1.68 (0.18), P=0.001 (vs LAM)		MADRS (Total) =7 LAM= 30.9% OFC= 37.1%, P=0.203 (vs LAM)	
	CGI-S: LAM= 4.63 (0.63) OFC= 4.63 (0.66)		CGI-S=3 LAM= 64.4% OFC= 71.8%, P=0.130 (vs LAM)		
		CGI-S: LAM= -1.18 (0.06) OFC= -1.43 (0.06), P=0.002 (vs LAM)	6 months	6 months	
		6 months	MADRS=50% Reduction LAM= 55.0% OFC= 64.4%, P=0.064 (vs LAM)	MADRS (Total) =12 LAM= 48.2% OFC= 55.9%, P=0.131 (vs LAM)	
		MADRS: LAM= -14.70 (0.52) OFC= -16.63 (0.52), P=0.005 (vs LAM)			
		YMRS: LAM= -1.05 (0.17) OFC= -1.92 (0.17), P<0.001 (vs LAM)	CGI-S=3 LAM= 58.1% OFC= 68.8%, P=0.036 (vs LAM)		
		CGI-S: LAM= -1.46 (0.07) OFC= -1.70 (0.07), P=0.008 (vs LAM)			
Tamayo 2009[29] [Lilly Registry ID 9370]		7 weeks	7 weeks	7 weeks	7 weeks
	MADRS: SP1 OFC= 32.3 (7.4) SP2 OFC= 32.1 (7.1) SP2 OLZ= 32.9 (7.7)	MADRS: SP1 OFC= -20.0 (10.0), P<0.001 (vs Baseline) SP2 OFC= -0.4 (7.55) SP2 OLZ= 8.2 (14.1), P<0.001 (vs Baseline)	MADRS=50% Reduction & CGI-S-D<3 SP1 OFC= 69.0% SP2 OFC= 31.3%, P<0.05 (vs OLZ) SP2 OLZ= 12.5%	MADRS (Total) =12 SP1 OFC= 58.7% SP2 OFC= 71.4%, P<0.01 (vs OLZ) SP2 OLZ= 39.6%	MADRS (Total) =20 SP2 OFC= 8.8%, P=0.014 (vs OLZ) SP2 OLZ= 28.1%
	CGI-BP-D: SP1 OFC= 4.5 (1.0) SP2 OFC= 4.5 (1.0) SP2 OLZ= 4.5 (1.2)	CGI-BP-D: SP1 OFC= -2.5 (1.4), P<0.001 (vs Baseline) SP2 OFC= NR SP2 OLZ= 1.3, P<0.001 (vs Baseline)			
		CGI-BP-Mania: SP1= 0.0 (0.4) SP2 OFC= NR SP2 OLZ= NR			
	CGI-BP-Mania: SP1= 1.2 (0.4) SP2 OFC= 1.1 (0.3) SP2 OLZ= 1.2 (0.4)				
Unpublished ClinicalTrials.gov NCT00844857[27]		8 weeks	8 weeks	8 weeks	NR
	CDRS-R: Pla= 53.7 (8.1) OFC= 54.6 (10.0)	CDRS-R: Pla= -23.4 (1.5) OFC= -28.4 (1.1), P=0.003 (vs Pla)	CDRS-R =50% Reduction, YMRS item 1 =2 Pla = 59.0% OFC= 78.0%, P=0.003 (vs Pla)	CDRS-R (total) =28, YMRS=8, CGI-S =3 Pla = 43.0% OFC= 59.0%, P=0.035 (vs Pla)	
	YMRS: Pla= 6.2 (3.9) OFC= 6.1 (3.8)	YMRS: Pla= -1.6 (0.6) OFC= -2.0 (0.5), P=0.527 (vs Pla)			
	CGI-BP: Pla= 4.3 (0.7) OFC= 4.4 (0.7)	CGI-BP: Pla= -1.8 (0.2) OFC= -2.2 (0.1), P=0.030 (vs Pla)			
	KINDL (Parent) Pla= 47.1 (16.7) OFC= 49.2 (20.1)				

Data shown as mean (SD), unless otherwise noted.
[a]Standard error (Least squares mean change) shown for NCT00844857
[b]Tohen MADRS (95% CI)
[c]Remitters – MADRS≤12
[d]Nonremitters – MADRS>12
Abbreviations: BD = bipolar depression, CDRS-R = Children's Depression Rating Scale, CGI-BP-S = Clinical Global Impressions-Severity of Illness – Bipolar, CGI-S = Clinical Global Impressions-Severity of Illness, HAM-A = Hamilton Anxiety Rating Scale, HAM- D = Hamilton Depression Rating Scale, KINDL = Quality of Life Questionnaire for Children and Adolescents, LAM = lamotrigrine, MADRS = Montgomery-Asberg Depression Rating Scale, NA = not applicable, NR = not reported, NS = not significant, OFC = olanzapine-fluoxetine combination, OLZ = olanzapine, Pla = placebo, SD = standard deviation, SP1 = Study phase 1, SP2 = Study phase 2, YMRS = Young Mania Rating Scale, vs = versus.

with OFC in the SP1 phase experienced a significant improvement from baseline in depressive symptoms (MADRS, CGI-BP-D) at 7 weeks (table 2). During this time, 69% of participants were considered to be responders (CGI-BP-D score ≤3, ≥50% reduction in MADRS) and 59% were considered to be in remission (MADRS ≤12). After randomization (SP2), significantly more patients in the OFC group than in the olanzapine group maintained a response (31.3% *vs* 12.5%) and remission (71.4% *vs* 39.6%). At 19 weeks, the mean change from baseline in MADRS total score was significantly decreased in the OFC group but increased in the olanzapine group (-0.4 ± 7.55 vs 8.2 ± 14.1; $p < 0.001$).

In the Amsterdam et al[32] study, there were significant reductions over time in mean HAM-D28 and MADRS scores for all treatment groups, including OFC ($p < 0.006$). However, absolute values for the change in scores were not reported.

Across all studies, the incidence of treatment-emergent mania was low and there were no significant increases in YMRS scores over time in any treatment group (Table 2). In the Tohen, *et al*[22] study, there were no differences in the incidence of treatment-emergent mania in the placebo (6.7%), OFC (6.4%), and olanzapine (5.7%) groups at 8 weeks. In addition, findings from the open-label extension phase of this study showed no statistically significant differences from baseline in YMRS scores at study endpoint in the OFC and olanzapine groups, irrespective of remission status at study entry (table 2). This suggests that the frequency of manic episodes in participants taking OFC or olanzapine monotherapy is equivalent during longer-term therapy. The proportions of participants who entered the extension phase in remission and experienced treatment-emergent mania during the study were 3.4% (OFC), 4.5% (olanzapine), and 9.7% (switched). The proportions of participants who entered the extension phase not in remission and experienced treatment-emergent mania were 6.4% (OFC), 3.8% (olanzapine), and 6.3% (switched). In the Brown et al[31] study, there was a significantly greater improvement in YMRS total scores from baseline in the OFC group compared with the lamotrigine group ($p = 0.001$) across the 7-week treatment period (table 2)[31].

Safety and tolerability measures

Overall, OFC was well tolerated with the most frequently reported adverse events being weight gain, somnolence, increased appetite, dry mouth, dizziness, sedation, headache, tremor, fatigue, and nausea (table 3). In general, after 8 weeks of therapy in the Tohen et al[22] study, the adverse event profile of participants in the OFC group was similar to those in the olanzapine group (table 3). However, the overall frequency of weight gain was increased for both olanzapine (17.3%) and OFC (17.4%) groups compared with placebo (2.7%), and there was a significantly greater frequency of nausea and diarrhea in the OFC group than in the olanzapine group (table 3). During longer-term treatment in the extension study[30], there was a greater frequency of weight gain, somnolence, and depression in the OFC group than in the olanzapine group (table 3). At 6 months, there was a significantly greater frequency of weight gain, somnolence, increased appetite, dry mouth, sedation, tremor, lethargy, disturbance in attention, and peripheral edema in the OFC group compared with the lamotrigine group in the Brown, *et al*[28] study. When reported, the emergence of extrapyramidal symptoms in the OFC group was low across all studies (table 3).

Overall, metabolic parameters were significantly elevated in the OFC group compared with placebo, olanzapine monotherapy, or lamotrigine after the first 7 to 8 weeks of treatment (table 3). The mean changes from baseline to endpoint for total cholesterol and nonfasting glucose levels were significantly greater in the OFC group compared with olanzapine monotherapy or placebo[31], and the mean changes from baseline to endpoint for cholesterol, triglycerides, and prolactin levels were significantly greater for OFC compared with lamotrigine[31]. Although abnormally high fasting glucose levels were reported in the OFC group after 7 weeks of treatment, there were no statistically significant differences in the levels of high fasting glucose levels between the OFC and lamotrigine groups[31]. Findings from longer-term studies[28, 30] demonstrated that the levels of cholesterol, trigylcerides, nonfasting glucose, and prolactin remained elevated in the OFC group after 6 months of treatment (table 3). Overall, the Latin American study population of Tamayo et al[29] showed significantly elevated levels of cholesterol, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase after 7 weeks of treatment (table 3).

Efficacy and safety of olanzapine-fluoxetine combination therapy in adolescents

One unpublished, 8-week, double-blind RCT was conducted to assess OFC for the treatment of major depressive episodes associated with bipolar I disorder in children and adolescents aged 10 to 17 years of age. Dosing was initiated at 3/25 mg/day and titrated up to 12/50 mg/day by the end of Week 2, with flexible dosing of 6/25, 6/50, 12/25, or 12/50 mg/day thereafter. A total of 68% of the OFC group versus 71%

Table 3. Safety Outcomes of Randomized and Nonrandomized Studies of Olanzapine-Fluoxetine Combination for Bipolar Depression.

Publication	Discontinuations (%)	Frequency of Treatment - Emergent Mania	Change in Metabolic Parameters (SD)	Extrapyramidal Symptoms (%)	Weight Gain	[a]Adverse Events (%)
Brown 2009[31] [Lilly Registry ID 7980]	Overall: LAM= 66.3% OFC= 66.8% AE: LAM= 13.2% OFC= 18.0%, P=0.221 (vs LAM)	LAM= 7.3% OFC= 5.0%, P=0.401 (vs LAM)	Fasting cholesterol (mg/dL): LAM= -6.0 (29.0) OFC= +13.9 (32.5), P<0.001 (vs LAM) Fasting triglycerides (mg/dL): LAM= -14.6 (112.8) OFC= +40.0 (114.6), P<0.001 (vs LAM) Fasting glucose (mg/dL): LAM= +0.4 (12.5) OFC= -0.8 (12.1), P=0.344 (vs LAM) Prolactin (ng/mL): LAM= 0.10 (11.0) OFC= +7.3 (21.0), P<0.001 (vs LAM)	NR	Mean (SD) kg LAM= -0.9 (4.3) OFC= 4.4 (5.2), P<0.001 (vs LAM)	OFC vs LAM, 6 months As in Brown 2006
Tamayo 2009 [29] [Lilly Registry ID 9370]	Overall: SP1: OFC= 29.2% SP2: OLZ= 31.6% OFC= 22.8% AE: SP1: OFC= 3.7% SP2: OLZ= 1.8% OFC= 5.3%	OLZ, 0% OFC, 1.8% NS	SP1: Fasting cholesterol (mg/dL): OFC= +14.4 (36.6), P<0.001 (vs Baseline) SP1: Fasting LDL cholesterol (mg/dL): OFC= +9.9 (31.6), P<0.001 (vs Baseline) SP1: Aspartate aminotransferase (U/L): OFC= +2.7 (7.7), P<0.001 (vs Baseline) SP1: Alanine aminotransferase (U/L): OFC= +5.2 (12.9), P<0.001 (vs Baseline) SP1: Alkaline phosphatase (U/L): OFC= +5.5 (12.7), P<0.001 (vs Baseline) SP2: Alkaline phosphatase (U/L): OLZ= +3.2 (11.7) OFC= +3.3 (14.6), P=0.009 (OLZ v OFC)	NR	Mean (SD) lb SP1: OFC = 4.8 (6.8), P<0.001 (vs Baseline) SP2: OLZ= +1.4 (8.3) SP2: OFC= 3.9 (7.9), NS	(7 weeks) SP1 Increased appetite 28 Increased weight 18.6 Somnolence 16.1 Anxiety 14.9 Tremor 12.4 Sedation 11.8 Dry mouth 11.2
Amsterdam 2005 [32]	Overall: Total = 41% AE: Total = 5.9% Lack of efficacy: Total = 23.5% Lost to follow-up: Total = 11.8%	FLUO= 35.3% OLZ= 12.5% OFC= 44.4% Pla= 33.3%, P=0.40	NR	NR	NR	NR
Unpublished ClinicalTrials.gov NCT00844857[27]	Overall: Pla = 29% OFC = 32% AE: Pla= 6.0% OFC= 14.0%, P= 0.06 (v Pla)	Pla = 0% OFC = 1.2%, P= 1.00 (vs Pla)	Fasting cholesterol (mmol/L): Pla= -0.11 (0.07) OFC= +0.42 (0.05), P<0.001 (vs Pla) Fasting triglycerides (mmol/L): Pla= -0.04 (0.08) OFC= +0.40 (0.06), P<0.001 (vs Pla) Fasting glucose (mmol/L): Pla= +0.03 (0.06) OFC= +0.03 (0.04), P=0.980 (vs Pla) Prolactin (?g/L): Pla= 0.7 (1.10) OFC= +8.7 (0.77), P<0.001 (vs Pla) Alanine aminotransferase (U/L): Pla= 0.46 (2.08) OFC= +7.63 (1.46), P=0.005 (vs Pla)	Parkinsonism: Pla= 1.3% OFC= 0.6%, NS Dyskinesia: Pla= 0% OFC= 0.6%, NS	Mean (SD) kg Pla= -+0.5 (0.3) OFC= +4.4 (0.2), P<0.001 (vs Pla)	8 weeks OFC vs P Weight increased 20.0 vs 1.2 Somnolence 15.9 vs 2.4 Increased appetite 16.5 vs 1.2 Dizziness 3.5 vs 3.5 Sedation 6.5 vs 0.0 Headache 15.9 vs 14.1 Tremor 8.8 vs 1.2 Fatigue 6.5 vs 7.1 Nausea 4.7 vs 12.9 Blood triglyceride increased 7.1 vs 2.4 Vomiting 6.5 vs 7.1 Nasopharyngitis 4.7 vs 9.4 Alanine transferase increased 3.5 vs 1.2 Epistaxis 3.5 vs 2.4

[a]Adverse events that occurred in at least 5% of participants.

Abbreviations: AE = adverse event, DB = double-blind, FLUO = fluoxetine, LAM = lamotrigine, LDL = Low Density Lipoprotein, NR = not reported, NS = not significant, OFC = olanzapine-fluoxetine combined, OLZ = olanzapine, Pla = placebo, SD = standard deviation, SP1 = study protocol 1, SP2 = study protocol 2.

of the placebo group completed the study. The most common reason for discontinuation in both groups was adverse events (14% OFC, 6% placebo) (table 3).

Severity of symptoms and response to treatment

Similar to the studies in adults, adolescent participants were primarily Caucasian, severely depressed, and had few manic symptoms (table 2). The mean baseline CDRS-R score was 54.6 for the OFC group and 53.7 for the placebo group (table 2).

Depressive symptoms improved in both the OFC and placebo groups at 8 weeks from baseline. However, there was a significantly greater improvement in depressive symptoms for participants in the OFC group (change in CDRS-R total score = -28.4) *vs* the placebo group (change in CDRS-R total score = -23.4, p = 0.003) (table 2). The improvement in CDRS-R total score in the OFC group was significantly greater than placebo at Week 1 (P = 0.02) and throughout the remaining 8 weeks (P values < 0.01). Significantly more participants in the OFC group than in the placebo group achieved a response (50% reduction in CDRS-R from baseline with YMRS item 1 ≤2) or remission (CDRS-R total ≥28 with YMRS total ≤8 and CGI-BP-S score ≤3). Response was achieved by 78% of the OFC group compared with 59% of the placebo group. Remission was achieved by 59% of the OFC group *vs* 43% of the placebo group.

Times to response and remission were significantly shorter in the OFC group than in the placebo group (P = 0.001, P = 0.028, respectively).

Improvements in partcipant- and parent-reported quality of life were observed between the treatment groups. The change from baseline ± standard error (SE) in combined KID-KINDL and KIDDO-Kindle total scores was significantly greater in the OFC group than in the placebo group (least squares [LS] mean change ± SE: 12.8 ± 1.7 *vs* 7.9 ± 2.40, P = 0.050), with the greatest change observed in the self-esteem subscale score (18.2 ± 2.7 *vs* 10.7 ± 3.40, P = 0.028). Although there were no significant differences in the change from baseline in KINDL parent total scores between the OFC and placebo groups (LS mean change ± SE: 16.0 ± 1.9 *vs* 10.9 ± 2.6, P = 0.066), there were significant differences in emotional well-being (22.6 ± 2.3 *vs* 15.8 ± 2.9, P = 0.020) and self-esteem subscale scores (20.3 ± 2.4 *vs* 13.6 ± 3.0, P = 0.030). Similar to the findings for adults, the frequency of treatment-emergent mania in the OFC and placebo groups was low (1 *vs* 0%).

Safety and tolerability measures

The profile of adverse events observed with OFC in children and adolescents was generally similar to the profile of adverse events observed in adults (table 3). However, the magnitude and frequency of some events were greater in children and adolescents than adults (table 3). After 8 weeks of treatment, mean weight gain was significantly greater in the OFC group than in the placebo group (4.4 kg *vs* 0.5 kg, P < 0.001) and the frequency of weight gain (increase ≥7% from baseline) was significantly greater in the OFC group than in the placebo group (52% *vs* 4%, P < 0.001).

The adolescent study group displayed similar changes in metabolic parameters in comparison to adults (table 3). Adolescent participants had significantly higher rates of treatment-emergent abnormally high levels of fasting total cholesterol (29% *vs* 8%) and triglycerides (52% *vs* 27%), but displayed no significant difference in fasting glucose (table 3) when comparing OFC with placebo. Notably, more adolescents had significantly higher alanine aminotransferase (46% *vs* 3%) and aspartate aminotransferase (34% *vs* 8%), and a greater mean increase in prolactin (8.7 *vs* 0.7 ng/mL, P < 0.001) with OFC compared with placebo.

Meta-analyses supporting the efficacy of olanzapine-fluoxetine combination therapy for acute treatment of bipolar depression

Overview of publication characteristics

Two meta-analyses were retrieved that collated data from double-blind, active comparator controlled-, or placebo-controlled randomized trials involving monotherapy and combination therapy for treatment of BD in participants diagnosed with type I or II bipolar disorder[33, 34]. Medications included lithium, quetiapine, lamotrigine, paroxetine, olanzapine, aripiprazole, phenelzine, divalproex, and OFC. Safety and tolerability data were not reported in either of the meta-analyses. Overall, these meta-analyses identified between 6,731 and 7,307 participants randomized to an active agent or placebo. However, comparisons across both meta-analyses were limited by the small number of placebo-controlled RCTs that were available for inclusion, particularly for medications where only 1 or 2 trials were available.

Data synthesis and meta-analysis

Only data from studies reporting continuous outcomes (HAM-D, MADRS) were pooled. Analyses included random-effects meta-analyses for individual trials, with pooling for overall assessments and for specific agents. Outcomes based on standardized mean

drug-placebo differences (SMD) in improvement, relative response rates, and number-needed-to-treat were considered in both studies. The studies used varying statistical methodologies: in Vieta et al[33], heterogeneity between studies was measured with the $[chi]^2$ test and the I^2 score. If the $[chi]^2$ test indicated heterogeneity, random-effects analysis was performed using DerSimonian and Laird methods; in Selle *et al*[34], correlations were tested with bivariate linear regression (r) or non-parametric Spearman rank correlation (r_s) methods. Potential covariates with SMD were assessed for at least suggestive associations ($P \leq 0.10$) in preliminary bivariate meta-regression analyses in preparation for multivariate meta-regression analysis.

Meta-analysis outcomes

Taken together, these two meta-analyses considered all of the available clinical trial data for OFC in BD to date with the exclusion of the more recent trial of adolescents. However, of all the studies identified, only OFC data from the placebo-controlled RCT conducted by Tohen et al[22] was suitable for inclusion in the meta-analyses. For the Vieta et al[33] meta-analysis, the greatest reductions in MADRS scores versus placebo were reported for OFC (1 trial: 6.6; 95% CI, -9.59 to -3.61; $P = 0.000$) and quetiapine monotherapy (5 trials: for 300 mg/day, -4.8 and for 600 mg/day, -4.8). Most medications that were assessed (except for paroxetine, lithium, aripiprazole, and phenelzine) significantly improved the rates of response and remission. In the Selle et al[34] meta-analysis, the 4 most effective agents ranked by observed response rate ratio (drug:placebo) were OFC (1.84; 95% CI, 1.44 to 2.36), lurasidone (1.72; 95% CI, 1.33 to 2.22), quetiapine (1.36; 95% CI, 1.24 – 1.49), and valproate (2.08; 95% CI, 1.18 to 3.65), with a pooled response rate ratio of 1.47 (95% CI, 1.32 to1.64). Averaged apparent efficacy (by SMD) was ranked highest for OFC (mean rank = 1.67), followed by valproate (2.0), carbamazepine (3.0), lurasidone (4.0), quetiapine (4.33), olanzapine (6.67), lamotrigine (7.0), lithium (7.33), ziprasidone (9.0), and aripiprazole (10.0). Efficacy by number-needed-to-treat was ranked highest for OFC (1.8), followed by carbamazepine (3.4), valproate (2.0), lurasidone (4.6), and quetiapine (5.9).

DISCUSSION

The findings of this systematic review examining the efficacy and safety of OFC contribute to the evidence that OFC is an effective and well-tolerated treatment for BD in adults and adolescents. The short- and longer-term improvements in symptoms of depression that were reported for OFC compared with placebo and active comparators in each of the clinical trials were supported by the findings from the 2 meta-analyses. Overall, OFC was well tolerated across the studies and the tolerability profile of OFC was consistent with the tolerability profile for olanzapine and fluoxetine monotherapy[35]. However, there was a greater frequency of nausea and diarrhea in participants receiving OFC compared with olanzapine monotherapy after 8 weeks of treatment, and a greater frequency of weight gain, somnolence, and depression in participants receiving OFC compared with olanzapine monotherapy after 6 months of treatment.

The 4 RCTs conducted in adults in this systematic review substantively support the efficacy of OFC for the treatment of BD, with a particular focus on the acute phase of treatment. An improvement in depressive symptoms (MADRS and CGI-BP scores) was observed within a week of commencing OFC therapy and was maintained for up to 8 to 12 weeks, and for up to 6 months in studies of longer duration. As confirmed in the 2 meta-analyses[33, 34], the efficacy of OFC for treatment of BD was greater compared with other active comparators, including olanzapine and lamotrigine monotherapy.

The FDA has approved OFC for use in children and adolescents 10 to 17 years of age for the acute treatment of depressive episodes associated with bipolar disorder. The recent placebo-controlled RCT[27] identified by this review represents the first systematic assessment of OFC in this patient population. This study showed that OFC is an efficacious treatment for BD in patients 10 to 17 years of age, with similar improvements in depressive symptoms compared with adults during acute treatment. Overall, CGI-BP outcomes for OFC and the levels of mania reported in this study were equivalent to and lower than, respectively, those reported for olanzapine alone[36].

The dilemma for the use of antidepressants in the treatment of bipolar disorder is that there are a subset of patients with this disease who do not respond to the exclusive use of mood stabilizers and for whom the inclusion of an antidepressant is necessary. A key issue when considering the inclusion of an antidepressant in therapy is the risk for a switch in mood to hypomania, mania, and mixed states[37]. The studies analyzed in this review demonstrate that overall, the frequency of treatment-emergent manic episodes with OFC is relatively low and similar to placebo. In addition, these studies demonstrate that the rates of treatment-emergent manic episodes with OFC groups are lower compared with reported rates for tricyclic

antidepressants and equivalent to those reported for serotonin reuptake inhibitors[38]. Furthermore, the mean change in YMRS reported in these studies was at least equivalent to, if not improved, compared with previous reports for olanzapine monotherapy[39]. Therefore, the analyzed studies demonstrate that OFC does not lead to an increase in manic symptoms, but rather agree with previously published findings[37] that an antidepressant such as fluoxetine can be used as an adjunct to a mood-stabilizing medication, such as olanzapine, for treatment of patients with BD. However, selection of the most appropriate pharmacotherapy for treatment of BD should take into account the short- and long-term tolerability of the selected therapy and patient needs.

Overall, the safety and tolerability profile of OFC was consistent across the RCTs and was consistent with the known tolerability profile for olanzapine and fluoxetine monotherapy[35]. The primary adverse events reported for OFC were somnolence, weight gain, increased appetite, dry mouth, dizziness, sedation, headache, tremor, fatigue, and nausea. In addition, the frequency of weight gain, somnolence, and depression appeared to be greater during longer-term (6-month) therapy in patients receiving OFC compared with olanzapine monotherapy. Although this may potentially be associated with OFC treatment, this finding may also be due to the limitations associated with the open-label, nonrandomized, flexible medication course, and treatment self-selection design of the longer-term study. Abnormal laboratory values were relatively uniform across studies with treatment-emergent elevations in total cholesterol, triglycerides, glucose, and prolactin levels observed with OFC treatment in adults.

Differences between adults and adolescents in metabolism, absorption, and distribution of drugs may lead to differences in the frequency and presentation of adverse events associated with pharmacotherapy[40, 41]. Despite this, the profile of adverse events observed with OFC in children and adolescents was generally similar to the profile of adverse events observed in adults[35]. However, the magnitude and frequency of some events were greater in children and adolescents than adults. Adverse events reported for adolescents, including weight gain, were similar to those reported for the adult population and adolescents treated with olanzapine monotherapy[42]. In comparison to reports on olanzapine alone, adolescents on OFC demonstrated an overall lower incidence of the most commonly reported adverse events of weight gain and somnolence[42]. However, adolescents who received OFC in the reported study experienced increased rates of sedation and tremor, and elevations in prolactin, compared with placebo[27].

In adults, atypical antipsychotics, such as olanzapine, have less impact on the levels of prolactin compared with conventional antipsychotics[43, 44]. Despite this, the combination of an antipsychotic with a serotonergic antidepressant, as in OFC therapy, may increase the probability of hyperprolactinemia[45]. In children and adolescents, the use of olanzapine monotherapy may be associated with a more prolonged elevation in prolactin levels, although lower than with risperidone[45,46] However, the duration (8 weeks) of the adolescent study reported here precludes any determination on the duration of hyperprolactinemia in adolescents on OFC treatment. Hence, despite the favorable safety and tolerability profile of OFC in adolescents reported here, it is important to remember that patient-to-patient effects may differ, so as recommended for any treatment, clinicians should make decisions on an individual basis for each patient and continue to carefully monitor and manage all treatment-emergent adverse events, including metabolic changes, in adolescent patients, particularly during long-term treatment.

The strength of this systematic review lies in the rigor with which the existing clinical trial literature was reviewed and filtered. A key strength across the clinical trials included in this review is the relative uniformity of the diagnostic inclusion criteria and primary outcome measures reported (with the exception of the adolescent study), allowing inter-study comparison. However, the meta-analyses included in this review highlighted the relative paucity of clinical trial data available, with very few trials focused on acute treatment for bipolar depression in both adults and adolescents. While findings from both meta-analyses suggested that the body of evidence is positively in favor of OFC for the treatment of BD in adults, the findings are based on a limited number of trials, and therefore, may be subject to bias. In an attempt to minimize reporting bias, this review included unpublished data identified using clinical trial databases and, in an attempt to minimize publication bias, there were no limits placed on language. In addition, several databases that focused on publications reported in Latin American journals were searched in an effort to identify studies not previously retrieved in previous systematic reviews that were specific to Latin America. However, very few trials were identified that were conducted in Latin American countries. Findings from the one study conducted in Puerto Rico[29] showed similar improvements in depressive symptoms and a similar tolerability profile for OFC compared with studies conducted in primarily Caucasian populations[22, 28, 31]. Therefore, there is little evidence to suggest that outcomes for Latin American patients are likely to be different to other study

populations. This conclusion is further supported by a previously published post hoc analysis of the efficacy and safety of olanzapine in Latino versus Caucasian patients with acute mania[47]. Thus, the few trials available to date do not support the perception that Latin American patients are more sensitive to adverse events with psychotropics than Caucasians, or that this group requires lower doses to obtain the same level of efficacy.

In conclusion, this systematic review of the literature has confirmed the efficacy and safety of OFC for acute treatment of BD in adults and has reported new data on the efficacy and safety of OFC in adolescents. A key finding was that the overall efficacy and safety of OFC in adolescents parallels the efficacy and safety profile observed in adults. The single study conducted in Latin America suggests that the overall efficacy and safety profile of OFC in this demographic does not differ from that of other study populations. However, because most of the existing evidence for the treatment of bipolar depression is produced in the US and Canada, there is a significant need for further data specific to Latin American populations, especially with respect to safety and tolerability. In the absence of further Latin American data, the findings presented here suggest that treatment guidelines developed in the US and Canada are a valid option for Latin American clinicians. While the study data assessed suggest that OFC is a suitable treatment option for bipolar depression, clinical decision-making should be based on the evidence of all available therapies to ensure that the prescribed treatment is best suited for individual patients and patient populations.

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