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Review

Olanzapine plus fluoxetine for bipolar disorder: A systematic review and meta-analysis

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ABSTRACT

Background: Olanzapine plus fluoxetine combination (OFC) is one of the current approaches for treating the depressive phase of bipolar disorder. Our objective was to synthesize the evidence on the efficacy of OFC therapy in bipolar depressed patients.
Methods: We searched for randomized controlled trials (RCTs) on MEDLINE, Embase and other databases. Independent researchers selected the studies and extracted the data. The GRADE approach was used to assess the quality of the evidence. The Mantel–Haenszel random effect model was used to perform the meta-analyses.
Results: From 627 unique records retrieved, four RCTs were included (1330 patients). OFC improved the response compared to olanzapine (relative risk [RR]=1.58; 95% confidence interval [95% CI]: 1.27, 1.97) and to placebo (RR=1.99; 95% CI: 1.49, 2.65) but not to lamotrigine (low-quality evidence). Similar results were found for remission and relapse rates. No differences were identified for levels of depression and mania symptoms (low-quality evidence) and incidence of mania (moderate-quality evidence). Adverse effects were more common in patients treated with OFC than in those treated with lamotrigine (RR=1.13; 95% CI: 1.04, 1.23), but no difference was found relative to the patients treated with olanzapine (low-quality evidence).
Limitations: Despite the totality of the evidence included, there are few RCTs available regarding the efficacy of OFC therapy for bipolar depression. The risk of attrition and reporting bias is also a concern.
Conclusions: OFC therapy improved the response, remission, and relapse rates among other outcomes. However, a worse profile of adverse reactions was observed in some comparisons. These data clarify the therapeutic use of OFC as an option to olanzapine in bipolar depression. The quality of the evidence could be improved by additional comparisons and higher rates of treatment adherence.

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1. Introduction

Investigations into the natural course of bipolar disorder performed within the last decade have shown that depressive episodes and symptoms, rather than mania or hypomania, dominate the course of bipolar disorder (Judd et al., 2003; Kupka et al., 2007). Clinical and research efforts were thus urged to focus on the management of depression in patients with bipolar disorder (Judd and Akiskal, 2003). As a result, new treatment options for the depressive phase of bipolar disorder emerged and became available for clinical use (Nivoli et al., 2011).

The use of antidepressants by patients with bipolar disorder is controversial, and some guidelines even discourage this use based on the hypothesized increased risk of mania (Post, 2012; Goodwin and Psychopharmacology, 2009; Yatham et al., 2009). However, assessments of this evidence have revealed several methodological flaws that may have led to inaccurate conclusions (Grunze, 2008; Licht et al., 2008). Publication bias in the reporting of more cases of switching to mania than depressive episodes was also suspected (Grunze et al., 2010). Thus, the use of antidepressants and antipsychotics or mood stabilizers has become an acceptable option for the management of bipolar depression (Miller, 2004; Goldberg and Citrome, 2005).

Olanzapine plus fluoxetine combination (OFC) was the first drug approved by the Food and Drug Administration specifically to treat the depressive phase of bipolar disorder (Goldberg and Citrome, 2005). The main advocated advantage of OFC was its combination of an antipsychotic with an antidepressant drug in a single tablet that could increase patient adherence (Miller, 2004).

A systematic review with meta-analysis summarizing the efficacy and safety of OFC in this context is not available. Our objective is to assess the evidence of OFC use for bipolar depression.

2. Methods

2.1. Protocol

The current review was registered with the International Prospective Register of Systematic Reviews (PROSPERO), registration number: CRD42012001971. The authors declare no conflicts of interest within the research field.

2.2. Study eligibility criteria

We included randomized controlled trials (RCTs) that assessed OFC efficacy in patients with bipolar I or II disorder-depressed, as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria. OFC, either in individual or separate tablets, was compared to placebo or other treatment. The outcomes of interest included the following: level of depression and mania symptoms on rating scales (Montgomery-Åsberg Depression Rating Scale [MADRS], Young Mania Rating Scale [YMRS]), proportion of participants with clinically important response to treatment (response: reduction $\geq 50\%$ in MADRS and associated measures as defined by RCT criteria; remission: MADRS score ≤ 12), time to remission, quality of life score, severity of symptoms scale, relapse (MADRS > 15 and variations depending on RCT criteria), hospital admission, rates of suicide attempts and ideation, discontinuation and adverse effects including mania (YMRS score ≥ 15 or as defined by RCT criteria), weight gain and clinically important weight gain (increase in weight $> 7\%$).

2.3. Information sources

We searched MEDLINE, Embase, Scopus, PsycINFO, PSYNDEX, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane Library, Center for Reviews and Dissemination (CRD), Cochrane Central Register of Controlled Trials (CENTRAL), metaRegister of Current Controlled Trials (mCRT), Latin American and Caribbean Center on Health Sciences Information (LILACS) and Scientific Electronic Library Online (SciELO). The databases were searched from their dates of inception to November 2012. We also screened the references of all relevant papers and manually searched all of the American Psychiatric Association (APA) Annual Meeting abstracts published since 2000. The grey literature search was designed to assess and avoid publication bias. We searched the full texts of the RCTs or contacted the authors of the studies for a complete appraisal of the RCTs identified from this search.

2.4. Search strategy

We used the following search strategy for MEDLINE (via PubMed): ((“olanzapine–fluoxetine hydrochloride”[tiab] or “olanzapine/fluoxetine”[tiab] or “olanzapine–fluoxetine”[tiab] or “symbyax”[tiab] or (“olanzapine”[tiab] and “fluoxetine”[tiab])) and (“bipolar”[tiab] or “psychosis”[tiab] or “psychoses”[tiab] or “disorders”[tiab] or “disorder”[tiab] or “manic-depressive”[tiab] or “manic depressive”[tiab] or “manic-depressive psychosis”-[tiab] or “manic depressive psychosis”[tiab] or “affective psychosis”[tiab] or “mania”[tiab] or “manias”[tiab] or “manic disorder”[tiab] or “manic disorders”)) and ((therapy/broad[filter])

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or systematic[sb]). Modified versions of this strategy were applied when searching the other databases.

2.5. Study selection and data collection process

Two researchers (MTS and IRZ) independently reviewed the retrieved studies. Disagreements were resolved by achieving author consensus or by a third reviewer (TFG).

We prepared a data extraction sheet to collect the relevant study data including country, dates of enrollment, inclusion and exclusion criteria, length of follow-up, intervention, control, sample size and outcomes. The data were extracted by duplicate reviewers (MTS, IRZ and TFG).

We contacted the corresponding authors of the studies to obtain any important data that were not published in the reports.

2.6. Risk of bias and quality assessment

To assess the risk of bias in individual studies, we used the Cochrane Collaboration tool as described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins and Green, 2011), which provides a domain-based evaluation for sequence generation, allocation sequence concealment, blinding, incomplete outcome data, selective outcome reporting and other potential sources of bias. This tool is composed of a description and judgment for each entry in a risk of bias table rated as "low", "unclear" or "high" risk of bias. The risk of bias plot was created using the RevMan 5.1 software.

For the outcomes considered to be critical or highly important, we used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the quality of each body of evidence as described in the GRADE Guidelines (Balshem et al., 2011) and the GRADE Handbook for Grading Quality of Evidence and Strength of Recommendation (Schünemann et al., 2009). In this approach, five items that can decrease the quality of evidence were assessed: limitations (risk of bias), inconsistency, indirectness, imprecision and publication bias. The quality of evidence was rated as high, moderate, low or very low. Based on the assessments, evidence profile tables were created using the GRADEpro 3.6 software.

The final judgments regarding the risk of bias and evidence quality were achieved by consensus. We considered the quality assessment results when interpreting the findings.

2.7. Data analysis

We recalculated the measures of association using the data available from the included RCTs. Continuous data were measured by standardized mean difference (SMD), and dichotomous data were measured by relative risk (RR). When feasible, the number needed to treat (NNT) or the number needed to harm (NNH) was calculated. For a better interpretation of the SMD, we calculated the odds ratio (OR)

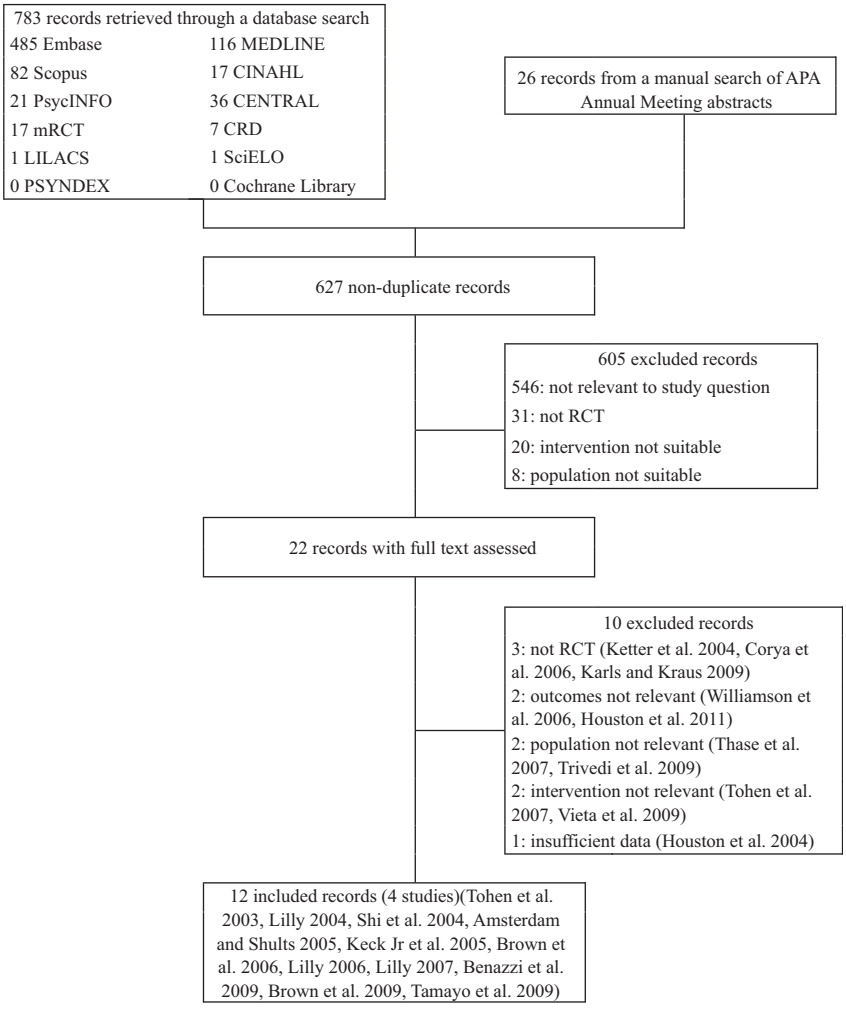

Fig. 1. Study search, selection and inclusion process.

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using the equation: $\text{Ln(OR)} = \pi/\sqrt{3} \times \text{SMD}$ (Chinn, 2000; Higgins and Green, 2011).

The meta-analyses of the RR and SMD from available comparisons were grouped using the random-effects Mantel–Haenszel model and are presented with 95% confidence intervals (95% CI). To assess the occurrence of adverse effects that can arise from the use of olanzapine only, we also assessed a "control without olanzapine" group, which included all comparisons except olanzapine, and an "active control" group, which summed all of the comparisons except the placebo. We estimated the statistical heterogeneity of the results using the Chi^2 ($p > 0.10$) and Tau^2 tests and estimated the effect magnitude by the I^2 test. We used the SMD and random effects inverse-variance method to combine different symptom severity scales (Higgins and Green, 2011). We planned to assess the publication bias by analyzing funnel plot asymmetry, Peters' test for small-study effects (Peters et al., 2006) and Harbord's modified test for small-study effects (Harbord et al., 2006). All analyses were performed using the STATA software (v. 10.1).

3. Results

Our literature search retrieved 627 unique records. We selected 22 records for full text assessment, from which we excluded ten as illustrated on Fig. 1 (Corya et al. (2006), Houston et al. (2011), Houston et al. (2004), Karls and Kraus (2009), Ketter et al. (2004), Thase et al. (2007), Tohen et al. (2007), Trivedi et al. (2009), Vieta et al. (2009), Williamson et al. (2006)). Four RCTs (totaling 12 records) were included in our review. All of the grey literature identified was found to have been published in full text. For simplicity, we cited only the main report when presenting the results.

3.1. Study characteristics

Table 1 depicts the main characteristics of the included RCTs. The Structured Clinical Interview for DSM-IV (SCID) was homogeneously used to diagnose eligible patients with bipolar I or II disorder. The RCTs enrolled 1330 patients in total. The time of follow-up ranged from 8 to 25 weeks. OFC was used either in

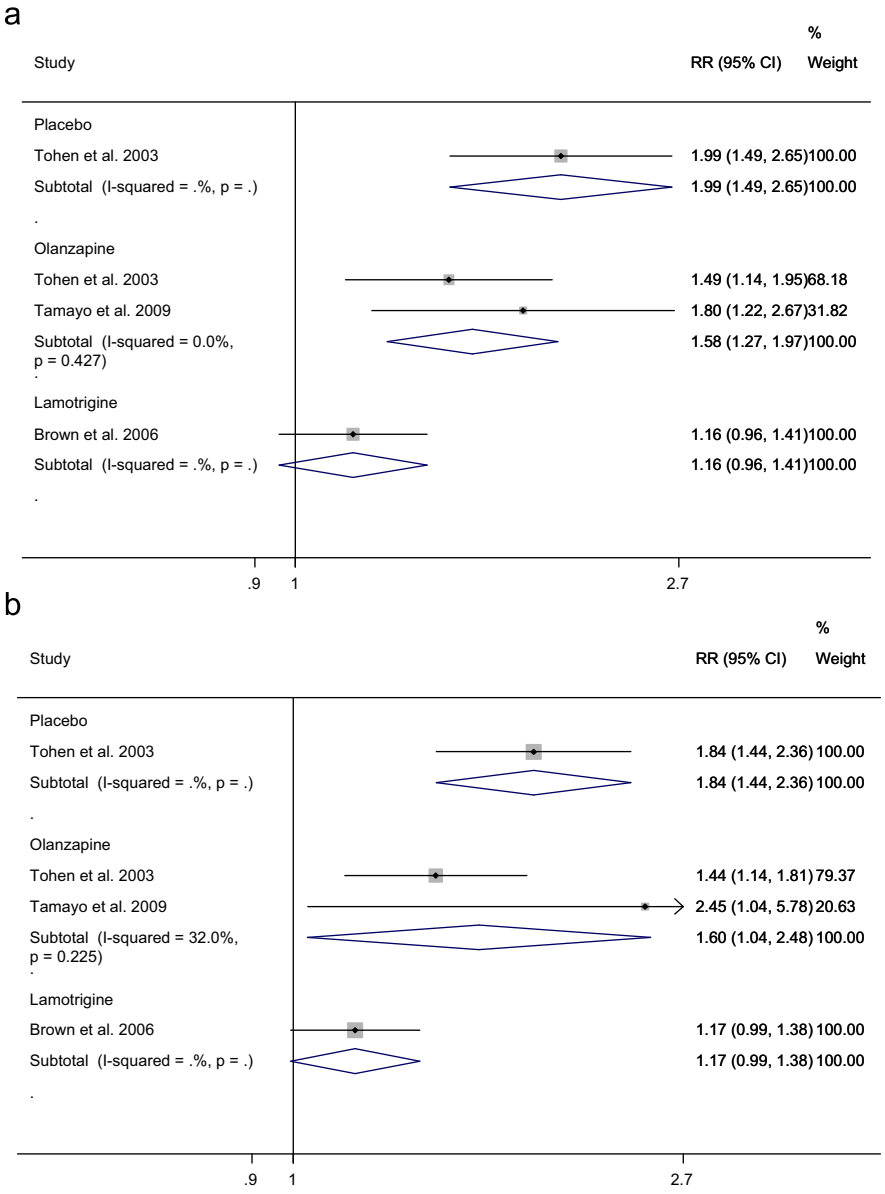

Fig. 2. Remission (a) and response (b) to olanzapine plus fluoxetine combination compared to olanzapine alone, lamotrigine and placebo.
Notes: Remission: Montgomery-Åsberg Depression Rating Scale (MADRS) score ≤ 12. Response: a reduction of $\geq 50\%$ in MADRS. For Tamayo et al. (2009), it was also considered an associated Clinical Global Impressions of Severity of Bipolar Depression score < 3.

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Table 1
Main characteristics of the included studies.

Study	Year (dates of enrollment)	Country	Age (mean ± SD)	Inclusion criteria	Length of follow-up (weeks)	OFC (*N*)	Comparisons (*N*)
Tohen et al. (2003), Tohen et al. (2003), Lilly (2004), Shi et al. (2004), Keck et al. (2005), Benazzi et al. (2009)	June 2000–December 2001	13[a]	41.8 ± 12.5	DSM-IV criteria (SCID): bipolar I disorder, depressed; MADRS ≥ 20; and at least 1 previous manic or mixed episode	8	Olanzapine 6 and fluoxetine 25 mg/day, 6 and 50, or 12 and 50 mg/day (82)	Olanzapine 5 to 20 mg/day (*n*=370); placebo (*n*=377)
Amsterdam and Shults (2005), Amsterdam and Shults (2005)	1998–2003	USA	40 ± 9[b]	DSM-IV criteria (SCID): bipolar I or II disorder	8	Olanzapine range 2.5–15 mg/day and fluoxetine range 5–20 mg/day (8)	Fluoxetine range 10–60 mg/day (8); olanzapine range: 5–20 mg/day (9); placebo (9)
Brown et al. (2006), Lilly (2006), Brown et al. (2006), Brown et al. (2009)	December 2003–January 2005	USA	37 ± 11.1	DSM-IV criteria (SCID): bipolar I disorder, depressed; MADRS ≥ 20; CGI-S ≥ 4 (moderately ill); and at least 1 previous manic or mixed episode	25	OFC 6/25, 6/50, 12/25, or 12/50 mg/day (205)[c]	Lamotrigine titrated to 200 mg/day (205)
Tamayo et al. (2009) Lilly (2007), Tamayo et al. (2009)	May 2004–March 2006	USA (Puerto Rico)	42.4 ± 11.2	DSM-IV criteria (SCID): bipolar I or II disorder; MADRS ≥ 20; and at least 1 previous hypomanic, manic, or mixed episode	12	OFC 12/25 mg/day, range 6/25–12/50 mg/day (57)[c]	Olanzapine 10 mg/day, range 5–20 mg/day (57)

Abbreviations: SD, standard deviation; *N*, number of patients; OFC, Olanzapine plus fluoxetine combination.
Notes:
[a] Country names not available.
[b] Total not available, age of the OFC group presented.
[c] Olanzapine and fluoxetine combination was administered in the same tablet.

Table 2
Quality assessment of the outcomes using GRADE. Question: Should olanzapine plus fluoxetine be used for acute bipolar depression?

Outcome	Number of studies	Study limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	Quality
Level of depression symptoms (MADRS)	3 (Tohen et al., 2003; Brown et al., 2006; Tamayo et al., 2009)	Serious[a]	Serious[c]	Serious[e]	No serious imprecision	⊕OOO VERY LOW
Level of mania symptoms (YMRS)	2 (Tohen et al., 2003; Brown et al., 2006)	Serious[a]	No serious inconsistency	Serious[e]	Serious[f]	⊕OOO VERY LOW
Response	3 (Tohen et al., 2003; Brown et al., 2006; Tamayo et al., 2009)	Serious[a]	No serious inconsistency[d]	Serious[e]	No serious imprecision	⊕⊕OO LOW
Remission	3 (Tohen et al., 2003; Brown et al., 2006; Tamayo et al., 2009)	Serious[a]	No serious inconsistency[d]	Serious[e]	No serious imprecision	⊕⊕OO LOW
Quality of life scores	2 (Tohen et al., 2003; Brown et al., 2006)	Serious[a]	No serious inconsistency[d]	Serious[e]	No serious imprecision	⊕⊕OO LOW
Symptom severity	2 (Tohen et al., 2003; Brown et al., 2006)	Serious[a]	No serious inconsistency	Serious[e]	No serious imprecision	⊕⊕OO LOW
Relapse	2 (Tohen et al., 2003; Brown et al., 2006)	Serious[a]	No serious inconsistency	Serious[e]	No serious imprecision	⊕⊕OO LOW
Hospitalization for psychiatric reason	2 (Tohen et al., 2003, Brown et al., 2006)	Serious[a]	No serious inconsistency	Serious[e]	Serious[f]	⊕OOO VERY LOW
Suicide attempt or ideation	1(Brown et al., 2006)	Serious[a]	No serious inconsistency	Serious[e]	Serious[f]	⊕OOO VERY LOW
Discontinuation due to mania	2 (Tohen et al., 2003; Brown et al., 2006)	Serious[a]	No serious inconsistency[d]	Serious[e]	Serious[f]	⊕OOO VERY LOW
Adverse effects	2 (Brown et al., 2006; Tamayo et al., 2009)	Serious[a,b]	No serious inconsistency	Serious[e]	No serious imprecision	⊕⊕OO LOW

[a] Potential risk of attrition (incomplete outcome data) and reporting bias (selective reporting).
[b] Potential bias because of lack of blinding.
[c] Significant heterogeneity between similar comparators.
[d] Overall heterogeneity can most likely be explained by the different comparators between studies.
[e] The range of comparators can only provide indirect evidence for a general recommendation.
[f] Wide confidence interval with a very low event rate.

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combined form (Tohen et al., 2003; Amsterdam and Shults, 2005) or in separate tablets (Brown et al., 2006; Tamayo et al., 2009).

3.2. Risk of bias and quality of evidence

The judgments regarding the risk of bias for each included RCT are detailed in Supplementary Table 1 and in Supplementary Fig. 2. The domains most frequently rated as having a high risk of bias were related to incomplete outcome data (attrition bias) and selective reporting (reporting bias).

The assessments of the quality of evidence for each outcome considered as critical or important for answering the question "Should OFC be used for acute bipolar depression?" are provided in Table 2. We could not statistically assess the potential publication bias due to the small number of studies included.

Outcomes were mostly rated down due to the risk of bias and indirectness. The indirectness issue was handled consistently because the range of comparisons that was included was not satisfactory to provide support for a unique answer concerning the superior effectiveness of OFC. For some outcomes, the quality of evidence was also downgraded due to inconsistency and imprecision.

3.3. Outcomes

3.3.1. Level of depression and mania symptoms on rating scales

There was no statistically significant difference between the groups in the level of depression (MADRS total score (mean change), MADRS suicidal thoughts (mean change)) or mania symptoms (YMRS (mean change), Table 3). The quality of evidence for such outcomes was very low.

Table 3
Main outcomes assessed.

Outcome (reference)	Measure of association	Olanzapine plus fluoxetine combination compared to:								
		Placebo			Olanzapine			Lamotrigine		
		Estimate	95% CI	N; I^2 (%)	Estimate	95% CI	N; I^2 (%)	Estimate	95% CI	N; I^2 (%)
MADRS, mean change (Tohen et al., 2003; Brown et al., 2006; Tamayo et al., 2009)	SMD	−0.05	−0.29, 0.19	437	−0.37	−1.10, 0.34	530; 89	−0.02	−0.21, 0.17	410
MADRS suicidal thoughts, mean change (Tohen et al., 2003; Brown et al., 2006)	SMD	−0.01	−0.24, 0.24	437	−0.01	−0.24, 0.24	433	−0.10	−0.30, 0.09	393
YMRS, mean change (Tohen et al., 2003; Brown et al., 2006)	SMD	−0.01	−0.25, 0.23	437	−0.01	−0.24, 0.24	433	−0.01	−0.20, 0.18	410
Quality of life (QLDS, mean change) (Tohen et al., 2003)	SMD	−0.57	−0.86, -0.27	308	−0.49	−0.79, −0.20	294	–	–	–
SF-36 mental component score, mean change	SMD	0.72	0.43, 1.01	323	0.48	0.19, 0.77	308	–	–	–
SF-36 physical component score, mean change	SMD	0.02	−0.26, 0.31	323	0.00	−0.28, 0.29	308	–	–	–
CGI, mean change (Brown et al., 2006, Tohen et al., 2003)	SMD	−0.54	−0.78, −0.29	437	−0.32	−0.56, −0.08	433	−0.20	−0.40, −0.01	410
Relapse (Tohen et al., 2003, Brown et al., 2006)	RR	–	–	–	0.31	0.12, 0.80	530	0.75	0.38, 1.50	393
Hospitalization for psychiatric reason (Tohen et al., 2003, Brown et al., 2006)	RR	1.46	0.15, 13.88	463	4.30	0.27, 68.10	456	0.36	0.12, 1.12	409
Suicidal ideation (Brown et al., 2006)	RR	–	–	–	–	–	–	0.40	0.08, 2.03	205
Suicide attempt (Brown et al., 2006)	RR	–	–	–	–	–	–	0.33	0.04, 3.16	205
Discontinuation (Tohen et al., 2003; Brown et al., 2006; Tamayo et al., 2009)	RR	0.58	0.44, 0.78	463	0.70	0.54, 0.92	570; 0	1.00	0.88, 1.16	410
Discontinuation due to mania (Tohen et al., 2003; Brown et al., 2006)	RR	0.73	0.26, 2.05	463	1.15	0.39, 3.37	456	1.49	0.25, 8.84	409
Adverse effect (Brown et al., 2006; Tamayo et al., 2009)	RR	–	–	–	0.88	0.69, 1.13	114	1.13	1.04, 1.23	409
Adverse effect, serious (Brown et al., 2006; Tamayo et al., 2009)	RR	–	–	–	3.00	0.32, 27.99	114	0.40	0.18, 0.88	409
Mania (Tohen et al., 2003; Brown et al., 2006, Amsterdam and Shults, 2005)	RR	0.97	0.40, 2.33	441; 0	1.10	0.45, 2.69	430	0.68	0.31, 1.48	393
Weight gain (Tohen et al., 2003; Brown et al., 2006; Tamayo et al., 2009)	RR	6.58	3.06, 14.13	463	1.01	0.63, 1.62	570; 0	7.63	3.33, 17.47	409
Weight gain clinically important (Tohen et al., 2003; Brown et al., 2006; Tamayo et al., 2009)	RR	69.27	9.32, 514.89	437	0.96	0.60, 1.52	536; 0	17.17	6.38, 46.16	409
Weight gain, mean change (Kg) (Tohen et al., 2003; Brown et al., 2006; Tamayo et al., 2009)	SMD	1.19	0.94, 1.44	463	−0.09	−0.45, 0.26	564; 62	1.11	0.90, 1.32	391

Abbreviations: N, number of patients; RR, relative risk; SMD, standardized mean difference; MADRS, Montgomery-Åsberg Depression Rating Scale; YMRS, Young Mania Rating Scale; CGI, Clinical Global Impressions scale; SF-36, 36-Item Short-Form Health Survey; QLDS, Quality of Life in Depression Scale

Notes: Hospitalization for psychiatric reason: hospitalization for depression, mania, mixed episode, or other psychiatric event Tohen et al. (2003) considered only hospitalization for manic or mixed symptoms.

Mania: YMRS ≥ 15. Amsterdam and Shults (2005) considered YMRS ≥ 12.

Relapse: Brown et al. (2006) considered relapse as a MADRS > 15; Tamayo et al. (2009) considered it as a MADRS ≥ 20 associated with a Clinical Global Impressions of Severity of Bipolar Depression scale (CGI-BP-D) ≥ 3 or hospitalization for depression.

CGI (severity of symptoms): combined by the random effects inverse-variance method of SMD. This outcome was assessed by Tohen et al. (2003) using the CGI-BP-D and by Brown et al. (2006) using the Clinical Global Impressions—Severity of Illness scale (CGI-S).

Weight gain clinically important: greater than 7% increase in weight.

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3.3.2. Clinically important response to treatment

The results of OFC therapy compared to olanzapine monotherapy showed a significant improvement in response rate (Fig. 2, NNT=6; 95% CI: 4, 13). No significant statistical heterogeneity was identified. Statistically significant results favoring OFC were also found in comparison to a placebo (NNT=4; 95% CI: 3, 7) but not in comparison to lamotrigine. Similar results were found for remission (OFC compared to olanzapine: NNT=5; 95% CI: 3, 14; OFC compared to placebo: NNT=4; 95% CI: 3, 8). The quality of this body of evidence was low.

The time to remission was assessed in two studies, but because of a lack of raw numeric data, these results could not be summarized. One RCT (Tohen et al., 2003) reported that the time to remission was significantly shorter for the OFC group than for the placebo ($p<0.001$) and olanzapine ($p=0.01$) groups, while another RCT (Brown et al., 2006) did not find a significant difference between the OFC and lamotrigine groups ($p=0.06$). Because of the lack of comparisons, this outcome was not assessed using the GRADE approach.

3.3.3. Quality of life

OFC therapy showed improvement in the quality of life as measured by the Quality of Life in Depression Scale (OR=0.36; 95% CI: 0.21, 0.61 compared to placebo; OR=0.40; 95% CI: 0.24, 0.69 compared to olanzapine) and the 36-Item Short-Form Health Survey (OR=3.66; 95% CI: 2.17, 6.19 compared to placebo; OR=2.38; 95% CI: 1.41, 4.01 compared to olanzapine). This evidence was rated as low-quality.

3.3.4. Severity of symptoms

OFC therapy significantly reduced the severity of symptoms when compared with a placebo (OR=0.38; 95% CI: 0.24, 0.59), olanzapine (OR=0.56; 95% CI: 0.36, 0.86) and lamotrigine (OR=0.70; 95% CI: 0.49, 0.99). This outcome was assessed using the Clinical Global Impressions Bipolar Version – Severity of Depression scale (CGI-BP-S) in one RCT (Tohen et al., 2003), and the Clinical Global Impressions – Severity of Illness scale (CGI-S) in another study (Brown et al., 2006). We rated the quality of the evidence as low.

3.3.5. Relapse

Patients treated with OFC experienced a reduced relapse rate compared to patients treated with olanzapine alone (NNT=5; 95% CI: 4, 18). The comparison to lamotrigine was not significant (low-quality evidence).

3.3.6. Hospital admission, suicidal ideation and suicide attempts

The rate of hospitalization for psychiatric reasons was not significantly different between the OFC group and the placebo, olanzapine or lamotrigine groups. Only one study reported suicidal ideation and suicide attempts, and such outcomes were not significantly different between the OFC and lamotrigine groups. The quality of this body of evidence was very low.

3.3.7. Discontinuation

Discontinuation rates were reduced in the OFC group compared with the placebo group (NNT=8; 95% CI: 4, 25) and the olanzapine group (NNT=4; 95% CI: 3, 7). No statistically significant difference was found in comparison to lamotrigine. However, when assessing discontinuation due to mania, no significant differences between groups were observed (very low-quality evidence).

3.3.8. Adverse effects

Adverse effects were more common in the OFC group than in the lamotrigine group (NNH=17; 95% CI: 9, 97), and no difference was found when the OFC group was compared to the olanzapine group. In contrast, serious adverse events were less common in the OFC group compared with the lamotrigine group (NNT=16; 95% CI: 9, 103). The quality of evidence for these outcomes was rated as low.

The risk of mania was not significantly different when comparing the OFC group to the placebo, olanzapine, lamotrigine (Table 3) or fluoxetine groups (RR=0.89; 95% CI: 0.07, 12.01). The quality of evidence for this outcome was rated as moderate.

OFC showed a significant increase in weight gain compared to all other treatments except olanzapine (lamotrigine: NNH=5; 95% CI: 4, 7; placebo: NNH=7; 95% CI: 4, 15). These associations were more pronounced for clinically important weight gain (lamotrigine: NNH=4; 95% CI: 3, 8; placebo: NNH=5; 95% CI: 9, 4). Similar results were found for mean weight gain (OFC group compared to placebo: OR=8.64; 95% CI: 5.52, 13.50; and to lamotrigine: OR=7.46; 95% CI: 5.07, 10.98). The quality of this evidence was rated as low.

Other adverse effects are described in Supplementary Table 2. Higher risks for the following clinical disturbances were observed with the OFC group compared to the lamotrigine and control without olanzapine groups: alanine aminotransferase, aspartate aminotransferase, cholesterol, low-density lipoprotein cholesterol, triglycerides, appetite, and disturbance in attention. Somnolence and tremors were more common in the OFC group compared to the placebo, lamotrigine and control without olanzapine groups.

4. Discussion

Our meta-analyses of OFC use relative to other monotherapies including lamotrigine, olanzapine and fluoxetine suggest that OFC therapy leads to significant improvements in various outcomes, such as response, remission and relapse rate in bipolar depression, without being associated with a greater increase in manic episodes. However, OFC was associated with worse adverse effects compared to all alternatives except olanzapine. These aspects may support a therapeutic role for OFC as an alternative for bipolar depressed patients with indications for olanzapine use. Investigations into health-related quality of life, an outcome that is particularly important to patients, were scarce. Nevertheless, positive effects on the quality of life have been shown and should be considered when selecting a therapy. The quality of the evidence for the outcomes assessed was either low or very low, supporting only limited confidence in the estimates and leaving concerns about the use of OFC in clinical practice.

Acute depression is a very important component of bipolar disorder. Targeted interventions for this phase, including antipsychotics associated with selective serotonin reuptake inhibitor antidepressants, such as fluoxetine, have been associated with stronger clinical responses (Citrome, 2011). This effect likely relies on the inhibition of neuronal uptake, which boosts serotonergic neurotransmission (Deeks and Keating, 2008). In addition, the mood-stabilizing properties of olanzapine might explain the absence of increases in treatment-emergent mania with serotonin reuptake inhibitor use (DelBello et al., 2006; Sachs et al., 2000; Post et al., 2006). The poor adverse effects profile appears to be strictly associated with olanzapine and not fluoxetine because the incidence of adverse effects was similar between the combined therapy and olanzapine alone, while weight gain, somnolence and tremor were less frequent in the controls without olanzapine. These findings are consistent with the clinical research and practice profile of olanzapine (De Fruyt et al., 2012; Deeks and Keating, 2008).

Although our review did not assess adjunctive non-pharmacological therapies, evidence supports the use of psychological

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interventions in bipolar disorder. Clinical guidelines recommend that all patients should be offered group or individual psychoeducation (Connolly and Thase, 2011). A health technology assessment report included three trials ($n=239$) that showed significantly fewer manic and depressive relapses in participants attending group psychoeducation than in those attending non-structured group meetings (Soares-Weiser et al., 2007). A subsequent multicenter RCT ($n=204$) compared brief psychoeducation to longer cognitive-behavior therapy and attested to similar efficacy at a cost that was ten times lower (Parikh et al., 2012). Caregiver psychoeducation also significantly improved patient recurrence in another RCT ($n=113$) compared with no intervention (Reinares et al., 2008). Two clinical trials assessed psychoeducation in an insufficient number of bipolar patients and lacked statistical power (Van Dijk et al., 2012; Madigan et al., 2012). One pragmatic cluster trial comparing psychoeducation to non-structured group support is now ongoing (planned sample=358) (Morriss et al., 2011). We believe that the results of this ongoing trial are unlikely to change the confidence in psychoeducation effects.

To the best of our knowledge, this is the first meta-analysis to address the efficacy of OFC in acute bipolar depression not focused on a single drug class comparison. Similar questions were handled in a review evaluating placebo comparisons (only one study) (Vieta et al., 2010). The findings of that study also favor the use of olanzapine–fluoxetine for better rates of response and/or remission. Similar positive findings with respect to response rates can also be found in other reviews (Deeks and Keating, 2008) and discussion papers (Citrome, 2011). These authors emphasize the fact that studies comparing OFC use to other antipsychotic treatments for bipolar depression, such as quetiapine (De Fruyt et al., 2012; Goodwin, 2009), have not been performed. The poor adverse events observed here, particularly increased somnolence, weight gain and elevation in metabolic factors, have also been widely discussed by other authors (Deeks and Keating, 2008; Citrome, 2011). However, some of our results, such as the improvement in depressive and manic symptoms in comparison with lamotrigine, are quite different from previous conclusions (Vieta et al., 2010; Deeks and Keating, 2008).

The present results are limited because of the small number of studies and the risk of attrition and reporting bias. Our quality assessment also has important limitations associated with the indirectness of translating the results of a range of comparisons into a single statement about the superiority of the association therapy. Publication bias might be suspected despite the use of a grey literature search to mitigate this risk because the pharmaceutical industry supported all of the RCTs. However, all of these limitations were considered when evaluating the quality of evidence, and they underlie the overall low- and very low-quality findings.

The strengths of this work are related to the breadth of the search, which retrieved a very confident diagnosis about the clinical research status of OFC intervention. Our systematic, paired selection and extraction argues against a methodological bias. Another particular feature is that the results discussed, including the evaluation of OFC against olanzapine, are based on studies with head-to-head comparisons, which are rare in studies of selective serotonin reuptake inhibitors. Finally, our assessment of the body of evidence based on evaluations of the risk of bias and the quality of evidence reinforce our critical appraisal of the studies included and provide transparent support for future recommendations (Higgins and Green, 2011).

Future studies with better treatment adherence rates would produce results that are more confident and provide the statistical power necessary to evaluate other major issues, such as the prevention of suicide attempts, which are a significant life-threatening occurrence in depressive episodes (Deeks and Keating, 2008). Moreover, study designs including additional outcomes, such as health-related quality of life, could provide a more thorough assessment of treatment effectiveness. Further comparisons, such as to other second-generation antipsychotics and mood stabilizers, would be desirable to establish the superiority of OFC. Ideally, these RCTs would also focus on bipolar II patients because of the higher severity of mood symptoms associated with bipolar II relative to bipolar I and the need for evidence to support related recommendations (Swartz and Thase, 2011; Merikangas and Lamers, 2012; Linnavuori and Hovi, 1987).

In conclusion, the use of OFC instead of some existing monotherapies, particularly olanzapine, shows benefits in response, remission, quality of life, severity of symptoms, relapse and discontinuation. No increased risk of mania, the most important contradiction to its use, was observed. However, OFC therapy is not harmless. A trade-off between the risks and potential benefits should be considered in clinical decisions about whether to adopt OFC therapy.

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Conflict of interest

None of the authors has any conflict of interest in the context of this work.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jad.2012.11.001.

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