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Artículo original

Olanzapine and fluoxetine combined as therapy for treatment-resistant depression: a systematic review

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ABSTRACT

Objective: we conducted a systematic review to evaluate the evidence for the efficacy and safety of olanzapine-fluoxetine combined (OFC) in patients with treatment-resistant depression (TRD). *Material and methods:* MEDLINE, EMBASE, Cochrane Library, ClinicalTrials.gov, and LillyTrials.com were searched (28 February 2014) using terms related to TRD and OFC (no language restrictions). All prospective studies of OFC treatment of TRD were included. *Results:* we included 16 studies (5 meta-analyses, 3 pooled analyses, 7 randomized controlled trials [RCTs], 1 nonrandomized, open-label trial); unpublished data of open-label extensions were available for 4 RCTs. The definition of TRD varied; most studies defined TRD as response failure after 2 antidepressant trials of≥4 weeks. All RCTs compared OFC with fluoxetine. Treatment duration was 4 12 weeks in RCTs, and 8 76 weeks in open-label studies. Depressive symptoms improved with OFC treatment in all studies; improvement was generally greater and occurred earlier than with fluoxetine and was sustained during longer-term treatment. Response (27.5%-80%) and remission (16.9%-73.3%) rates were generally greater than with fluoxetine. Weight gain and changes in metabolic parameters were generally more common in patients treated with OFC than with fluoxetine. Other adverse events and discontinuation rates were similar to those seen with fluoxetine. *Conclusions:* evidence from prospective studies supports the efficacy of OFC in the treatment of TRD, which is sustained with longer-term treatment. However, there may be a greater risk of weight gain and changes in metabolic parameters. Physicians may consider OFC as treatment for TRD, provided the risks of weight gain and metabolic changes are actively managed.

Key words: antipsychotic agents, depressive disorder, treatment-resistant, olanzapine-fluoxetine combination.

La combinación olanzapina/fluoxetina como tratamiento para la depresión resistente al tratamiento: una revisión sistemática

RESUMEN

Objetivo: se realizó una revisión sistemática para evaluar la evidencia de la eficacia y seguridad de la combinación olanzapina/fluoxetina (COF) en pacientes con depresión resistente al tratamiento (DRT). *Material y métodos:* se realizaron búsquedas a través de MEDLINE, EMBASE, Cochrane Library, ClinicalTrials.gov, y LillyTrials.com (28 de febrero de 2014) utilizando términos relacionados con DRT y COF (restricciones de idioma). Todos los estudios prospectivos de tratamiento con COF en DRT fueron incluidos. *Resultados:* se incluyeron 16 estudios (5 meta-análisis, 3 análisis agrupados, 7 ensayos controlados aleatorios [ECA], y un estudio abierto no aleatorizado); los datos no publicados de la extensión abierta estuvieron disponibles para 4 ECA. La definición de DRT varió; la mayoría de los estudios definieron DRT como una respuesta insuficiente después de 2 ensayos con antidepresivos de ≥4 semanas. Todos los ECA compararon COF con fluoxetina. En los ECA, la duración del tratamiento fue de 4 a 12 semanas, y de 8 a 76 semanas en los estudios abiertos. Los síntomas depresivos mejoraron con el tratamiento de COF en todos los estudios; la mejoría fue; por lo general, mayor y ocurrió más temprano que con fluoxetina y se mantuvo durante el tratamiento a largo plazo. Las tasas de respuesta (27.5 a 80%) y remisión (16.9 a 73.3%) fueron; por lo general, mayores que con fluoxetina. La ganancia de peso y cambios en los parámetros metabólicos

fueron por lo general más comunes en pacientes tratados con COF que con fluoxetina. Otros eventos adversos y las tasas de discontinuación fueron similares a los observados con fluoxetina. *Conclusiones:* la evidencia de estudios prospectivos apoya la eficacia de COF en el tratamiento de DRT, la cual se mantiene con el tratamiento a largo plazo. Sin embargo, puede existir un riesgo mayor de ganancia de peso y cambios en los parámetros metabólicos. Los médicos pueden considerar COF como un tratamiento para DRT, siempre que los riesgos de ganancia de peso y cambios metabólicos sean activamente manejados.

Palabras clave: agentes antipsicóticos, trastorno depresivo mayor, trastorno depresivo resistente al tratamiento, combinación olanzapina/fluoxetina.

Major depressive disorder (MDD) is a common, difficult-to-treat problem, associated with significant personal and societal costs. The global lifetime prevalence of MDD averages 11.1% in low- to middle-income countries and 14.6% in high-income countries, and MDD is almost twice as common in women as in men[1]. Within Latin America, lifetime prevalence rates of 8.0%, 9.2%, 13.3%, and 18.8% have been reported for Mexico, Chile, Colombia, and Brazil, respectively[1,2]. As expected, MDD is a major risk factor for suicide[3] and leads to loss of productivity and the ability to work[4]. Depression is challenging to treat and is often characterized by multiple treatment attempts and relapse after response and remission[5] (figure 1).

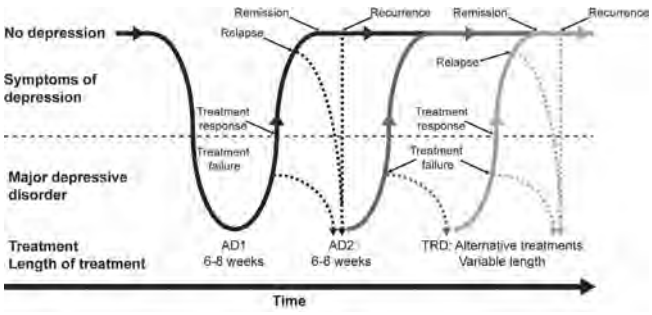

Figure 1. Phases of treatment of major depressive disorder[5]. Abbreviations: AD1 = first antidepressant treatment, AD2 = second antidepressant treatment, TRD = treatment-resistant depression.

Approximately 50% of patients do not experience remission after first- or second-line antidepressant therapy, and approximately 30% do not experience remission after third- or fourth-line therapy[6,7]. Treatment-resistant depression (TRD; also known as refractory depression) is commonly defined as the failure to respond to two or more adequate antidepressant trials (figure 1)[8]. Patients with TRD are more likely to be substance abusers, be admitted to hospital, and have higher healthcare costs compared with patients with MDD who do not have TRD[9,10]. Given the chronic nature of MDD, identifying effective strategies for managing the large proportion of patients with MDD who experience TRD is critical. However, information on the diagnosis and treatment of TRD in Latin American countries is limited, particularly among primary care physicians[11]. In addition, few prospective studies have been conducted within Latin America, as demonstrated by the inability of a previous systematic review to identify any such studies[12].

Both non-pharmacological and pharmacological strategies have been used for the management of TRD. Non-pharmacological strategies include psychotherapy, electroconvulsive therapy, and neurostimulation[8,13], whereas pharmacological strategies include switching to a different antidepressant, combining antidepressants that have different mechanisms of action, and augmenting antidepressants with other neuroactive agents, such as lithium, thyroid hormone, anticonvulsants, or second-generation antipsychotics (SGAs)[8,14]. In particular, the SGAs aripiprazole, quetiapine, risperidone, and olanzapine have been successfully used to augment selective serotonin reuptake inhibitors (SSRIs) in patients with TRD[8, 15]. The combination of olanzapine and the SSRI fluoxetine (olanzapine-fluoxetine combined [OFC]; Symbyax®, Eli Lilly and Company) was approved for TRD in the United States in 2009 after previously being approved for the treatment of depressive episodes associated with bipolar I disorder[15]. Within Latin America, OFC is approved for TRD in Mexico and for depressive episodes associated with bipolar disorder in Mexico, Chile, and Argentina.

A number of reviews, systematic reviews, and meta-analyses have published on the efficacy and safety of OFC for TRD[16-20]. However, most previous reviews have not included information available in clinical trial databases, in particular, information from studies involving longer-term treatment with OFC. Collation of this information may provide important additional detail

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regarding both the immediate and long-term efficacy and safety of OFC treatment for TRD. In this systematic review, we sought to assess the available evidence on efficacy and safety of OFC treatment for TRD, with a particular emphasis on its longer-term profile.

METHODS

Literature search strategy

The following databases were searched on 28 February 2014: MEDLINE via PubMed (1946+), EMBASE via OVID (1974+), The Cochrane Library via www.thecochranelibrary.com (1996+), the ClinicalTrials.gov results database (2008+), and the LillyTrials.com database. Searches of ClinicalTrials.gov and LillyTrials.com were restricted to trials with results. Free-text terms and medical subject headings (MeSH) or EMTREE terms (where possible) were used to search for OFC (olanzapine-fluoxetine combination, fluoxetine plus olanzapine, olanzapine AND fluoxetine, Symbyax) and TRD (including "depressive disorder, treatment-resistant, treatment resistant depression, refractory, major depressive disorder). Searches were conducted with truncation symbols and Boolean operators (AND, OR) as needed. To maximize retrieval of published articles, there were no restrictions on publication type or language, although database search filters that restricted the search output to human studies were used where available.

Eligibility criteria

We included publications of studies that assessed male or female patients of any age with TRD (regardless of definition) who received OFC therapy at any dose. Full-text publications and ClinicalTrial.gov or LillyTrials.com trials with posted results were eligible for inclusion. Study types considered included meta-analyses, systematic reviews, randomized and nonrandomized clinical trials, and prospective observational studies. Narrative reviews, systematic reviews that did not report original data, case reports, case series, nonclinical letters, conference abstracts, editorials, and commentaries were excluded from the review. Excluded publications included studies that were not conducted in humans, studies of patients with conditions other than TRD (eg, bipolar disorder), studies of therapies other than OFC, studies in which data for OFC therapy were pooled with data for other therapies (eg, other augmentation strategies), studies in which data for patients with TRD were pooled with data for patients with other conditions (eg, MDD that was not treatment resistant), studies that did not report relevant outcomes, and retrospective studies.

Study selection and data extraction

One person (not an author) conducted the literature search and screened the titles and abstracts of all publications retrieved using the predefined eligibility criteria. The full text of publications identified for potential inclusion 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 relevant data from the included publications. Data were collected using predefined selection criteria determined by all the persons involved in this review and included publication type and year, study design, patient characteristics, definition of TRD, doses, and efficacy and safety outcomes. For primary studies, aspects relating to study quality (eg, presence/absence and method of randomization, presence/absence of blinding, study population used for analysis) were also assessed. Efficacy outcome measures that were collected included the Montgomery-Asberg Depression Rating Scale (MADRS), the Hamilton Depression Rating Scale (HDRS), the Hamilton Rating Scale for Anxiety (HAM-A), the Clinical Global Impressions-Severity of Illness scale (CGI-S), the Brief Psychiatric Rating Scale, response rates, remission rates, relapse rates, and any other reported efficacy outcomes. Safety outcome measures that were collected included the type, frequency, and severity of adverse events (AEs), the number and reasons for discontinuations, changes in metabolic parameters (eg, weight gain; plasma glucose, cholesterol, triglycerides, and glycosylated hemoglobin [HbA1c] concentrations), and any other reported safety outcomes.

RESULTS

Literature search results

A total of 428 potentially relevant publications were retrieved from the literature search of MEDLINE, EMBASE, and The Cochrane Library and were screened for inclusion (Figure 2). After exclusion of duplicate publications between databases, the primary reason for exclusion was the wrong publication type, followed by publications that did not describe patients receiving OFC therapy. No publications were excluded on the basis of non-English language, and four included publications

were published in Chinese[21-24]. Seven systematic reviews that did not present any new data were excluded (as "wrong publication type")[17, 25-30]. No relevant trials with posted, but unpublished, data were identified on the ClinicalTrials.gov database. Four relevant studies were identified on the LillyTrials.com database[31-34]; all four studies included both published[35-38] and unpublished data. Manual screening of systematic reviews identified 3 additional relevant studies[21-23]. Overall, 16 publications[18, 20-24, 35-44] met the eligibility criteria for inclusion.

Overview of study characteristics

Study design

Of the 16 included publications, 5 described meta-analyses of data from literature searches[18,20,24,41,42], 3 described pooled analyses of in-house trial data[40, 43, 44], 7 described randomized controlled trials (RCTs[21-23,35-38], and 1 described a prospective, nonrandomized trial[39] (table 1). One of the RCT publications described two separate studies, and both separate and pooled data were reported[38]. Additional data for four of the RCTs[35-38], including data from open-label trial extensions, were reported in the LillyTrials.com database.

Of the meta-analyses[18, 20,24,41,42] and pooled analyses[40,43,44] that met the eligibility criteria, all included data from OFC studies that were identified in our search. Only 1 meta-analysis[24] included data from all RCTs identified in our search. Of the other meta-analyses, 1[41] included data from 5 of the 7 RCTs[21, 35-38] identified in our search, 2[18,20] included data from 4 of the 7 RCTs[35-38], and 1[42] included data from 2 of the 7 RCTs[36,38]. Two of the pooled analyses[43, 44] included data from 4 of the 7 RCTs[35-38] identified in our search, and the other[40] included data from 2 of the 7 RCTs[36,37]. The results described hereafter are focused on those from the RCTs and the prospective, nonrandomized trial, except where indicated. Main results from meta-analyses and pooled analyses are described in relation to the collective results from individual studies, particularly where meta-analyses address inconclusive individual results.

The included prospective studies were conducted in a broad range of countries, but predominantly in North America and China (table 1). No studies reported inclusion of Latin American participants; one multinational study[33, 37] did not specify the countries of origin. The RCTs were variable in design, particularly regarding the inclusion/length of screening, washout, dose-escalation, and open-label phases before the start of randomized treatment (table 1). None of the RCTs described the method of randomization. Most, but not all, RCTs specified that the study was double-blinded, that placebos were used, and that analysis was conducted on the intention-to-treat population. Study sample sizes ranged from 52 to 605; a total of 895 participants with TRD received OFC in these studies. The doses of olanzapine and fluoxetine varied between studies, ranging from 1 to 20 mg/day and from 5 to 75 mg/day, respectively. In the RCTs, the duration of treatment in the randomized treatment phase ranged from 4 to 12 weeks, but was most commonly 8 weeks (6 of 8 studies[21, 22, 35, 36, 38]). All of these studies included participants treated with fluoxetine alone as a comparator group. Five studies also included participants treated with olanzapine alone as a comparator group[35-38], and 1 study each included participants treated with nortriptyline[36] or venlafaxine[37] as an additional comparator group. Five of the RCTs[35-38] included an open-label extension phase, which ranged in duration from 8 to 52 weeks. In the nonrandomized trial[39], the duration of open-label treatment was 76 weeks.

TRD definition and baseline depression scores

All studies included participants diagnosed with MDD[35-39] as per the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, or depression[21-23] as per the Chinese Classification and Diagnosis of Mental Diseases, Third edition (table 1). However, the definition of TRD varied between studies. In 5 studies[21-23,35,39], TRD was defined as a failure to respond to 2 different classes of antidepressants after≥4 weeks of treatment (after≥6 weeks in 2 studies[21,23]), whereas in 2 studies[36, 37], TRD was defined as a failure to respond to an SSRI after≥4 weeks of treatment. In 2 of these studies[35, 36], the failure to respond was confirmed during an open-label screening phase. In 2 studies published together[38], TRD was defined as failure to respond to an antidepressant (except fluoxetine) during the current depressive episode. The severity of depression at baseline was assessed using the MADRS in 5 studies[36-39], the HDRS in 3 studies[21-23], and both the MADRS and HDRS in 1 study[35]. In participants treated with OFC, baseline MADRS scores ranged from 28.5 to 32.8 and HDRS scores ranged from 24.5 to 31.4, indicating moderate levels of depression.

Efficacy outcomes

Depression scores

All studies reported a significant improvement in depression scores in participants treated with OFC (table 2). In most studies, but not all, the improvement at endpoint was significantly greater than in participants treated with fluoxetine alone. In the RCTs[21-23,35-38], the

Table 1. Characteristics of included primary studies on the use of olanzapine-fluoxetine combined in patients with treatment-resistant depression.

Publication Country	Study Design	Study Quality	TRD Definition	Other Inclusion Criteria	N	Dose (mg/day)	Mean (SD) Baseline Depression Scores	
							MADRS	HDRS
Randomized controlled trials								
Shelton 2001[35] Lilly registry ID #1034[31] US	6-wk OL screening (FLU 20-60 mg/day); 8-wk DB RCT; 8-wk OLE (OFC)	RCT (method NR); DB (placebos); ITT	Recurrent MDD (DSM-IV); history of failure to respond to 2 AD classes (1 not SSRI) after ≥4 wks; confirmed by no response to FLU during screening	HDRS ≥20	28 in DB OFC: 10 FLU: 10 OLZ: 8 OLE: 22	OLZ: 5-20; FLU: 20-60	OFC: 29.5 (9.2) FLU: 23.8 (8.3) OLZ: 25.0 (3.8)	OFC: 26.4 (7.5) FLU: 23.5 (6.0) OLZ: 24.5 (5.2)
Shelton 2005[36] Lilly registry ID #3079[32] US, Canada	2-7-day screening/ washout; 7-wk OL NOR dose-escalation phase (25-175 mg/day); 8-wk DB RCT Unpub. OLE up to 5 months	RCT (method NR); DB (placebos); ITT	MDD (DSM-IV) diagnosis; history of failure to respond to an SSRI after ≥4 wks; confirmed by failure to respond (<30% ↓MADRS) to NOR dose-	MADRS ≥20 at start & end of screening	500 OFC: 146 FLU: 142 OLZ: 144 NOR: 68 Unpub. OLE: 402	OLZ: 6-12 FLU: 25-50 NOR: 25-175	OFC: 28.5 (7.5) FLU: 28.4 (7.3) OLZ: 28.4 (7.3) NOR: 28.8 (6.5)	NR
Corya 2006[37] Lilly registry ID#3641[33] 16 countries worldwide	2-7 day screening; 7-wk OL lead-in (VEN 75-375 mg/day); 5-9 day DB taper phase; 12-wk DB acute phase Unpub. OLE up to 52 wks	RCT (method NR); DB (placebos); ITT	Single or recurrent MDD (DSM-IV) without psychotic features and history of treatment failure with SSRI for ≥6 wks	Single or recurrent MDD (DSM-IV) without psychotic features and history of treatment failure with SSRI for ≥6 wks; CGI-S≥4	483 OFC 1/5 mg/day (pseudo-placebo): 59 OFC: 243 FLU: 60 OLZ: 62 VEN: 59 Unpub. OLE: 345	OLZ: 1, 6, or 12 FLU: 5, 25, or 50 VEN: 75-375	30.0 (6.8)	NR
Li 2006[22] China	8-wk DB RCT	RCT (method NR); DB (placebo use NR); analysis population NR	HDRS≥18 after treatment with ≥2 AD (different classes, 1 not an SSRI) for ≥4 wks	Diagnosis of depression using CCMD-3 criteria; HDRS≥18	OFC: 26 FLU: 26	OLZ: 5-20 FLU: 20-40	NR	OFC: 29.2 (5.8) FLU: 31.2 (4.7)
Wang 2006[23] China	RCT 1-wk washout; 4-wk treatment	RCT (method NR); blinding NR; analysis population NR	Failure to respond (↓HDRS<30%) to ≥2 AD (different classes) for ≥6 wks	Diagnosis of depression using CCMD-3 criteria; HDRS≥18	OFC: 36 FLU: 38	OLZ: 5-10 FLU: 20	NR	OFC: 24.45 (6.01) FLU: 24.18 (5.82)
Thase 2007[38] Lilly registry ID#6272[34] US, Canada	2 identical parallel studies 3-14 day screening; 8-wk OL lead-in (FLU 25-50 mg/day); 8-wk DB Unpub. 8-wk OLE	RCT (method NR); DB (placebos implied; investigators blind to scores); ITT	History of treatment failure to AD (except FLU) after ≥6 wks within current episode of MDD	MDD (DSM-IV) diagnosis without psychotic features, confirmed by SCID-I, HDRS ≥22	605 OFC: 200 FLU: 206 OLZ: 199 Unpub. OLE: 460	OLZ: 6, 12, or 18 FLU: 50	Pooled OFC: 30.1 (6.7) FLU: 29.9 (6.4) OLZ: 29.9 (6.7)	NR
Feng 2008[21] China	OL 8-wk RCT	RCT (method NR); OL; analysis population NR	History of treatment failure to ≥2 different classes of AD after ≥6 wks each	Diagnosis of depression using CCMD-3 criteria	60 OFC: 30 FLU: 30	OLZ: 2.5-5 FLU: 20-40	NR	OFC: 31.43 (6.26) FLU: 31.10 (5.98)
Prospective, nonrandomized, open-label study								
Corya 2003[39] 7 countries	2-7 day screening/ washout; 76-wk OL	Not randomized; OL	History of treatment failure to ≥2 AD classes after ≥4 wks	MDD (DSM-IV) diagnosis: CGI-S score ≥3	560 (enrolled) 552 (analyzed) TRD: 145 Non-TRD: 407	OLZ: 6, 12, or 18 FLU: 25, 50, or 75	32.8 (6.9)	NR

Abbreviations: AD = antidepressant, CCMD-3 = Chinese Classification and Diagnosis of Mental Diseases, Third edition, CGI-S = Clinical Global Impressions-Severity of Illness Scale; DB = double-blind, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, FLU = fluoxetine, HDRS = Hamilton Depression Rating Scale, ITT = intention-to-treat population, MADRS = Montgomery-Åsberg Depression Rating Scale, MDD = major depressive disorder, NOR = nortriptyline, NR = not reported, OFC = olanzapine-fluoxetine combination, OL = open-label, OLE = open-label extension, OLZ = olanzapine, RCT = randomized controlled trial, SCID-I = Structured Clinical Interview for DMS-IV Axis I Disorders-Clinician Version, SD = standard deviation, SSRI = selective serotonin reuptake inhibitor, TRD = treatment-resistant depression, unpub. = unpublished data from study (obtained via Lilly Trials), US = United States, VEN = venlafaxine, wk = week.

improvement in depression scores at the end of the randomized treatment phase was significantly greater or similar for participants treated with OFC compared with participants treated with fluoxetine. In 2 of 5 studies[35,38] in which MADRS scores were assessed, participants treated with OFC had significantly greater improvement at endpoint compared with participants treated with fluoxetine alone. In the other 3 studies[36-38], there was no significant difference in MADRS score improvement at endpoint between participants treated with OFC and those treated with fluoxetine alone. In 3 of 4 studies[21-23] in which HDRS scores were assessed, participants treated with OFC had significantly greater improvement compared with participants treated with fluoxetine alone. In the other study[35], there was no significant difference in HDRS score improvement at endpoint between participants treated with OFC and those treated with fluoxetine alone. In 6 studies[21-23, 35-37], improvement in depression scores occurred significantly earlier (after 1 to 6 weeks of treatment) in participants treated with OFC compared with participants treated with fluoxetine alone. In all but one RCT (Study 1 in Thase *et al*[38]) that included a comparator group treated with olanzapine only[35-38], OFC was associated with a greater reduction in depression scores than olanzapine alone at some or all timepoints.

In all RCTs with open-label extensions[32-35], depression scores improved from the start of the randomized treatment phase to the end of the extension phase. In 3 studies[32-34], MADRS scores significantly improved from the start to the end of the open-label extension phase (8 to 52 weeks). In the other study[35], significant improvements in MADRS and HDRS scores observed at the end of the randomized treatment phase were maintained during the 8-week, open-label extension phase. In the nonrandomized trial[39], MADRS scores were significantly improved from baseline at the 72-week endpoint.

Consistent with the individual studies, meta-analyses and pooled analyses of RCTs reported greater improvements in depression scores in participants treated with OFC compared with those treated with fluoxetine[20,24,41,43,44].

Response rate

Although response rate definitions varied among the studies, overall, a considerable proportion (27.5% to 80%) of participants responded to OFC treatment (Table 2). In the 7 RCTs reporting data[21,23,35-38], the response rate at the end of the randomized treatment phase was higher or similar for participants treated with OFC compared with participants treated with fluoxetine. In the 3 RCTs that defined response as a decrease in MADRS score of≥50%[35-38], the response rate for participants treated with OFC ranged from 27.5% to 60% (vs 10% to 33.9% for participants treated with fluoxetine). In the 3 RCTs that defined response as a decrease in HDRS score of ≥30%[23,35], the response rate for participants treated with OFC ranged from 66.7 % to 80% *(vs* 30.6% to 40% for participants treated with fluoxetine). In one other RCT that reported multiple measures of response based on the extent of change in HDRS score[21], 73.3% of participants treated with OFC responded with a decrease in HDRS score of ≥25% compared with 61.8% of participants treated with fluoxetine. In the RCTs that included an olanzapine only treatment group, the response rate for this group ranged from 0% to 35.8% and was lower than or similar to the OFC response rate[35-38].

Two RCTs with open-label extension phases reported response rate results[32,33] (table 2). Response rates at the end of the open-label extension phase were 33.7% and 70.91% among participants who met response criteria at the end of the randomized phase, and 20.63% and 29.8% among those who did not meet response criteria at the end of the randomized phase. In the nonrandomized trial[39], the response (decrease in MADRS score by≥50%) rate was 53.1%.

Three meta-analyses[18,24,41] and two pooled analyses[43,44] reported significantly higher response rates in participants treated with OFC compared with those treated with fluoxetine, whereas one meta-analysis[20] reported that the response rates did not differ between treatment groups.

Remission rate

Although remission rate definitions varied among the studies, overall, a considerable proportion (16.9% to 73.3%) of participants treated with OFC experienced remission (table 2). In the 6 RCTs reporting data[21,31,36-38], the remission rate at the end of the randomized treatment phase was higher for participants treated with OFC compared with participants treated with fluoxetine alone. In the 3 studies[31,36,37] that defined remission as a MADRS score ≤8 at 2 consecutive visits, remission rates for participants treated with OFC ranged from 16.9% to 60% (vs 13.3% to 20% for participants treated with fluoxetine). In 3 other studies that defined remission differently[21, 38], remission rates for participants treated with OFC in these studies were 23.8%[38], 30.9%[38], and 73.3%[21] *(vs* 17.6%, 15.8%, and 40.0%, respectively, for participants treated with fluoxetine). In the RCTs that included an olanzapine only treatment group, the remission rate for this group ranged from 10.8% to 25% and was lower than or similar to the OFC

Table 2. Primary efficacy outcomes of studies of combined olanzapine-fluoxetine in patients with treatment-resistant depression.

Publication	Mean (SD) Change in Depression Score (*P* value vs OFC)	Response Rate	Remission Rate	Relapse Rate
Randomized controlled trials				
Shelton 2001[35] Lilly registry ID #1034[31]	MADRS: OFC: -13.6 (11.9) FLU: -1.2 (11.0) (*P*=0.006) OLZ: -2.8 (6.0) (*P*=0.03) Change significant through OL for OFC HDRS: OFC: -11.7 (10.6) FLU: -3.8 (9.6) (*P*=0.07) OLZ: -5.9 (5.2) (*P*=0.03) Change significant through OL for OFC	Unpub. MADRS ↓≥50%: OFC: 60% FLU: 10% OLZ: 0% (*P*=0.013 vs OFC) HDRS ↓≥30%: OFC: 80% FLU: 40% OLZ: 25%	Unpub. MADRS ≤8 at 2 consecutive visits: OFC: 60% FLU: 20% OLZ: 25% All NS	Unpub. MADRS ≥16 after remitting: OFC: 33.3% FLU: 0% OLZ: 100% All NS
Shelton 2005[36] Lilly registry ID #3079[32]	MADRS LSM (SE) for OFC Wk 0.5: -3.63 (0.65), NS Wk 1: -6.90 (0.65), *P*=0.007 vs NOR Wk 2: -8.99 (0.65), *P*<0.001 vs FLU & NOR *P*=0.029 vs OLZ Wk 3: -9.22 (0.65), *P*<0.001 vs FLU & NOR Wk 4: -9.94 (0.66), *P*≤0.001 vs FLU & NOR, *P*=0.026 vs OLZ Wk 5: -9.00 (0.67), *P*=0.05 vs FLU Wk 6: -9.36 (0.68), *P*=0.043 vs OLZ Wk 7: -8.91 (0.69), *P*=0.036 vs OLZ Wk 8: -8.71 (0.70), NS Unpub. OLE Mean (SE) OLE baseline: 20.03 (0.48); change,-2.13 (0.49), *P*<0.001	MADRS ↓≥50%: OFC: 27.5% FLU: 28.9% OLZ: 19.3% NOR: 30.3% NS Unpub. OLE 70.91% in pts who met response criteria at DB end; 20.63% in pts who did not meet response criteria at DB end (NS between DB phase groups)	MADRS ≤8 at 2 consecutive visits: OFC: 16.9% FLU: 13.3% OLZ: 12.9% NOR: 18.2% NS Unpub. OLE 17.86% (NS between DB phase groups)	Unpub. MADRS ≥16 after remitting: OFC: 20.8% FLU: 5.6% OLZ: 5.6% NOR: 0% All NS Unpub. OLE (remitters with MADRS ≥16 at 2 later visits): 16.67% (NS between DB phase groups)
Corya 2006[37] Lilly registry ID#3641[33]	MADRS: Wk 1: OFC, -7.2; OLZ, -4.8 (*P*=0.03); FLU, -4.7 (*P*=0.03); VEN, -3.7 (*P*=0.002) Wk 1-6: Significantly greater change in OFC than other groups Wk 7-11: Significantly greater change in OFC than OLZ and FLU Wk 12: Significantly greater change in OFC (-14.1) than OLZ (-7.7, *P*<0.001) Unpub. OLE Mean (SD) OL baseline: 16.128 (9.551), change: -1.918 (9.617), *P*<0.001 Changes maintained during OL	≥50%↓MADRS OFC: 43.3% FLU: 33.9% OLZ: 25.4% VEN: 50.0% OFC 1/5: 36.4% Overall *P*=0.04 OFC greater than OLZ, *P*=0.017 Unpub. OLE 33.7% in pts who met response criteria at DB end 29.8% in pts who did not meet response criteria at DB end (NS between groups)	MADRS ≤8 at 2 consecutive visits OFC: 29.9% FLU: 17.9% OLZ: 13.6% VEN: 22.4% OFC 1/5: 20.0% Overall *P*=0.05 OFC greater than OLZ, *P*=0.013 Unpub. OLE 36.9% (NS between DB groups)	Unpub. Remitters with MADRS ≥16 at 2 consecutive visits DB phase OFC: 15.9% FLU: 0% OLZ: 37.5% VEN: 7.7% OFC 1/5: 9.1% NS between groups Unpub. OLE 12.6%, NS between DB groups
Li 2006[22]	HDRS Wk 2: OFC: -7.69 (5.02); FLU: -5.54 (3.31) Wk 4: OFC: -14.38 (6.39); FLU: -10.23 (5.83) Wk 6: OFC: -31.85 (12.78); FLU: -19.00 (11.88), *P*<0.05 Wk 8: OFC: -48.46 (20.75); FLU: -29.54 (16.85), *P*<0.05	NR	NR	NR
Wang 2006[23]	HDRS Wk 1: OFC: 18.38 (7.43); FLU: 20.12 (6.81) Wk 2: OFC: 14.27 (7.63); FLU: 17.95 (7.39), *P*<0.05 Wk 4: OFC: 11.91 (7.85); FLU: 17.19 (7.58), *P*<0.01	↓HDRS≥30% OFC: 66.7%, *P*<0.01 vs FLU FLU: 30.6%	NR	NR

Table 2. Primary efficacy outcomes of studies of combined olanzapine-fluoxetine in patients with treatment-resistant depression.

Publication	Mean (SD) Change in Depression Score (*P* value vs OFC)	Response Rate	Remission Rate	Relapse Rate
Thase 2007[38] Lilly registry ID#6272[34]	MADRS: Study 1 (OFC NS vs OLZ and FLU) OFC: -10.8 (10.0) FLU: -9.4 (9.9) OLZ: -10.1 (9.6) Study 2 (OFC *P*<0.001 vs OLZ and FLU) OFC: -14.6 (10.2) FLU: -9.0 (9.5) OLZ: -7.7 (8.2) Pooled (OFC *P*<0.001 vs OLZ and FLU) OFC: -12.6 (10.3) FLU: -9.2 (9.7) OLZ: -8.9 (9.0) Unpub. OLE Mean (SE) OL baseline: 18.92 (0.48); change, -4.26 (0.42), *P*<0.001 HAM-A Study 1 (OFC NS vs OLZ and FLU) OFC: -6.0 (6.6) FLU: -6.3 (6.3) OLZ: -5.1 (7.2) Study 2 (OFC *P*<0.001 vs OLZ, *P*=0.001 vs FLU) OFC: -8.0 (6.8) FLU: -5.1 (6.7) OLZ: -4.7 (5.8) Pooled (OFC *P*=0.002 vs OLZ, *P*=0.051 vs FLU) OFC: -6.9 (6.8) FLU: -5.7 (6.6) OLZ: 4.9 (6.5)	↓MADRS ≥50% Study 1 (NS between groups) OFC: 36.6% FLU: 29.4% OLZ: 35.8% Study 2 OFC: 44.3% FLU: 29.7%, *P*=0.039 vs OFC OLZ: 16.7%, *P*<0.001 vs OFC Pooled OFC: 40.4% FLU: 29.6%, *P*=0.028 vs OFC OLZ: 25.9%, *P*=0.003 vs OFC	MADRS ≤10 at end Study 1 (NS between groups) OFC: 23.8% FLU: 17.6% OLZ: 18.9% Study 2 OFC: 30.9% FLU: 15.8%, *P*=0.018 vs OFC OLZ: 10.8%, *P*<0.001 vs OFC Pooled OFC: 27.3% FLU: 16.7%, *P*=0.012 vs OFC OLZ: 14.7%, *P*=0.003 vs OFC	NR
Feng 2008[21]	HDRS Scores Wk 1: OFC: 27.40 (5.24); FLU: 30.63 (5.82), *P*<0.05 Wk 2: OFC: 22.03 (4.30); FLU: 26.23 (5.53), *P*<0.01 Wk 4: OFC: 16.17 (5.67); FLU: 22.23 (6.85), *P*<0.01 Wk 8: OFC: 12.96 (7.56); FLU: 19.93 (8.10), *P*<0.01 HDRS % reduction Wk 1: OFC: 12.21 (8.41); FLU: 1.45 (2.20), P<0.01 Wk 2: OFC: 28.37 (14.11); FLU: 15.42 (9.65), *P*<0.01 Wk 4: OFC: 45.64 (23.26); FLU: 28.18 (18.03), *P*<0.01 Wk 8: OFC: 55.26 (29.18); FLU: 35.50 (23.72), *P*<0.05	Cured (HDRS<7) OFC, 23.3%; FLU, 10% Significant improvement (↓HDRS≥50%): OFC, 26.7%; FLU,13.3% Some improvement (↓HDRS 25-49%): OFC, 23.3%; FLU, 38.5% No improvement (↓HDRS<25%): OFC, 26.7%; FLU,60.0%	↓HDRS≥50% or HDRS<7 OFC, 73.3%; FLU, 40.0%	NR
Prospective, nonrandomized, open-label study				
Corya 2003[39]	MADRS Wk 0.5: -7.2 (19.5%) Wk 1: -10.8 (31.7%) Wk 8: -16.2 (46.8%) Wk 76: -19.2 (55.9%) *P*=0.0001 vs baseline at all time points	↓MADRS ≥50% TRD: 53.1% Log-rank *P*=0.026 vs non-TRD	MADRS ≤8 at 2 consecutive visits TRD: 44.1% Log-rank *P*=0.029 vs non-TRD	MADRS ≥16 at 2 visits after remission TRD: 25.0% Log-rank *P*=0.007 vs non-TRD

Abbreviations: DB = double-blind, FLU = fluoxetine, HAM-A = Hamilton Rating Scale for Anxiety, HDRS = Hamilton Depression Rating Scale, LSM = least squares mean, MADRS = Montgomery-Åsberg Depression Rating Scale, NOR = nortriptyline, NR = not reported, NS = not significant, OFC = olanzapine-fluoxetine combined, OL = open-label, OLE = open-label extension, OLZ = olanzapine, pts = participants, SD = standard deviation, SE = standard error, unpub. = unpublished data from study (obtained via Lilly Trials), VEN = venlafaxine, wk = week.

remission rate[35-38]. Only 1 RCT with an open-label extension[33] reported the remission rate (36.9%). In the nonrandomized trial[39], the remission (MADRS score ≤8 at 2 consecutive visits) rate was 44.1%. Consistent with the individual studies, meta-analyses and pooled analyses reported significantly higher remission rates in participants treated with OFC compared with those treated with fluoxetine[18,20,41,43,44].

Relapse rate

Few studies reported relapse rates (table 2). In the RCTs reporting data[31-33], the relapse rate in the randomized treatment phase was consistently higher for participants treated with OFC compared with participants treated with fluoxetine alone. In these studies[31-33], relapse was defined as a MADRS score ≥16 at 2 consecutive visits after remission. Relapse rates for participants treated with OFC ranged from 15.9% to 33.3% *(vs* 0% to 5.6% for participants treated with fluoxetine alone). Only 1 RCT with an open-label extension[33] reported the relapse rate (12.6%). In the nonrandomized trial[39], the relapse (MADRS score ≥16 at 2 consecutive visits after remission) rate was 25.0%. Consistent with the individual studies, 1 meta-analysis reported an odds ratio (fluoxetine relative to OFC) for relapse of 0.27 (95% CI, 0.08 to 0.90), indicating that participants went into remission after treatment with OFC were more likely to relapse than those treated with fluoxetine[20].

Safety outcomes

Discontinuations

In the RCTs[21-23, 35-38], the proportion of participants who discontinued during the randomized treatment phase was similar for participants treated with OFC and those treated with fluoxetine alone (table 3). The discontinuation rate for any reason ranged from 0% to 26.0% (vs 0% to 30% for fluoxetine), because of an AE from 0% to 13.5% *(vs* 0% to 5.0% for fluoxetine), and because of lack of efficacy from 0% to 5.3% (vs 0% to 10% for fluoxetine). In the RCTs with open-label extensions[31-34], the proportion of participants who discontinued was generally low and increased with the duration of the extension phase. The discontinuation rate for any reason ranged from 4.5% to 47.0%, because of an AE from 10.2% to 18.8%, and because of lack of efficacy from 5.7% to 18.4%. In the nonrandomized trial[39], the proportion of participants who discontinued for any reason, an AE, and lack of efficacy was 74.5%, 24.5%, and 14.1%, respectively. Three meta-analyses[18, 41,42] and one pooled analysis[44] examined discontinuation rates. The odds ratio or the increase in absolute risk of discontinuation for any reason was not significant in participants treated with OFC compared with those treated with fluoxetine alone[18, 41]. The odds ratio or the increase in absolute risk of discontinuation because of an AE was significant in participants treated with OFC compared with those treated with fluoxetine alone[18,41,42,44].

Weight gain

In the RCTs reporting data[21,35-38], participants treated with OFC consistently experienced more weight gain in the randomized phase compared with participants treated with fluoxetine alone. Mean weight gain for participants treated with OFC ranged from 3.28 kg to 6.67 kg *(vs* -1.42 kg to 0.88 kg for participants treated with fluoxetine). In the RCTs with open-label extensions[31-34], the proportion of participants treated with OFC who had weight gain ≥10% total body weight ranged from 8.3% to 24.5%. In the nonrandomized trial[39], mean weight gain was 5.6 kg and the proportion of participants who had weight gain ≥10% total body weight was 31%. Consistent with the individual studies, 1 meta-analysis[20] and 1 pooled analysis[44] reported significantly greater weight gain in participants treated with OFC compared with those treated with fluoxetine. The meta-analysis reported an odds ratio for weight gain ≥10% of 16.28 (95% CI, 7.02 to 37.76), an effect size of +4.20 kg (95% CI, 3.79 to 4.61; $P < 0.001$) and a number needed to harm for weight gain of 9 (95% CI, 5 to 29)[20]. The pooled analysis reported a higher proportion of participants with weight gain ≥ 7% and a greater mean (SD) weight gain for those treated with OFC (40.4%; +4.42 [3.75] kg) than those treated with fluoxetine (2.3%; –0.15 [2.64] kg; $P < 0.001$ both comparisons)[44]. Another pooled analysis identified early weight gain (≥2 kg after 2 weeks) as a predictor of substantial weight gain (≥10 kg after 26 weeks)[40].

Metabolic parameters

Data on metabolic parameters (plasma glucose, total cholesterol, triglycerides, HbA1c) were mixed, with some, but not all, RCTs reporting differences between treatment groups in the change from baseline or incidence of low/high levels. Three RCTs[36-38] reported a significantly greater change in plasma total cholesterol in participants treated with OFC than in those treated with fluoxetine for 8 to 12 weeks. In all studies reporting data[31-34,38,39], including the longer-term, open-label studies, the proportion of participants treated with OFC whose metabolic parameters were abnormally high ranged from 0.8% to 7.7%. One pooled analysis[44] reported that increases in plasma glucose and total cholesterol concentrations were significantly greater in participants treated with OFC than in participants treated with fluoxetine. One meta-analysis[20] reported an odds ratio (OFC relative to fluoxetine) for elevated metabolic parameters of 4.46 (95% CI, 2.07 to 9.58) and a number needed to harm of 10 (95% CI, 5 to 29).

Table 3. Safety outcomes of studies of olanzapine-fluoxetine combined in patients with treatment-resistant depression.

Publication	Discontinuations	Common Adverse Events[a]	Weight Gain	Metabolic Parameters[b]	Extrapyramidal Symptoms
Randomized controlled trials					
Shelton 2001[35] Lilly registry ID #1034[31]	Unpub.DB Any reason: OFC, 10%; FLU, 30%; OLZ, 25% AE: OLZ, 12.5% (1 ataxia) Lack of efficacy: FLU, 10% Unpub.OLE 4.5% (1 AE, fever secondary to infection)	Unpub. DB Somnolence: OFC, 60%; FLU, 50%; OLZ, 75% Increased appetite: OFC, 80%; FLU, 20%; OLZ, 75% (*P*=0.018) Asthenia: OFC, 50%; FLU, 40%; OLZ, 62.5% Weight gain: OFC, 70%; FLU, 10%; OLZ, 87.5% (*P*=0.002) Headache: OFC, 40%; FLU, 10%; OLZ, 25% Dry mouth: OFC, 30%; FLU, 0%; OLZ, 37.5% Nervousness: OFC, 20%; FLU, 20%; OLZ, 25% Unpub. OLE Somnolence: 18.2% Weight gain: 18.2% Anxiety: 13.6% Asthenia: 13.6% Increased appetite: 13.6%	Mean (SD) weight gain (kg): OFC, 6.67 (4.54), *P*=0.002; FLU, 0.88 (1.33), *P*=0.06; OLZ, 6.07 (2.57), *P*=0.008 Unpub. Weight gain >10%: OFC, 30%; FLU, 0%; OLZ, 50% Unpub. OLE Weight gain >10%: 18.2%	Unpub. DB: Incidence of high glucose, low glucose, low cholesterol, and high cholesterol NS between groups Unpub. OLE: Low cholesterol: 4.8% Low nonfasting glucose: 5.6% High nonfasting glucose: 4.5%	Unpub. DB Parkinsonism: OFC, 0.0%; FLU 33.3%; OLZ, 12.5% Akathisia: OFC, 30.0%; FLU, 22.2%; OLZ, 25.0% Unpub. OLE Parkinsonism: 4.5% Akathisia: 15.0%
Shelton 2005[36] Lilly registry ID #3079[32]	Any reason: OFC, 20.5%; FLU, 19.7%; OLZ: 22.2%; NOR, 11.8% AE: OFC, 6.8%; OLZ, 9.7%; FLU, 2.8%; NOR, 2.9% Lack of efficacy: OFC, 3.4%; OLZ, 4.2%; FLU, 6.3%; NOR, 2.9% Unpub. OLE Any reason: 41.8% AE: 10.2% Lack of efficacy: 18.4%	Unpub. DB Somnolence: OFC, 17%; FLU, 12%; OLZ, 22%; NOR, 15% Increased appetite: OFC, 15%; FLU, 5%; OLZ, 25%; NOR, 6% (*P*<0.001) Asthenia: OFC, 21%; FLU, 12%; OLZ, 18%; NOR, 12% Weight gain: OFC, 17%; FLU, 4%; OLZ, 20%; NOR, 9% (*P*<0.001) Headache: OFC, 13%; FLU, 19%; OLZ, 12%; NOR, 21% Insomnia: OFC, 10%; FLU, 23%; OLZ, 10%; NOR, 9% (*P*=0.002) Anxiety: OFC, 12%; FLU, 10%; OLZ, 9%; NOR, 7% Nervousness: OFC, 11%; FLU, 5%; OLZ, 14%; NOR, 9% Nausea: OFC, 10%; FLU, 16%; OLZ, 3%; NOR, 6% (*P*=0.001) Thinking abnormal: OFC, 10%; FLU, 7%; OLZ, 10%; NOR, 3% Tremor: OFC, 12%; FLU, 2%; OLZ, 5%; NOR, 7% Unpub. OLE Weight gain: 18.5%, asthenia: 16.0%, headache: 15.5%, somnolence: 13.5%, anxiety: 12.0%, increased appetite: 12.0%, insomnia: 10.0%	Mean (SD) weight gain (kg): OFC, 3.28 (3.5); FLU, -1.42 (2.61); OLZ, 2.94 (2.98); NOR, 0.80 (3.06); overall *P*<0.001 Weight gain >10%: OFC, 7.8%; FLU, 0%, *P*=0.001; OLZ, 4.3%, *P*=0.32; NOR, 0%, *P*=0.02 Unpub. OLE Weight gain ≥10%: 13.7% Mean weight gain (OL only): 2.9 kg	Total nonfasting cholesterol: change from baseline greater in OFC (+0.36 mmol/L) than FLU (+0.06 mmol/L, *P*<0.001), OLZ (+0.12 mmol/L, *P*=0.007), and NOR (+0.03 mmol/L, *P*=0.004) Nonfasting glucose: no difference between groups in change from baseline or % pts with baseline glucose <200 mg/dL who had glucose ≥200 mg/dL during study Unpub. OLE Low cholesterol: 0.3% High cholesterol: 3.4% Low nonfasting glucose: 4.9% High nonfasting glucose: 2.7%	Unpub. DB Parkinsonism: OFC, 5.0%; FLU 0.0% (*P*=0.015); OLZ, 2.9%; NOR, 1.5% Akathisia: OFC, 10.1%; FLU, 9.1%; OLZ, 16.2%; NOR, 12.5% Dyskinesia: OFC, 1.4%; FLU, 0.0%; OLZ, 1.4%; NOR, 0.0% Unpub. OLE Parkinsonism: 1.8% Akathisia: 7.3% Dyskinesia: 2.3%

Publication	Discontinuations	Common Adverse Events[a]	Weight Gain	Metabolic Parameters[b]	Extrapyramida l Symptoms
Corya 2006[37] Lilly registry ID#3641[33]	Unpub. DB Any reason: OFC, 25%; OLZ, 29%; FLU, 20%; VEN, 25%; OFC 1/5, 22% AE: OFC, 11.9%; OLZ, 8.1%; FLU, 5.0%; VEN, 1.7%; OFC 1/5, 3.4% Lack of efficacy: OFC, 5.3%; OLZ, 8.1%; FLU, 6.7%; VEN, 11.9%; OFC 1/5, 6.8% Unpub. OLE Any reason: 47.0% Lack of efficacy: 18.9% AE: 11.0%	Weight gain: OFC, 25% (*P*=0.001 vs VEN); FLU, 13%; OLZ, 26%; VEN, 5%; OFC 1/5, 19% Somnolence: OFC, 22% (*P*=0.001 vs FLU, *P*=0.017 vs VEN & OFC 1/5); FLU, 5%; OLZ, 18%; VEN, 8%; OFC 1/5, 8% Increased appetite: OFC, 16% (*P*=0.034 vs VEN); FLU, 7%; OLZ, 16%; VEN, 5%; OFC 1/5, 14% Dizziness: OFC, 14%; FLU, 10%; OLZ, 10%; VEN, 5%; OFC 1/5, 22% Dry mouth: OFC, 13%; FLU, 7%; OLZ, 16%; VEN, 5%; OFC 1/5, 7% Asthenia: OFC, 12%; FLU, 8%; OLZ, 18%; VEN, 8%; OFC 1/5, 8% Peripheral edema: OFC, 11% (*P*=0.004 vs FLU, *P*=0.038 vs VEN); FLU, 0%; OLZ, 8%; VEN, 2%; OFC 1/5, 5% Headache: OFC, 10% (*P*=0.008 vs OFC 1/5); FLU, 17%; OLZ, 10%; VEN, 17%; OFC 1/5, 24% Unpub. OLE Weight gain 23%, somnolence 13%, asthenia 11%, rhinitis 10%, depression 10%	Mean (SD) weight gain (kg): OFC, 4.3 (4.1), significantly greater than FLU or VEN; FLU, 0.0 (2.7); OLZ, 3.5 (3.7); VEN, 0.6 (3.0) Unpub. OLE Weight gain ≥10%: 24.5% Mean weight gain (OL only): 2.9 kg	Nonfasting glucose: NS between groups Cholesterol: mean change significantly greater in OFC (+0.24 mmol/L) than FLU (-0.04 mmol/L, *P*=0.04) and OLZ (-0.09 mmol/L, *P*=0.01), but not VEN (+0.05 mmol/L, *P*=0.14) Unpub. DB phase: Incidence of low glucose, low cholesterol, high cholesterol, low HbA1c, and high HbA1c NS between groups Unpub. OLE: Low cholesterol: 0.9% High cholesterol: 4.4% Low nonfasting glucose: 1.6% High nonfasting glucose: 1.9% Low HbA1c: 0% High HbA1c: 7.7%	Unpub. DB Parkinsonism: OFC, 2.7%; FLU 8.9%; OLZ, 0.0%; VEN, 3.5%; OFC 1/5, 3.8% Akathisia: OFC, 10.1%; FLU, 3.6%; OLZ, 14.3%; VEN, 5.6%; OFC 1/5, 3.8% Dyskinesia: OFC, 0.4%; FLU, 3.6%; OLZ, 1.7%; VEN, 1.8%; OFC 1/5, 0.0% Unpub. OLE Parkinsonism: 1.8% Akathisia: 4.5% Dyskinesia: 2.7%
Li 2006[22]	Any reason: 0%	NR	NR	NR	NR
Wang 2006[23]	AE: 1 pt discontinued due to weight gain	Dry mouth: OFC, 21.2%; FLU, 19.4% Weight gain: OFC, 12.1%; FLU, NR Blurred vision: OFC, 12.1%; FLU, 13.9% Sleepiness: OFC, 18.2%, FLU, 16.7% Constipation: OFC, 15.2%; FLU, NR	NR	NR	NR
Thase 2007[38] Lilly registry ID#6272[34]	Pooled Any reason: OFC, 26.0%; OLZ, 36.2% (*P*=0.031 vs OFC, *P*<0.001 vs FLU); FLU, 19.4% AE: OFC, 13.5%; OLZ, 16.1%; FLU, 2.4%, *P*<0.001 vs OFC and OLZ Lack of efficacy: OFC, 3.5%; OLZ, 9.6% (*P*=0.015 vs OFC); FLU, 6.3% Unpub. OLE Any reason: 18.5% AE: 7.2% Lack of efficacy: 5.7%	Pooled Weight increased: OFC, 35.0% (*P*<0.001 vs FLU): FLU, 6.8%; OLZ, 39.7% Somnolence: OFC, 17.5% (*P*<0.001 vs FLU); FLU, 5.3%; OLZ, 12.1% Increased appetite: OFC, 32.0% (*P*<0.001 vs FLU); FLU, 5.8%; OLZ, 30.7% Dry mouth: OFC, 28.5% (*P*<0.001 vs FLU); FLU, 8.7%; OLZ, 31.7% Peripheral edema: OFC, 12.0% (*P*<0.001 vs FLU); FLU, 1.0%; OLZ, 7.5% Hypersomnia: OFC, 10.5% (*P*<0.001 vs FLU); FLU, 2.4%; OLZ, 11.1% Headache: OFC, 12.5%;	Mean (SD) weight gain (kg): OFC, 4.9 (3.5); FLU. 0.4 (2.3), *P*<0.001 vs OFC; OLZ, 5.5 (3.9) Unpub. OLE Weight gain ≥10% (from OL start): 8.3% Mean weight gain: 2.8 kg	Total cholesterol: change (mean mg/dL [SD]) greater in OFC (+15.1 [32.0]) than FLU (+0.8 [31.7]) and OLZ (+2.7 [34.0]), *P*<0.001 for both Triglycerides: change NS between groups Nonfasting glucose: % with <140 mg/dL at baseline and ≥200 mg/dL: OFC, 1.9%; FLU, 1.8%; OLZ, 4.2%; all NS High HbA1c: OFC 5.6%; FLU, 0%, *P*=0.002 Unpub. DB phase: High triglycerides: OFC, 5.3%; FLU, 1.5%; *P*=0.05	Unpub. DB Parkinsonism: OFC, 2.6%; FLU 1.0%; OLZ, 1.5% Akathisia: OFC, 9.6%; FLU, 6.9%; OLZ, 9.2% Dyskinesia: OFC, 0.5%; FLU, 1.5%; OLZ, 1.0% Unpub. OLE Parkinsonism: 0.9% Akathisia: 2.6% Dyskinesia: 0.2%

Publication	Discontinuations	Common Adverse Events[a]	Weight Gain	Metabolic Parameters[b]	Extrapyramida l Symptoms
		FLU, 19.4%; OLZ, 13.1% Fatigue: OFC, 14.0%; FLU, 7.8%; OLZ, 14.1% Tremor: OFC, 10.5%; FLU, 8.7%; OLZ, 8.0% Unpub. OLE Weight increased 16.3%, increased appetite 10.7%, dry mouth 8.7%, fatigue 7.0%, somnolence 6.3%, hypersomnia 5.4%, dizziness 5.2%, sedation 5.0%		No differences between groups in incidence of low or high cholesterol, low or high fasting glucose, or low or high nonfasting glucose Unpub. OLE: Low cholesterol: 0.9% High cholesterol: 2.1% Low fasting glucose: 1.1% High fasting glucose: 3.2% Low nonfasting glucose: 2.9% High nonfasting glucose: 0.8% Low HbA1c: 0% High HbA1c: 4.5% Low triglycerides: 0.2% High triglycerides: 1.7%	
Feng 2008 [21]	No discontinuations due to AE	OFC: 14 AEs (weight gain, dry mouth, hypersomnia, headache, transient decrease in white blood count, minor liver function abnormality) FLU: 8 AEs (dry mouth, hypersomnia, blurred vision)	OFC: 6.7% had weight gain >5 kg	NR	NR
Prospective, nonrandomized, open-label study					
Corya 2003[39]	Any reason: 74.5% AE: 24.5% Lack of efficacy: 14.1%	Somnolence: 47.7%; weight gain: 39.8%; dry mouth: 37.1%; increased appetite: 32.0%; headache: 22.3%; rhinitis: 22.1%; asthenia: 19.3%; tremor: 18.8%; nausea: 15.7%; anxiety: 13.9%; pain: 12.7%; diarrhea: 12.5%; dizziness: 12.5%; insomnia: 11.8%; nervousness: 11.6%; libido decreased: 11.4%; pharyngitis: 10.4%	Mean (SD) weight gain: 5.6 (6.6) kg, *P*<0.001 Weight gain ≥10%: 31%	Nonfasting glucose increased by 6.2 (32.3) mg/dL Abnormally high glucose (≥200 mg/dL): anytime, 2.9%; at end, 1.3% Treatment-emergent diabetes: 1.1% Abnormally high cholesterol: anytime, 4.6%; at end, 1.5%	Parkinsonism: 4.5% Akathisia: 11.3% Dyskinesia: 1.8%

[a] Adverse events that occurred in at least 10% of participants treated with olanzapine-fluoxetine combined.
[b] Not all studies reported whether metabolic parameters were measured under fasting or nonfasting conditions.
Abbreviations: AE = adverse event, DB = double-blind, FLU = fluoxetine, HbA1c = glycosylated hemoglobin, NOR = nortriptyline, NR = not reported, NS = not significant, OFC = olanzapine-fluoxetine combined, OL = open-label, OLE = open-label extension, OLZ = olanzapine, pts = participants, SD = standard deviation, unpub. = unpublished data from study (obtained via Lilly Trials), VEN = venlafaxine.

Common AEs

In the RCTs[23,35-38], participants treated with OFC consistently experienced a higher incidence of increased appetite and weight gain during the randomized phase compared with participants treated with fluoxetine alone (table 3). Not including the study reported by Shelton et al 2001[35], in which only 10 participants were treated with OFC, weight gain/increased was experienced by 12 to 35% of participants (*vs* 4 to 13% of participants treated with fluoxetine) and increased appetite was experienced by 15 to 32% of participants *(vs* 5% to 7% of participants treated with fluoxetine). These findings are supported by a pooled analysis of 5 RCTs[44]. The incidence of other AEs was generally similar between participants treated with OFC and those treated with fluoxetine alone. These findings are supported by 2 meta-analyses[24, 41], which reported no increased risk of experiencing any AE in participants treated with OFC compared with those treated with fluoxetine alone. In addition to weight gain, other adverse events that were consistently reported as being common among the

studies for participants treated with OFC included dry mouth, somnolence/sleepiness/sedation, asthenia, and headache. One meta-analysis[20] and one pooled analysis[44] reported that some of these AEs were more likely in participants treated with OFC compared with those treated with fluoxetine alone. The same AEs were also reported in the RCTs with open-label extensions[31-34] and the nonrandomized trial[39], with generally higher incidence rates in studies with longer duration.

Extrapyramidal symptoms

In the RCTs reporting data[31-34], the incidence of extrapyramidal symptoms (parkinsonism, akathisia, dyskinesia) in participants treated with OFC (0.0% to 30.0%) was similar to those treated with fluoxetine (0.0% to 33.3%). In the RCTs with open-label extensions[31-34], the proportion of participants who experienced extrapyramidal symptoms was generally low (0.2 to 15.0%). Similar incidence rates (1.8 to 11.3%) were reported in the nonrandomized trial[39]. One pooled analysis[44] reported no difference in extrapyramidal symptoms between participants treated with OFC and those treated with fluoxetine or olanzapine only.

DISCUSSION

In this systematic review, we have compiled evidence from prospective studies on the use of OFC in patients with TRD. Importantly, we have included unpublished evidence from longer-term, open-label extension studies that have not been presented previously. Although the definition of TRD varied among the studies, the collective evidence indicates that OFC is more efficacious than fluoxetine alone in the alleviation of depressive symptoms in patients with TRD. Treatment with OFC was associated with earlier improvements and higher response and remission rates than fluoxetine treatment, and these improvements were sustained during longer-term treatment. However, weight gain, increased appetite, and changes in metabolic parameters were commonly reported by participants treated with OFC. Clinicians should consider the potential benefits of short- and/or long-term OFC treatment and the risk of changes in metabolic parameters in individual patients with TRD. Active management of patients with TRD, in which lifestyle modifications are combined with pharmacological intervention, may help improve depressive symptoms whilst minimizing the potential risk of changes in metabolic parameters.

Efficacy

The evidence from double-blind RCTs suggests that short-term (4 to 8 weeks) treatment with OFC is at least as efficacious as fluoxetine. All studies reported significant improvements from baseline in depression scores (MADRS, HDRS) in participants treated with OFC. The greater efficacy of OFC compared with fluoxetine was confirmed by meta-analyses[20, 24, 41, 43, 44]. Although OFC treatment did not always result in significantly greater improvements at endpoint than fluoxetine or other antidepressants (table 2), the time to response was usually much more rapid, occurring within the first few weeks of treatment. This rapidity of response could be especially critical in patients who are despondent after repeatedly failing to respond to treatment or who may have suicidal tendencies. Both response and remission rates were generally higher in participants treated with OFC than in those treated with fluoxetine. However, in the few studies where it was reported, the relapse rate was higher, although not significantly, with OFC than with fluoxetine. The lower relapse rate among participants treated with fluoxetine may reflect a subpopulation who did not have “true” TRD and were therefore able to respond and maintain their response to fluoxetine. Alternatively, patients may find fluoxetine more tolerable than OFC, as suggested by the rates of discontinuation because of an AE, and thus may adhere better to treatment. Finally, relapses among those who responded to OFC may reflect the persistent, cyclical nature of TRD (figure 1).

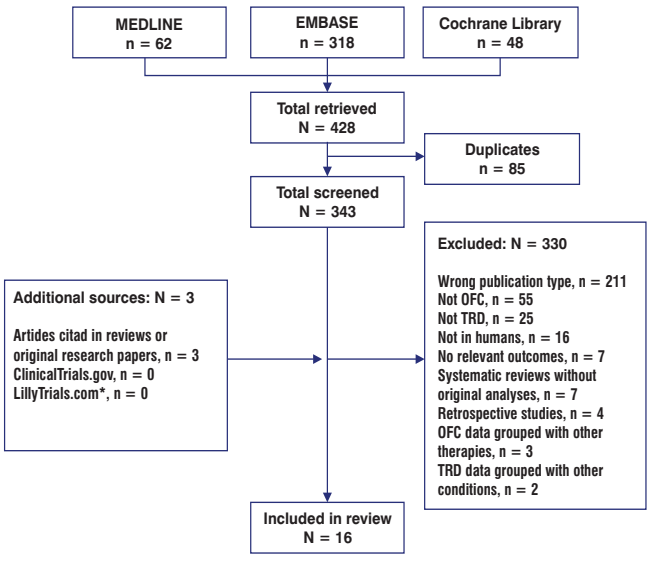

Figure 2. Publication flow diagram. *No additional studies were identified on LillyTrials.com; however, unpublished data from the website were used in this review. Abbreviations: OFC = olanzapine-fluoxetine combined, TRD = treatment-resistant depression.

The efficacy of OFC is sustained during longer-term treatment, as demonstrated by open-label studies lasting up to 76 weeks. Improvements in depressive symptoms seen in the double-blind RCTs were maintained or improved further during open-label extension phases, even in those studies with long (e" 20 weeks) treatment duration. Response and remission rates were also maintained during longer-term treatment. Interestingly, in 2 studies[32, 33], a considerable proportion (approximately 20%-30%) of participants who did not respond to OFC treatment during the double-blind phase responded during longer-term treatment. These results, together with those from short-term studies, suggest that although some patients respond to OFC treatment rapidly, others may take longer to respond. We cannot know if these late responders would also have responded to their previous treatments or to fluoxetine alone, if they had persisted longer. Relapse rates during longer-term treatment with OFC (12.6-25.0%) were similar to those during short-term treatment (15.9-33.3%), which again suggests that the effectiveness of OFC is maintained in most patients. The effectiveness of OFC in the prevention of relapse during long-term treatment was addressed recently in a study published after we conducted our literature search[45]. In this study, participants with TRD who responded to 18 to 20 weeks of open-label OFC treatment were randomized to continue OFC (n = 221) or switch to fluoxetine treatment (n = 223) for up to 27 weeks[45]. The relapse rate was significantly lower (15.8 *vs* 31.8%) and the time-to-relapse was significantly longer in participants who continued OFC treatment compared with those who switched to fluoxetine[45]. However, as reported by the studies included in this review, continued treatment with OFC was associated with greater weight gain and metabolic changes than treatment with fluoxetine[45]. The results of this study suggest that continuation of OFC treatment in patients who respond may be preferable to switching to fluoxetine alone, but that this must be weighed against the potential risk of changes in metabolic parameters.

Safety

The potential risk of weight gain and changes in metabolic parameters should be considered when prescribing OFC, particularly in the longer term. In the RCTs, weight gain was generally greater or more common in participants treated with OFC than in those treated with fluoxetine. In the open-label studies, the proportion of participants with weight gain ≥10% generally increased with treatment duration, reaching 24.5% in a 52-week study[33] and 31% in a 76-week study[39]. Changes in metabolic parameters, such as plasma glucose and cholesterol concentrations, were less consistent between studies. However, when data from several short-term RCTs were pooled, participants treated with OFC experienced generally greater treatment-emergent increases from normal to high cholesterol levels (but not glucose or triglycerides)[44] or abnormally high metabolic parameters (pooled cholesterol, glucose, HbA1c, and triglycerides)[20, 44]. Prescribing physicians should ensure that patients treated with OFC are aware of the risk of increased weight, and both physicians and patients should take appropriate measures, such as preventive weight management programs[46], to minimize weight gain and potential changes in metabolic parameters. Other common AEs experienced by participants treated with OFC included dry mouth, somnolence/sleepiness/sedation, asthenia, and headache. Although some of these AEs were more commonly associated with OFC treatment than with fluoxetine treatment, they were generally well tolerated, as demonstrated by the relatively low rates of discontinuation due to an AE (< 15% in short-term RCTs). Indeed, where reported, the most common AE leading to discontinuation was weight gain[23, 32, 33, 37, 39]. The incidence of extrapyramidal symptoms was generally similar in participants treated with OFC, fluoxetine, or olanzapine.

Definition of TRD

Although all studies in this review focused on the treatment of TRD, the precise definition of TRD varied, reflecting both an evolving definition of the condition and a lack of consensus amongst clinical psychiatrists. Elements of the TRD definition that varied among studies included the number and duration of failed treatment trials, whether failed treatment occurred in the current or previous depressive episodes, and whether failed treatments included different or specific classes of antidepressants. Thus, the disparate definitions of TRD in the studies included in this review are likely to have contributed to the variation in efficacy, response rates, and remission rates. However, despite the variation across the studies, the relative efficacy of OFC reported in the studies was remarkably consistent. Currently, the most clinically accepted, and most frequently used in clinical practice, definition of TRD specifies that patients should have a demonstrated failure to respond to at least 2 adequate trials of antidepressants with different mechanisms of action[47]. Only 4 of the included RCTs used this definition of TRD[21-23, 35]; in 3 of these RCTs, OFC was more efficacious than fluoxetine at study endpoint[21-23].

Unfortunately, these RCTs were small, not blinded, and/or poorly reported. In contrast, greater efficacy of OFC at endpoint was reported by only 1[38] of the 4 RCTs that did not require at least 2 previous treatment failures[36-38]. The conflicting results across these RCTs may, in part, be because some of the included participants may not have been truly treatment resistant and were able to respond to pharmacotherapy by study endpoint. Another more stringent definition of TRD requires treatment failures to be documented within the current depressive episode[48]. Only 2 of the included RCTs confirmed treatment resistance during a screening or lead-in phase[35, 36]. Studies without a confirmatory phase may have included subgroups of participants that were not truly treatment resistant. The 2 parallel RCTs published by Thase et al required treatment failure to be within the current episode; however, a single treatment failure was sufficient for study entry[38]. In the RCT of Corya et al published in 2006[37], subgroup analysis indicated that participants whose previous treatment failure occurred during the current episode achieved significantly greater improvements in MADRS scores at endpoint when treated with OFC than when treated with fluoxetine.

An accurate assessment of the effectiveness of OFC or other treatments in patients with TRD depends on the use of a uniform and clinically accepted definition of the condition. As mentioned, the definition most commonly used in clinical practice, as well as in many trials, is based on the failure to respond to two adequate antidepressant trials[47]. The term "adequate" is generally interpreted as sufficient dosing for at least 4 weeks. However, as demonstrated by the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study[6] and the Group for the Study of Resistant Depression (GSRD)[49], 4 weeks is often not long enough to achieve a response. The need for longer antidepressant trials has been recognized by some clinical guidelines for MDD, such as those from the National Institute for Health and Clinical Excellence (NICE)[50] and the Institute for Clinical Systems Improvement (ISCI)[51]. Both the NICE and ISCI guidelines suggest that antidepressant therapies be trialed for at least 6 weeks before considering alternative treatment strategies[50, 51] (Figure 1). However, in practice, it may be difficult for clinicians and patients to persist with an apparently ineffective therapy, especially if the patient has very severe depressive symptoms. Further, the true goal of treatment is not just response, but remission; as reported in the pooled analysis of Tohen et al, the absence of early (within 2 weeks) improvement with OFC treatment is highly predictive of ultimate treatment failure[43]. Thus, clinicians may decide to switch treatments after only a few weeks if the patient is not responding. Notably, neither the NICE nor the ISCI guidelines specifically address the definition of TRD; indeed, the most recent (2009) update of the NICE guidelines has moved away from the term, suggesting that it may be used to inappropriately categorize patients[50]. In Latin America, most clinicians prefer the term "refractory depression"; however, the definitions are essentially the same as those used in the United States or Europe[52]. In the absence of a precise and universally accepted definition of TRD, the collective evaluation of prospective, comparative trials of treatment options is limited.

Strengths and limitations

Unlike previous systematic reviews of OFC in the treatment of TRD, our review included both published and unpublished data and focused specifically on data from longer-term studies. In addition, there were no restrictions on language, which allowed inclusion of several studies published in Chinese. However, as with other systematic reviews, our review is limited by the quality and heterogeneity of the studies available for inclusion. In addition, the few longer-term studies identified varied widely in duration and were all open-label, noncomparative studies. In addition, a large proportion of participants in the longer-term studies discontinued, preventing extended follow-up of their outcomes. Longer-term RCTs that compare OFC with other treatment options would help address the existing gaps in knowledge, but such trials could be difficult if participants are unwilling to remain on treatments that are not efficacious or tolerable.

CONCLUSION

In this systematic review, we have presented evidence from prospective studies that supports the efficacy of OFC in the treatment of TRD, despite differences in the functional definition of the condition. Importantly, we have included unpublished data from longer-term studies that indicate that OFC efficacy is sustained. However, in both short- and longer-term studies, changes in metabolic parameters were reported in participants treated with OFC, which may be clinically significant in patients who require ongoing treatment. Physicians should consider OFC as an effective and generally well-tolerated treatment for patients with TRD, although the risks of weight gain and changes in metabolic parameters should be carefully managed.

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Conflicts of interest: Jorge M TAMAYO has been a consultant and speaker for Eli Lilly, Pfizer, Glaxo SmithKline, Axon-Pharma/Biocodex, and Janssen. Yolanda PICA-RUIZ has been a consultant and/or speaker for Eli Lilly, Roche, and Merck Sharp & Dohme. Ignacio RUIZ is an employee of Eli Lilly and Company, Mexico.

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ARTÍCULO SIN CONFLICTO DE INTERÉS