EXPERT REVIEWS

Olanzapine/fluoxetine combination for treatment-resistant depression: efficacy and clinical utility

Expert Rev. Neurother. 8(9), 1299–1306 (2008)

Seetal Dodd[†] and Michael Berk

[†]Author for correspondence
Department of Clinical & Biomedical Sciences, University of Melbourne, Geelong, Australia
seetald@barwonhealth.org.au

Antidepressant monotherapy is a first-line treatment for depression; however, not all sufferers will adequately respond to treatment. When treating a patient with treatment-resistant depression, the clinician needs to consider all factors which may contribute to an inadequate response to an antidepressant. These include accuracy of diagnosis and medication adherence, as well as the patient's personality, lifestyle, life events and social circumstances. If it is determined that treatment resistance is due to failure of efficacy of antidepressant monotherapy, then an augmentation strategy using an atypical antipsychotic may be considered. Treatment using olanzapine/fluoxetine combination (OFC) is one of many options. Four randomized, acute-phase trials have suggested OFC is useful for reducing Montgomery–Åsberg Depression Rating Scale scores after inadequate response to antidepressant monotherapy. OFC has been useful at doses of olanzapine/fluoxetine 6/25, 6/50, 12/25 and 12/50 mg/day, with 1/5 mg/day suggested to be an ineffective dose. Treatment with OFC has been associated with some side effects, including weight gain and the metabolic syndrome, somnolence, dry mouth, increased appetite and headache. Treatment decisions therefore need to be made to balance the risks and benefits.

Keywords: antidepressant • atypical antipsychotic • olanzapine/fluoxetine combination • treatment-resistant depression

Depression is a complex and heterogeneous condition with a range of diverse etiologies, which include genetic, traumatic, medical, personality and social interpersonal factors. In consort, it has both a pleomorphic phenomenology and treatment needs, which may reflect such divergence in its roots. Unsurprisingly, up to 53% of patients suffering from a major depressive episode will fail to respond to an adequate trial of treatment with a single antidepressant [1]. In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, outpatients (n = 2,876; baseline Hamilton Depression Rating Scale [HAM-D] ≥14) were treated with citalopram. Remission (HAM-D ≤7) was achieved by 27.5% (n = 790) of outpatients and required on average 12 weeks of treatment [1]. These data suggest that failure of antidepressant monotherapies is commonplace. Consequently, other psychological, social and pharmacological treatment options, which may include antidepressant and atypical antipsychotic combinations, may need to be considered.

There is no broadly accepted definition of treatment-resistant depression (TRD). A pragmatic definition is failure to respond after adequate trials of treatment with two or more antidepressants for an adequate time and at an adequate dose [2]. Thase proposed staging criteria for TRD, where stage 1 was failure on an adequate trial of an antidepressant, stage 2 was failure of two antidepressants with distinct mechanisms of action, stage 3 was stage 2 resistance plus failure of a tricyclic antidepressant, stage 4 was stage 3 resistance plus failure of a monoamine oxidase inhibitor and stage 5 was stage 4 resistance plus failure of bilateral electroconvulsive therapy [3]. This proposed staging model omits many important treatment options, particularly combination and augmentation therapies; however, the model can be adapted to include specific therapies and the concept remains useful.

Many pharmacological and nonpharmacological treatment strategies have been investigated for the management of TRD. Pharmacological

 10.1586/14737175.8.9.1299 ISSN 1473-7175

strategies have included antidepressant dose optimization [4], antidepressant combinations [5] and antidepressant augmentation strategies [6]. Several psychological therapies have been shown to be useful for treating depression and augmenting antidepressant response. In a study of adolescents with major depressive disorder (MDD) who had not responded to 2-month treatment with a selective serotonin reuptake inhibitor (SSRI; n = 334), 12 weeks of switching to cognitive–behavioral therapy (CBT) plus a different SSRI or venlafaxine was superior to switching to a different SSRI or venlafaxine alone for change in Clinical Global Impression (CGI) score [7], suggesting that adjunctive psychotherapy may be a useful strategy for TRD. There are some data to suggest that CBT may be more effective than supportive or family therapies for depression [8]. Mindfulness-based cognitive therapy may be useful for TRD [9].

A pharmacological strategy for the treatment of TRD is to combine a SSRI with an atypical antipsychotic. Olanzapine/fluoxetine combination (OFC) is one such treatment option. Other atypical/antidepressant combinations have also been studied, including aripiprazole and quetiapine [10–13,101]. The use of OFC is supported by a theoretical rationale for its use and clinical evidence of efficacy in TRD. Olanzapine and fluoxetine are both well established medications used for the treatment of various mental illnesses. The first randomized, controlled trial of olanzapine in schizophrenia was published in 1996 [14] and trialed in combination with fluoxetine for MDD in 2001 [15]. Fluoxetine is an older drug with many controlled trials in depression conducted in the 1980s [16]. OFC can be administered as any combination of the olanzapine and fluoxetine moieties, or a single capsule containing the two agents in combination in olanzapine/fluoxetine equivalent doses of 3/25, 6/25, 6/50, 12/25 and 12/50 mg.

Few treatments have been registered by regulatory authorities for the treatment of TRD. Vagus nerve stimulation (VNS) is the only treatment for TRD currently approved by the US FDA [102]. Aripiprazole was recently approved by the FDA and indicated for use as an adjunctive treatment to antidepressants for MDD after its efficacy was demonstrated in two 6 week, placebo-controlled trials of patients with MDD with an inadequate response to prior antidepressant therapy [101]. Currently, OFC is only recognized as indicated for TRD in Mexico. At this stage, FDA approval for the use of OFC has been granted only for the treatment of bipolar depression. Other treatment options for TRD include antidepressant combination therapies [5] and augmentation strategies [6], which have been reviewed elsewhere.

Berman *et al.* randomized patients with a current major depressive episode with inadequate response to one prospective and at least one previous antidepressant to 6 weeks of adjunctive aripiprazole (n = 184) or adjunctive placebo (n = 178) [12]. Mean change in the Montgomery–Åsberg Depression Rating Scale (MADRS) total score was -8.8 with adjunctive aripiprazole and -5.8 with adjunctive placebo, which was statistically significant ($p < 0.001$).

McIntyre *et al.* found significant improvement in HAM-D and Hamilton Anxiety Rating Scale (HAM-A) total scores in a randomized, placebo-controlled trial of quetiapine as an adjunct to an antidepressant (SSRI or serotonin–norepinephrine reuptake inhibitor [SNRI]) in patients (n = 58) who had failed to respond to 6 weeks of antidepressant monotherapy [11]. El-Khalili *et al.* found that adjunctive quetiapine 300 mg/day, but not 150 mg/day, was superior to placebo for change in MADRS total score in a 6-week, double-blind, randomized trial of MDD (n = 446), in patients who had not adequately responded to treatment with a SSRI, SNRI, tricyclic antidepressant or bupropion [13]. Martinez *et al.* found that quetiapine plus fluoxetine was superior to fluoxetine plus placebo for patients with insomnia in an 8-week trial of patients with MDD (n = 114) [10]. Efficacy in MDD of quetiapine monotherapy has been shown in two randomized, double-blind, placebo controlled trials. Quetiapine (50 mg/day, n = 182; 150 mg/day, n = 178; 300 mg/day, n = 184) was superior to placebo (n = 184) for reduction in MADRS scores in a 6-week trial of acute depression [17]. In a 52-week maintenance trial, the risk of depressive relapse was significantly less for quetiapine (n = 391) compared with placebo (n = 385) [18].

In a 6-month trial, Lecrubier *et al.* randomized patients with dysthymia and major depression to amisulpride (n = 73), imipramine (n = 73) or placebo (n = 73) and found that amisulpride was equivalent to imipramine and superior to placebo for response measured using the CGI rating [19].

Patients who did not respond to 6 weeks of open-labeled sertraline monotherapy were randomly assigned by Dunner *et al.* to sertraline monotherapy (n = 20), sertraline plus ziprasidone 80 mg/day (n = 22) or sertraline plus ziprasidone 160 mg/day (n = 19) for 8 weeks [20]. The mean changes in MADRS scores were -5.98 with monotherapy, -8.27 with ziprasidone 80 mg/day and -4.45 with ziprasidone 160 mg/day, with no statistically significant difference between any of the treatment arms.

Gharabawi *et al.* trialed adjunctive risperidone (n = 141) or adjunctive placebo (n = 133) for 6 weeks in patients who had insufficiently responded to 8 weeks of treatment with antidepressant monotherapy [21]. The discontinuation rate owing to adverse events was 6% in risperidone- and 2% in placebo-treated patients. Adjunctive risperidone treatment was associated with significant improvement in HAM-D scores from weeks 4 to 6 when compared with placebo ($p < 0.03$). Ostroff and Nelson reported remission following risperidone augmentation in patients with MDD who failed to respond to treatment with fluoxetine (n = 5) or paroxetine (n = 3) [22].

Chemistry of OFC

The two agents, olanzapine and fluoxetine, are combined to form OFC. Olanzapine is a thienobenzodiazepine with the structure 2-methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno[2,3-b][1,5]benzodiazepine and the structure of fluoxetine is (±)-*N*-methyl-3-phenyl-3-[(α,α,α,-trifluoro-p-tolyl)oxy]propylamine (Figure 1).

Pharmacokinetics

The pharmacokinetics of OFC appears to be similar to that of the individual components, olanzapine and fluoxetine; however, fewer data are available for the combination therapy than for the components. The potential for a pharmacokinetic interaction

between olanzapine and fluoxetine exists by inhibition of CYP2D6 by fluoxetine. Following 8 days of treatment with fluoxetine (60 mg/day), Gossen *et al.* dosed healthy, nonsmoking adults (n = 15; age 32 ± 5 years [mean ± standard deviation; SD]) with olanzapine (5 mg) and found that olanzapine achieved a maximum plasma concentration 18% higher compared with the same olanzapine dose in the same subjects without fluoxetine pretreatment [23]. This interaction has not been demonstrated at lower doses of fluoxetine.

No data are available on OFC in special populations; the elderly, renal or hepatically impaired individuals, and the impact of gender differences and smoking status is unknown. No studies of OFC and CYP2D6 polymorphisms have been reported. The reported modest pharmacokinetic interaction between olanzapine and fluoxetine is thus of unclear clinical significance.

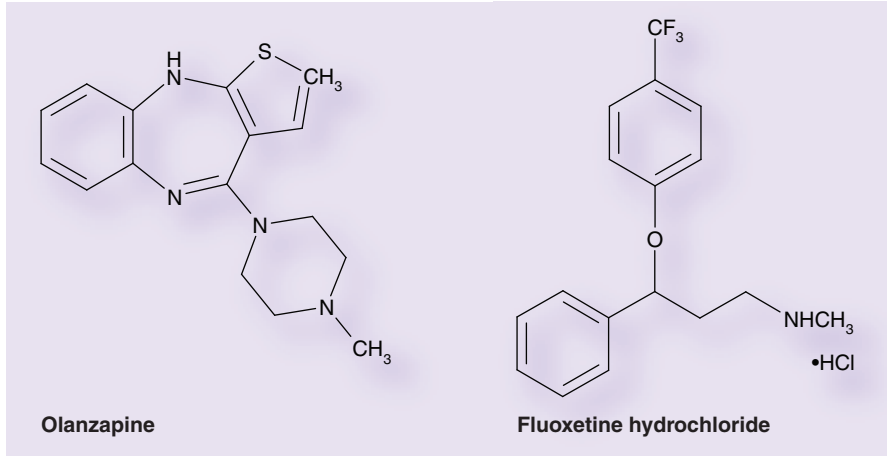

Figure 1. Olanzapine and fluoxetine are combined to form the olanzapine/fluoxetine combination

Olanzapine undergoes extensive Phase I and II metabolism, with 10-*N*-glucoronidation being the prominent metabolic pathway. Minor metabolic pathways for olanzapine involve CYP2D6 and CYP1A2. There is little potential for CYP450 inhibition by olanzapine within the therapeutic dose range. Following oral administration in physically healthy subjects, olanzapine (0.5–15 mg) has linear and dose-proportional pharmacokinetics with the following parameters (mean ± SD): elimination half-life: 33.1 ± 10.3 h; apparent volume of distribution: 1148 ± 360 l; apparent plasma clearance: 26.1 ± 12.1 l/h. Maximum plasma concentration of olanzapine occurs approximately 6 h following a single dose. Olanzapine is extensively metabolized in the liver to form several nonactive demethylated, hydroxylated and glucuronidated metabolites. Olanzapine clearance does not vary with CYP2D6 metabolizer status [24].

Fluoxetine is a racemic mixture of *S*- and *R*-enantiomers, each of which has a different pharmacokinetics profile, with *R*-fluoxetine cleared more efficiently than *S*-fluoxetine. Additionally, fluoxetine has a major active metabolite, *S*- and *R*-norfluoxetine. Fluoxetine has the following pharmacokinetic parameters: volume of distribution 14–100 l/kg; elimination half-life 1–4 days for fluoxetine and 7–15 days for norfluoxetine. Fluoxetine has a nonlinear pharmacokinetic profile with plasma concentrations increasing disproportionately with dose escalation. Fluoxetine is metabolized by CYP2C9, CYP2C19, CYP2D6 and CYP3A4 to norfluoxetine, and is an inhibitor of CYP2D6 and other P450 enzymes with known consequent drug–drug interactions. Glucuronide and other nonactive metabolites are also formed [25]. Clearance varies with CYP2D6 metabolizer status [26].

Pharmacodynamics

Olanzapine has a high affinity (K_i < 100 nM) for dopamine D_1, D_2 and D_4, serotonin (5-hydroxytryptamine [5-HT])$_{2A}$, 5-HT_{2C}, 5-HT_3, α_1-adrenergic, histamine H_1 and muscarinic $M_{1–5}$ receptors, moderate affinity (1000 nM > K_i > 100 nM) for α_2-adrenergic receptors and 5-HT_{1D}, and low affinity (K_i > 1000 nM) for 5-$HT_{1A,}$ 5-HT_{1B}, β-adrenergic, $GABA_A$ and benzodiazepine receptor binding sites [27]. The psychotropic activity of olanzapine is thought to be due to antagonism of these dopamine, serotonin, α_1-adrenergic and muscarinic receptors [28].

Fluoxetine inhibits reuptake by the serotonin transporter (K_i = 5.7 nM/l), and weakly inhibits the norepinephrine transporter (K_i = 574 nM/l) and the dopamine transporter (K_i = 5960 nM/l). Fluoxetine binds to the serotonin 5-HT_{2C} (K_i = 72 nM/l), α_1-adrenergic (K_i = 3171 nM/l), histamine H_1 (K_i = 1548 nM/l) and muscarinic M_1 (K_i = 702 nM/l) receptors [29]. The psychotropic activity of fluoxetine is due to inhibition of presynaptic serotonin reuptake by binding with the serotonin reuptake transporter [30].

The mechanism of action of OFC in TRD may be due to additive affects of the mechanisms of action of the two components, or due to synergistic effects, or both. The action of olanzapine at 5-HT_{2A} and 5-HT_{2C} receptors may enhance the serotonergic efficacy of fluoxetine [3]. Zhang *et al.* demonstrated significant increases in extracellular serotonin, dopamine and norepinephrine in the prefrontal cortex of OFC-treated rats [31]. Over a 4-h period, extracellular serotonin increased 338%, dopamine increased 332% and norepinephrine increased 260% compared with baseline. At the 4-h time point, the increases in extracellular dopamine and norepinephrine, but not serotonin, were significantly greater ($p < 0.05$) for the OFC-treated rats than for either monotherapy. Similar results were obtained for a related study, where increases in extracellular dopamine and norepinephrine, but not serotonin, compared with either monotherapy were observed in the prefrontal cortex of rats when risperidone and citalopram were co-administered [32].

Atypical antipsychotics share pharmacological mechanisms, which may be significant for their antidepressant effect. Antagonism of the 5-HT_{2A} receptor has been suggested to be of particular importance [33] and is an important part of the mechanism of action of three known effective antidepressants: nefazodone, trazodone and mirtazapine. All of the atypical antipsychotics have a greater

affinity for the 5-HT_{2A} receptor than for the D_2 receptor. Agonists of the 5-HT_{1A} receptor and antagonists of the 5-HT_{2A} receptor modulate dopaminergic neurotransmission [33]. The antidepressant activity of quetiapine has been attributed to norepinephrine reuptake inhibition and 5-HT_{1A} agonism [34]. These data suggest that efficacy of atypical antipsychotics as augmenting agents for antidepressants may be a function of intrinsic properties specific to individual agent and their interaction with the mechanism of the partner antidepressant. The usefulness of individual agents and the effectiveness of specific combinations may thus vary.

Clinical studies

Efficacy of olanzapine/fluoxetine combination in treatment-resistant depression

Several clinical trials of OFC in TRD have been published. In two 8-week, double-blind trials (n = 124 and 125), Rothchild *et al.* found OFC to be superior to placebo and olanzapine monotherapy for the treatment of depression with psychotic features in one trial [35]. Several studies have shown OFC to be useful for the treatment of bipolar depression, both in the acute phase [36,37] and in maintenance [38]. Treatment of bipolar depression with OFC is associated with a rapid onset of antidepressant effect [39], improvement of health-related quality of life [40], and is not associated with significantly increased rates of treatment-emergent mania [41]. In an 8-week double-blind trial, Zanarini *et al.* randomized women with borderline personality disorder to fluoxetine (n = 14), olanzapine (n = 16) and OFC (n = 15) with improvement in depressive and impulsive aggression symptoms observed in all treatment arms [42]. Clinical trials of OFC in TRD are summarized in Table 1.

Dubé *et al.* conducted a meta-analysis of the two TRD trials [43]: Shelton *et al.* [44] and Corya *et al.* [45] (first 8 weeks of double-blind treatment included in the meta-analysis only). In the meta-analysis, early onset of action and efficacy of OFC compared with olanzapine or fluoxetine monotherapies was confirmed, with effects evident from day 7 and maintained for 8 weeks.

Thase *et al.* conducted a large efficacy study of OFC in TRD [46]. Outpatients with a current depressive episode who had failed to respond to at least one 6-week trial of an antidepressant (excluding fluoxetine) during the current episode were treated for 8 weeks with fluoxetine. Fluoxetine nonresponders began an 8-week, double-blind, randomized trial with three treatment arms: OFC (n = 200), fluoxetine (n = 206) and olanzapine (n = 199). The

Table 1. Summary of clinical trials of olanzapine/fluoxetine combination in treatment-resistant depression.

Investigators	Participants	Treatment arms	Study comments	Findings	Ref.
Corya *et al.*	Nonpsychotic TRD with history of failure of an SSRI and prospective failure of 7 weeks of venlafaxine	12-week, double-blind, randomized trial of OFC (n = 302), olanzapine (n = 62), fluoxetine (n = 60) or venlafaxine (n = 59)	Five-dose arms of OFC (olanzapine 1 mg/day, fluoxetine 5 mg/day to olanzapine 12 mg/day, fluoxetine 50 mg/day)	With low dose OFC excluded from the analysis, OFC was superior to monotherapy arms from week 1 to 6 for MADRS change from baseline, but equivalent to venlafaxine from weeks 7 to 12 and to fluoxetine at week 12	[45]
Shelton *et al.*	Recurrent TRD without psychotic features. Prospective failure of 6 weeks of fluoxetine	8-week, double-blind, randomized trial of OFC (n = 10), olanzapine (n = 8) or fluoxetine (n = 8)	Participants who completed the blinded study entered an 8-week open-labeled OFC extension	MADRS change from baseline superior for OFC at weeks 1–8 versus fluoxetine and weeks 1–2, 4–8 versus olanzapine	[15]
Shelton *et al.*	TRD with history of failure to an SSRI and prospective failure of 7 weeks of nortriptyline	8-week, double-blind, randomized trial of OFC (n = 146), olanzapine (n = 144), fluoxetine (n = 142) or nortriptyline (n = 68)	Asthenia, somnolence, weight gain, increased appetite, headache, anxiety, tremor, nervousness, insomnia and nausea reported with OFC treatment	MADRS change from baseline superior for OFC at weeks 2–5 versus fluoxetine, weeks 2, 4, 6–7 versus olanzapine and weeks 1–4 versus nortriptyline	[44]
Thase *et al.*	MDD with history of antidepressant failure in the current episode and prospective failure of 8 weeks of fluoxetine	8-week, double-blind, randomized trial of OFC (n = 200), olanzapine (n = 199) or fluoxetine (n = 199)	52 (26%) of participants treated with OFC discontinued before 8 weeks, 27 (13.5%) owing to an adverse event	MADRS change from baseline superior for OFC at weeks 1, 4–8 versus fluoxetine, weeks 1–8 versus olanzapine	[46]
Corya *et al.*	MDD (n = 560)	76-week, open-labeled treatment with OFC	Study included 145 participants with TRD	Response, remission and relapse rates were 53, 44 and 25%, respectively, for TRD patients	[47]

MADRS: Montgomery-Åsberg Depression Rating Scale; MDD: Major depressive disorder; OFC: Olanzapine/fluoxetine combination; SSRI: Selective serotonin reuptake inhibitor; TRD: Treatment-resistant depression.

mean doses were OFC 8.6/48.8 mg/day, fluoxetine 49.5 mg/day and olanzapine 8.7 mg/day. Improvements in MADRS scores were greater for OFC (-12.7) than fluoxetine (-9.0, $p < 0.001$) or olanzapine (-8.8, $p < 0.008$). Remission rates were 27% for OFC, 17% for fluoxetine and 15% for olanzapine.

An 8-week, double-blind, pilot study of TRD was conducted with participants who had failed to respond to two different classes of antidepressants. After a 6-week fluoxetine open-label lead-in phase, participants were randomized to OFC 5–20/20–60 mg/day (n = 10), fluoxetine 20–60 mg/day plus placebo (n = 10) and olanzapine 5–20 mg/day plus placebo (n = 8). OFC was superior to fluoxetine or olanzapine for reduction of MADRS score ($p < 0.05$) after 1 week of treatment and the difference remained significant at the study end point [15]. A larger, similar study was conducted with participants who had failed to respond to a SSRI (including fluoxetine). After a 7-week nortriptyline lead-in open-labeled phase, participants were randomized to 8 weeks of OFC 6–12/25–50 mg/day (n = 146), fluoxetine 25–50 mg/day (n = 142), olanzapine 6–12 mg/day (n = 144) or nortriptyline 25–175 mg/day (n = 68). Improvement in MADRS scores was greater with OFC compared with all other treatment arms at several early time points. However, there was no significant difference between treatment arms at the study end point [44].

Corya *et al.* conducted a study of TRD in depressed subjects who had failed to respond to at least 6 weeks of treatment with a SSRI [45]. After a 7-week venlafaxine lead-in open-labeled phase, participants were randomized to 12 weeks of OFC 1/5 (olanzapine 1 mg/day, fluoxetine 5 mg/day; n = 59), OFC 6/25 (olanzapine 6 mg/day, fluoxetine 25 mg/day; n = 63), OFC 6/50 (olanzapine 6 mg/day, fluoxetine 50 mg/day; n = 63), OFC 12/25 (olanzapine 12 mg/day, fluoxetine 25 mg/day; n = 60), OFC 12/50 (olanzapine 12 mg/day, fluoxetine 50 mg/day; n = 57), fluoxetine (25 or 50 mg/day; n = 60), olanzapine (6 or 12 mg/day; n = 144) or venlafaxine (75–375 mg/day; n = 68). The lowest dose of OFC failed to differentiate from antidepressant or the olanzapine monotherapy treatment arm for change in baseline of MADRS scores. Other doses of OFC were superior to all monotherapy treatment arms from weeks 1–6 ($p < 0.05$); however, by study end point, week 12, OFC was only superior to olanzapine monotherapy. Of the different OFC doses, OFC 1/5 (olanzapine 1 mg/day, fluoxetine 5 mg/day) appears to be subtherapeutic and OFC 6/25 mg/day (olanzapine 6 mg/day, fluoxetine 25 mg/day) was superior to higher doses at weeks 8–12. Corya *et al.* found OFC 6–18/25–75 mg/day to be useful for the treatment of MDD in a 76-week, open-labeled study of 560 patients [47]. It is worth noting that the trial of Thase *et al.* was the only study that supports the superiority of OFC over fluoxetine monotherapy at the study end point [46].

While there have been several acute-phase studies, there is a paucity of data from maintenance studies of OFC in TRD. In an open-labeled study, Corya *et al.* treated participants with MDD with OFC for 76 weeks [47]. Participants were grouped as treatment resistant and nontreatment resistant by physician-defined diagnosis. Mean MADRS scores were 31.3 at baseline and fell by 22.3 points at 76 weeks for the non-TRD participants (n = 407), and the mean MADRS scores at baseline were 32.6 and fell by 19.2 points at 76 weeks for the TRD participants (n = 145). Response rates were 64.6 and 53.1%, and relapse rates were 12.1 and 25.0% for non-TRD and TRD participants, respectively.

The clinical importance of the time of onset of action of OFC seen in several trials is unclear. In all TRD studies, OFC treatment arms separated from other treatment arms from week 1 following 6–8-week antidepressant monotherapy lead-in phases. The lead-in phase may have contributed to treatment response. In trials of bipolar depression without a lead-in phase, response to OFC has been documented from week 1 [39].

Tolerability of olanzapine/fluoxetine combination

OFC has a similar qualitative side-effect profile to its combined components, olanzapine and fluoxetine, although of potentially greater severity and frequency than with monotherapy. Adverse effects associated with monotherapy with either of the two components also appear to be present in OFC treatment. OFC is associated with weight gain similar to olanzapine monotherapy and an increased QTc interval similar to fluoxetine. However, increased cholesterol with OFC treatment was shown to be significantly greater compared with monotherapy with olanzapine or fluoxetine [45]. OFC is associated with greater diarrhea and nausea [37], and elevated prolactin levels [44] compared with olanzapine monotherapy, and greater somnolence and peripheral edema compared with fluoxetine [45]. In a 76-week study, mean weight gain for participants treated with OFC was 5.6 kg, which is similar to that reported for olanzapine monotherapy [47]. In 8 weeks of OFC treatment, participants (n = 500) showed a small increase in mean cholesterol (+0.36 mmol/l), QTc prolongations consistent with those shown for fluoxetine monotherapy and a mean weight gain of 3.28 kg [44]. Treatment with OFC has been associated with orthostatic hypotension in some patients, although this is usually only during the initial dose-titration period [103].

In overdose, OFC may be fatal, although most (possibly all) reports are in combination with alcohol or other substances. Respiratory depression due to OFC overdose and alcohol has been reported [48]. OFC has not been studied in special populations. No clinical trial data are available for the use of OFC in people under 18 or over 65 years of age, or during pregnancy.

Expert commentary

When encountering treatment resistance the clinician must first consider factors other than choice of medication. First, the diagnosis needs to be reconfirmed. Some individuals with TRD later turn out to have other diagnoses, including organic pathologies, personality disorder and bipolar disorder. In a study of bipolar disorder and schizoaffective disorder (n = 240), a prior diagnosis of depression was reported by 26.6% of participants [49]. Unrecognized and untreated medical or psychiatric comorbidities, persistent stressors, personality factors or substance use may also underpin treatment resistance and merit specific attention. Secondly, attention needs to be paid to medication adherence. Nonadherence with antidepressant treatment has been estimated to range from 20.0 to 38.2% of patients [50], and has been associated with side effects and poor patient-physician communication [51]. When it has been established

that treatment resistance is due to failure of efficacy of at least two different antidepressants, then a specific treatment for TRD can be considered.

Few evidence-based therapies for TRD exist. The only therapy with current FDA approval is VNS. In November 2007, approximately 3000 VNS devices had been implanted for TRD worldwide [52], suggesting that VNS is only used in a very small percentage of cases. For the great majority of patients psychotherapy and pharmacotherapy will be the predominant approaches.

Augmentation of antidepressants using atypical antipsychotics is a second- or third-line treatment for depression, used when patients have failed to respond or only partially responded to antidepressant monotherapy. Treatment options are derived from a consideration of factors including flexibility in dosing of fixed and nonfixed combinations, real or perceived differences in efficacy of different treatment strategies and different tolerability profiles of the different treatment options. Choice of agents can be made on a case-by-case basis taking into account an individual patient's symptoms, history of response to previous medications, patient's preference and side-effect profile.

Left untreated, TRD may develop into a chronic, debilitating illness with reduced quality of life and functional outcomes. More commonly, TRD is aggressively treated and associated with greater rates of hospitalization, greater medication use and a greater likelihood of receiving electroconvulsive therapy [53]. Pharmacotherapies, including augmentation and combination strategies, will continue to be the first line of treatment for TRD. Treatment with atypical/antidepressant combinations in general and OFC specifically are one of the options available.

Five-year view

A combination of the impacts of chronicity and individual biology may underpin TRD. The allostatic stress model supports a mechanism whereby there is a cumulative effect of multiple episodes, stressors and exogenous factors such as substance use [54]. A longer duration of chronic depression has been associated with reduced volumes in specific brain gray matter areas, such as the hippocampus [55], which may suggest a neurotoxic process possibly mediated via mechanisms including cortisone, oxidative stress and cytokines [56–58]. Other factors, such as personality, social support, lifestyle and adverse life events influence the development of treatment resistance.

The mechanism by which olanzapine augments the antidepressant efficacy of fluoxetine is still to be clarified. The role of the 5-HT_{2A} receptor has been suggested to be of particular importance; however, further work is required. Increased dopamine has been associated with pleasure, reward and motivation [59], and increased dopamine and norepinephrine seen in the cortex of rats receiving olanzapine augmentation may also be a factor in its efficacy [31]. It is not known whether the olanzapine binding to dopaminergic, adrenergic, histaminic and muscarinic receptors contributes to its efficacy as an augmenting agent and this will need to be investigated. Indeed, much of our understanding of pathophysiology has been reverse engineered from understanding the mechanisms of useful agents.

There is no head-to-head clinical trial data for atypical antipsychotics as augmenting agents, or of atypical augmentation compared with other augmentation strategies. SSRIs appear to have equivalent efficacy for the long-term management of MDD [60]. By contrast, as atypical agents differ substantially in their receptor profiles, the precise mechanisms responsible for the efficacy of atypicals in depression remain to be defined. Class effects cannot be assumed and data on specific agents are needed. The prospects for treating TRD with combinations of atypical antipsychotics with antidepressants need to be balanced against the increased risk of adverse events associated with these combinations.

Financial & competing interests disclosure

Seetal Dodd has received grant/research support from: Stanley Medical Research Foundation, NHMRC, Beyond Blue, Geelong Medical Research Foundation, Bristol Myers Squibb, Eli Lilly, GlaxoSmithKline, Organon, Novartis, Mayne Pharma, Servier. Seetal Dodd has also acted as a speaker for Eli Lilly.

Michael Berk has received grant/research support from: Stanley Medical Research Foundation, MBF, NHMRC, Beyond Blue, Geelong Medical Research Foundation, Bristol Myers Squibb, Eli Lilly, GlaxoSmithKline, Organon, Novartis, Mayne Pharma, Servier. Michael Berk has also acted as a consultant or speaker for: Astra Zeneca, Bristol Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen Cilag, Lundbeck, Pfizer, Sanofi Synthelabo, Servier, Solvay, Wyeth.

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Key issues

- Treatment-resistant depression (TRD) is a debilitating illness.
- Efficacy data from clinical trials of TRD are limited.
- Clinical trial data for atypical/antidepressant combinations including the olanzapine/fluoxetine combination (OFC) suggest some efficacy and tolerability in accordance with the known profile of the individual agents.

References

Papers of special note have been highlighted as:

- • of interest
- •• of considerable interest

1 Trivedi MH, Rush AJ, Wisniewski SR *et al.* Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *Am. J. Psychiatry* 163(1), 28–40 (2006).

2 Burrows GD, Norman TR, Judd FK. Definition and differential diagnosis of treatment-resistant depression. *Int. Clin. Psychopharmacol.* 9(Suppl. 2), 5–10 (1994).

3 Thase ME. What role do atypical antipsychotic drugs have in treatment-resistant depression? *J. Clin. Psychiatry* 63(2), 95–103 (2002).

4 Souery D, Papakostas GI, Trivedi MH. Treatment-resistant depression. *J. Clin. Psychiatry* 67(Suppl. 6), 16–22 (2006).

5 Dodd S, Horgan D, Malhi GS, Berk M. To combine or not to combine? A literature review of antidepressant combination therapy. *J. Affect. Disord.* 89(1–3), 1–11 (2005).

6 Nemeroff CB. Augmentation strategies in patients with refractory depression. *Depress. Anxiety* 4(4), 169–181 (1996).

7 Brent D, Emslie G, Clarke G *et al.* Switching to another SSRI or to venlafaxine with or without cognitive behavioral therapy for adolescents with SSRI-resistant depression: the TORDIA randomized controlled trial. *JAMA* 299(8), 901–913 (2008).

8 Brent DA, Holder D, Kolko D *et al.* A clinical psychotherapy trial for adolescent depression comparing cognitive, family, and supportive therapy. *Arch. Gen. Psychiatry* 54(9), 877–885 (1997).

9 Lau MA. New developments in psychosocial interventions for adults with unipolar depression. *Curr. Opin. Psychiatry* 21(1), 30–36 (2008).

10 Martinez J, Garakani A, Marcus S *et al.* A randomized, double-blind, placebo controlled trial of quetiapine combined with fluoxetine in major depressive disorder. Presented at: *59th Institute of Psychiatric Services Conference.* LA, USA, 11–14 October 2007.

11 McIntyre A, Gendron A. Quetiapine adjunct to selective serotonin reuptake inhibitors or venlafaxine in patients with major depression, comorbid anxiety, and residual depressive symptoms: a randomized, placebo-controlled pilot study. *Depress. Anxiety* 24(7), 487–494 (2007).

12 Berman RM, Marcus RN, Swanink R *et al.* The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled study. *J. Clin. Psychiatry* 68(6), 843–853 (2007).

13 El-Khalili N, Joyce M, Atkinson S *et al.* Adjunctive extended-release quetiapine fumarate (quetiapine XR) in patients with major depressive disorder and inadequate antidepressant response. Presented at: *American Psychiatric Association Annual Meeting.* DC, USA, 3–8 May 2008.

14 Beasley CM Jr, Tollefson G, Tran P *et al.* Olanzapine versus placebo and haloperidol: acute phase results of the North American double-blind olanzapine trial. *Neuropsychopharmacology* 14(2), 111–123 (1996).

15 Shelton RC, Tollefson GD, Tohen M *et al.* A novel augmentation strategy for treating resistant major depression. *Am. J. Psychiatry* 158(1), 131–134 (2001).

• **Although small, this is still an important acute-phase clinical trial of the olanzapine/fluoxetine combination (OFC).**

16 Beasley CM Jr, Dornseif BE, Bosomworth JC *et al.* Fluoxetine and suicide: a meta-analysis of controlled trials of treatment for depression. *BMJ* 303(6804), 685–692 (1991).

17 Weisler R, Joyce M, McGill L *et al.* Extended release quetiapine fumarate (quetiapine XR) monotherapy for major depressive disorder (MDD): a double-blind, placebo-controlled study. Presented at: *American Psychiatric Association Annual Meeting.* DC, USA, 3–8 May 2008.

18 Datto C, Lam RW, Lepola U *et al.* Double-blind study of extended release quetiapine fumarate (quetiapine XR) monotherapy for maintenance treatment of major depressive disorder (MDD). Presented at: *American Psychiatric Association Annual Meeting.* DC, USA, 3–8 May 2008.

19 Lecrubier Y, Boyer P, Turjanski S, Rein W. Amisulpride versus imipramine and placebo in dysthymia and major depression. Amisulpride Study Group. *J. Affect. Disord.* 43(2), 95–103 (1997).

20 Dunner DL, Amsterdam JD, Shelton RC, Loebel A, Romano SJ. Efficacy and tolerability of adjunctive ziprasidone in treatment-resistant depression: a randomized, open-label, pilot study. *J. Clin. Psychiatry* 68(7), 1071–1077 (2007).

21 Gharabawi G, Canuso C, Pandina G *et al.* A double-blind placebo-controlled study of adjunctive risperidone for treatment-resistant major depressive disorder. *Int. J. Neuropsychopharmacology* 9(Suppl. 1), S236 (2006).

22 Ostroff RB, Nelson JC. Risperidone augmentation of selective serotonin reuptake inhibitors in major depression. *J. Clin. Psychiatry* 60(4), 256–259 (1999).

23 Gossen D, de Suray JM, Vandenhende F, Onkelinx C, Gangji D. Influence of fluoxetine on olanzapine pharmacokinetics. *AAPS PharmSci.* 4(2), E11 (2002).

24 Callaghan JT, Bergstrom RF, Ptak LR, Beasley CM. Olanzapine. Pharmacokinetic and pharmacodynamic profile. *Clin. Pharmacokinet.* 37(3), 177–193 (1999).

25 Hiemke C, Hartter S. Pharmacokinetics of selective serotonin reuptake inhibitors. *Pharmacol. Ther.* 85(1), 11–28 (2000).

26 Mandrioli R, Forti GC, Raggi MA. Fluoxetine metabolism and pharmacological interactions: the role of cytochrome p450. *Curr. Drug Metab.* 7(2), 127–133 (2006).

27 Bymaster FP, Calligaro DO, Falcone JF *et al.* Radioreceptor binding profile of the atypical antipsychotic olanzapine. *Neuropsychopharmacology* 14(2), 87–96 (1996).

28 Bymaster FP, Hemrick-Luecke SK, Perry KW, Fuller RW. Neurochemical evidence for antagonism by olanzapine of dopamine, serotonin, α1-adrenergic and muscarinic receptors *in vivo* in rats. *Psychopharmacology (Berl.)* 124(1–2), 87–94 (1996).

29 Owens MJ, Knight DL, Nemeroff CB. Second-generation SSRIs: human monoamine transporter binding profile of escitalopram and R-fluoxetine. *Biol. Psychiatry* 50(5), 345–350 (2001).

30 DeVane CL. Differential pharmacology of newer antidepressants. *J. Clin. Psychiatry* 59(Suppl. 20), 85–93 (1998).

31 Zhang W, Perry KW, Wong DT *et al.* Synergistic effects of olanzapine and other antipsychotic agents in combination with fluoxetine on norepinephrine and dopamine release in rat prefrontal cortex. *Neuropsychopharmacology* 23(3), 250–262 (2000).

32 Huang M, Ichiwaka J, Li Z, Dai J, Meltzer HY. Augmentation by citalopram of risperidone-induced monoamine release in rat prefrontal cortex. *Psychopharmacology (Berl.)* 185(3), 274–281 (2006).

33 Moller HJ. Antipsychotic and antidepressive effects of second generation antipsychotics: two different pharmacological mechanisms? *Eur. Arch. Psychiatry Clin. Neurosci.* 255(3), 190–201 (2005).

•• **Insightful review of the pharmacology of atypical antipsychotics.**

34 Jensen NH, Rodriguiz RM, Caron MG *et al. N*-desalkylquetiapine, a potent norepinephrine reuptake inhibitor and partial 5-HT1α agonist, as a putative mediator of quetiapine's antidepressant activity. *Neuropsychopharmacology* 33(10), 2303–2312 (2008).

35 Rothschild AJ, Williamson DJ, Tohen MF *et al.* A double-blind, randomized study of olanzapine and olanzapine/fluoxetine combination for major depression with psychotic features. *J. Clin. Psychopharmacol.* 24(4), 365–373 (2004).

36 Brown EB, McElroy SL, Keck PE Jr *et al.* A 7-week, randomized, double-blind trial of olanzapine/fluoxetine combination versus lamotrigine in the treatment of bipolar I depression. *J. Clin. Psychiatry* 67(7), 1025–1033 (2006).

37 Tohen M, Vieta E, Calabrese J *et al.* Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. *Arch. Gen. Psychiatry* 60(11), 1079–1088 (2003).

38 Corya SA, Perlis RH, Keck PE Jr *et al.* A 24-week open-label extension study of olanzapine-fluoxetine combination and olanzapine monotherapy in the treatment of bipolar depression. *J. Clin. Psychiatry* 67(5), 798–806 (2006).

39 Dube S, Tollefson GD, Thase ME *et al.* Onset of antidepressant effect of olanzapine and olanzapine/fluoxetine combination in bipolar depression. *Bipolar Disord.* 9(6), 618–627 (2007).

40 Shi L, Namjoshi MA, Swindle R *et al.* Effects of olanzapine alone and olanzapine/fluoxetine combination on health-related quality of life in patients with bipolar depression: secondary analyses of a double-blind, placebo-controlled, randomized clinical trial. *Clin. Ther.* 26(1), 125–134 (2004).

41 Keck PE Jr, Corya SA, Altshuler LL *et al.* Analyses of treatment-emergent mania with olanzapine/fluoxetine combination in the treatment of bipolar depression. *J. Clin. Psychiatry* 66(5), 611–616 (2005).

42 Zanarini MC, Frankenburg FR, Parachini EA. A preliminary, randomized trial of fluoxetine, olanzapine, and the olanzapine-fluoxetine combination in women with borderline personality disorder. *J. Clin. Psychiatry* 65(7), 903–907 (2004).

43 Dube S, Andersen SW, Paul S *et al.* Metanalysis of olanzapine/fluoxetine use in treatment-resistant depression. Presented at: *XXIII CINP Congress – Collegium Internationale Neuro-Psychopharmacologicum (CINP).* QC, Canada, 23–27 June 2002.

44 Shelton RC, Williamson DJ, Corya SA *et al.* Olanzapine/fluoxetine combination for treatment-resistant depression: a controlled study of SSRI and nortriptyline resistance. *J. Clin. Psychiatry* 66(10), 1289–1297 (2005).

- **Important acute-phase clinical trial of OFC.**

45 Corya SA, Williamson D, Sanger TM *et al.* A randomized, double-blind comparison of olanzapine/fluoxetine combination, olanzapine, fluoxetine, and venlafaxine in treatment-resistant depression. *Depress. Anxiety* 23(6), 364–372 (2006).

- **Important acute-phase clinical trial of OFC.**

46 Thase ME, Corya SA, Osuntokun O *et al.* A randomized, double-blind comparison of olanzapine/fluoxetine combination, olanzapine, and fluoxetine in treatment-resistant major depressive disorder. *J. Clin. Psychiatry* 68(2), 224–236 (2007).

- **Important acute-phase clinical trial of OFC.**

47 Corya SA, Andersen SW, Detke HC *et al.* Long-term antidepressant efficacy and safety of olanzapine/fluoxetine combination: a 76-week open-label study. *J. Clin. Psychiatry* 64(11), 1349–1356 (2003).

- **Important maintenance-phase trial of OFC.**

48 Girgis RR, Duggal HS, Douaihy AB. Respiratory depression from Symbyax overdose and binge drinking. *Gen. Hosp. Psychiatry* 28(3), 255–256 (2006).

49 Berk M, Dodd S, Callaly P *et al.* History of illness prior to a diagnosis of bipolar disorder or schizoaffective disorder. *J. Affect. Disord.* 103(1–3), 181–186 (2007).

50 Goethe JW, Woolley SB, Cardoni AA, Woznicki BA, Piez DA. Selective serotonin reuptake inhibitor discontinuation: side effects and other factors that influence medication adherence. *J. Clin. Psychopharmacol.* 27(5), 451–458 (2007).

51 Bull SA, Hu XH, Hunkeler EM *et al.* Discontinuation of use and switching of antidepressants: influence of patient-physician communication. *JAMA* 288(11), 1403–1409 (2002).

52 Moore D. Dan Moore, President and CEO, Cyberonics, Inc. Presented at: *Lazard Capital Markets, Fourth Annual Healthcare Conference.* NY, USA, 27 November 2007.

53 Crown WH, Finkelstein S, Berndt ER *et al.* The impact of treatment-resistant depression on health care utilization and costs. *J. Clin. Psychiatry* 63(11), 963–971 (2002).

54 Kapczinski F, Vieta E, Andreazza AC *et al.* Allostatic load in bipolar disorder: implications for pathophysiology and treatment. *Neurosci. Biobehav. Rev.* 32(4), 675–692 (2008).

55 Sheline YI, Sanghavi M, Mintun MA, Gado MH. Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. *J. Neurosci.* 19(12), 5034–5043 (1999).

56 Ng F, Berk M, Dean O, Bush AI. Oxidative stress in psychiatric disorders: evidence base and therapeutic implications. *Int. J. Neuropsychopharmacol.* 21, 1–26 (2008).

57 Berk M, Ng F, Dean O, Dodd S, Bush AI. Glutathione: a novel treatment target in psychiatry. Trends Pharmacol. Sci. 29, 346–351 (2008).

58 Pasco JA, Jacka FN, Williams LJ *et al.* Leptin in depressed women: cross-sectional and longitudinal data from an epidemiologic study. *J. Affect. Disord.* 107(1–3), 221–225 (2008).

59 Berk M, Dodd S, Kauer-Sant'anna M *et al.* Dopamine dysregulation syndrome: implications for a dopamine hypothesis of bipolar disorder. *Acta Psychiatr. Scand. Suppl.* (434), 41–49 (2007).

60 Shelton CI. Long-term management of major depressive disorder: are differences among antidepressant treatments meaningful? *J, Clin. Psychiatry* 65(Suppl. 17), 29–33 (2004).

Websites

101 US FDA. Aripiprazole prescribing information (2008) www.fda.gov/MedWatch/safety/2008/Feb_PI/Abilify_PI.pdf

102 Food and Drug Administration. Approval Order: VNS Therapy System (P970003/S50) (2005) www.fda.gov/ohrms/dockets/dockets/05m0283/05m-0283-aav0001-02-Approval-Order-vol1.pdf

103 Food and Drug Administration. Olanzapine/Fluoxetine (marketed as Symbyax) Information (2008) www.fda.gov/cder/drug/infopage/olanzapine_fluoxetine/default.htm

Affiliations

- Seetal Dodd, PhD
Department of Clinical & Biomedical Sciences, University of Melbourne, Geelong, Australia
seetald@barwonhealth.org.au
- Michael Berk, MBBCh, MMed(Psych), FF(Psych)SA, PhD, FRANZCP
Orygen Research Centre; Mental Health Research Institute, Parkville, Australia; Department of Clinical & Biomedical Sciences, University of Melbourne, Geelong, Australia