Drug Profile

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. 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. 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. 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.

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...
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 and 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 [11]. 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). Oストロフ 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)-10H-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.

Olanzapine undergoes extensive Phase I and II metabolism, with 10-α-glucuronidation 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; maximum plasma concentration 18% higher compared with fluoxetine pretreatment. 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.

Fluoxetine inhibits reuptake by the serotonin transporter (Kᵢ = 5.7 nM/l), and weakly inhibits the norepinephrine transporter (Kᵢ = 574 nM/l) and the dopamine transporter (Kᵢ = 5960 nM/l). Fluoxetine binds to the serotonin 5-HT₁C (Kᵢ = 72 nM/l), α₁-adrenergic (Kᵢ = 3171 nM/l), histamine H₁ (Kᵢ = 1548 nM/l) and muscarinic M₄ (Kᵢ = 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 effects of the mechanisms of action of the two components, or due to synergistic effects, or both. The action of olanzapine at 5-HT₁A and 5-HT₂C 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-HT₁A 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

**Pharmacodynamics**

Olanzapine has a high affinity (Kᵢ < 100 nM) for dopamine D₁, D₂ and D₄, serotonin (5-hydroxytryptamine [5-HT]₁A, 5-HT₂C, 5-HT₃, α₁-adrenergic, histamine H₁ and muscarinic M₄ receptors,
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

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

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

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 non-treatment 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 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.

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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.

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• of interest
** of considerable interest


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


- Insightful review of the pharmacology of atypical antipsychotics.

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• Important acute-phase clinical trial of OFC.


• Important acute-phase clinical trial of OFC.


• Important acute-phase clinical trial of OFC.


• Important maintenance-phase trial of OFC.


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