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SYMBYAX®: THE FIRST MEDICATION APPROVED FOR TREATMENT-RESISTANT DEPRESSION

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In 2003, Eli Lilly's Symbyax® (olanzapine/fluoxetine) was granted the first FDA-approved indication for the treatment of depressive episodes in association with bipolar I disorder.[1] In March of this year, Symbyax® became the first drug approved for the acute treatment of treatment-resistant depression (TRD), most often defined as adults with Major Depressive Disorder (MDD) that do not respond to two separate trials of different antidepressants of adequate dose and duration during the current episode.[1-2] This article will briefly discuss TRD as well as the pharmacology, efficacy and safety of the olanzapine/fluoxetine combination (OFC).

It is estimated that up to 35% of patients with depression (approximately 2% of the general population) fail to achieve an adequate response after two antidepressant drug therapy attempts.[3] Untreated depression often results in social, physical, psychological and economic consequences. Those with MDD are at an increased risk of alcohol and drug-related problems, tobacco dependence, physical health problems, and premature death due to medical illness. Up to 15% of individuals with MDD die by suicide.[4] In 1990, it was estimated that depression-related costs of direct treatment, lost earnings, and indirect workplace costs translated into an economic burden between $44 and $53 billion per year. The total economic burden of depression remained relatively stable between 1990 and 2000.[5] A 2002 study of patients with TRD estimated the mean total cost of general health care services at approximately $11,000 per patient year. Another study found that mean total general health care expenditures increased from $6,852 per year at the first medication change to $13,980 per year at the eighth medication regimen, suggesting that cost may be directly related to degree of treatment resistance. Therefore, there is a need for rapid, effective pharmacotherapy for TRD.[6]

Although the exact causes of depression and the reasons behind pharmacological treatment failure remain a mystery, evidence suggests that depression is the result of a complex interaction among biological, genetic, psychosocial, and environmental factors.[5] According to the DSM-IV, MDD is defined as the presence of a single major depressive episode in a patient that has never experienced a manic episode, mixed episode or hypomanic episode. A major depressive episode must include ≥ 5 out of 9 specific symptoms present during the same 2-week period and represent a change from previous functioning. At least one of the symptoms must either be depressed

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mood or loss of interest or pleasure.[7]

Years before the approval of OFC, the American Psychiatric Association's (APA) 2005 Guideline Watch, an update to the 2000 practice guideline: *Treatment of Patients With Major Depressive Disorder*, mentioned OFC as a useful treatment for episodes of major depression with psychotic features as well as TRD. The updated guideline, expected in December of 2009, will likely include OFC in its section on TRD. According to the APA, initial treatment failure is defined as a lack of at least moderate improvement after 4-8 weeks of antidepressant therapy. The next step is to assess adherence, consider pharmacokinetic or pharmacodynamic factors and, if necessary, draw serum antidepressant medication levels, and then revise the treatment plan. Treatment plan revisions may include maximizing the initial therapeutic treatment dose; adding, changing or increasing the frequency of psychotherapy; switching to another non-monoamine oxidase inhibitor (MAOI) medication in either the same class or a different class; augmentation; switching to an MAOI, or electroconvulsive therapy (ECT).[8] According to the labeling, OFC is indicated after the failure of 2 separate trials of different antidepressants of adequate dose and duration in the current episode.[9] Thus, the initiation of OFC therapy for TRD is considered an augmentation strategy.

PHARMACOLOGY AND PHARMACOKINETICS

Olanzapine is an atypical antipsychotic and fluoxetine is a selective serotonin reuptake inhibitor (SSRI). In animal studies, OFC synergistically increases norepinephrine and dopamine release in the prefrontal cortex, along with increases in serotonin.[10] Although OFC's exact mechanism of action is unknown; it is proposed that activation of serotonin, norepinephrine, and dopamine is responsible for the antidepressant effect.[9]

Regarding the pharmacodynamics of OFC, olanzapine has a high binding affinity for serotonin $5HT_{2A/2C}$, $5HT_6$ as well as histamine H_1 (antagonism here may explain somnolence) and adrenergic α_1 receptors (antagonism here may explain orthostatic hypotension). It is also an antagonist with moderate binding affinity for serotonin $5HT_3$ and muscarinic M_{1-5} receptors (a possible cause of anticholinergic effects). It only weakly binds $GABA_A$, BZD, and β-adrenergic receptors. Fluoxetine is a serotonin transporter inhibitor as well as a weak inhibitor of norepinephrine and dopamine transporters. It has a relatively low affinity for muscarinic, α_1 adrenergic, and histamine H_1 receptors.[9]

The pharmacokinetics of olanzapine and fluoxetine are listed separately in Table 1. The pharmacokinetics of each component are expected to represent

Table 1. Pharmacokinetics of olanzapine and fluoxetine[9]

	ABSORPTION	DISTRIBUTION	METABOLISM	ELIMINATION

Olanzapine	• Peak plasma concentration ~4 hrs*
	• Unaffected by food
		• 93% plasma protein bound	• Extensive 1st-pass metabolism
			• Highly metabolized
			  • direct glucuronidation
			  • CYP450 (1A2, 2D6, flavin-containing monooxygenase system)
			• Mean $t_{1/2}$ ≈ 30 hrs
			• $t_{1/2}$ ~1.5x greater in elderly
				• 57% recovered in urine (~7% as unchanged drug)
				• 30% recovered in feces

Fluoxetine	• Peak plasma concentration ~6 hrs*
	• Food may delay absorption by 1-2 hrs (clinically insignificant)
		• 94.5% bound to plasma proteins	• Extensively metabolized to active metabolite (norfluoxetine) via CYP2D6
			• $t_{1/2}$ elimination
			  • 1-3 days (acute use)
			  • 4-6 days (chronic use)
			  • 9.3 days (norfluoxetine)
				• Hepatic metabolism to inactive metabolites, excretion by kidney

*Following a single oral 12/50 mg dose of olanzapine/fluoxetine

the pharmacokinetics of the combination. Although both drugs are highly protein-bound, the in vitro binding to plasma proteins of the combination is similar to the binding of the individual components. However, the interaction between the two and other highly protein-bound drugs has not been fully evaluated. When the two drugs are combined, minor changes in olanzapine clearance have been observed, but this is of unclear clinical significance. The decreased clearance is likely due to fluoxetine's inhibition of CYP2D6, a minor metabolic pathway for olanzapine.[9]

The plasma concentrations, half-life, and clearance of olanzapine may vary based on smoking status, gender, and age. Olanzapine clearance is ~40% higher in smokers than nonsmokers, but dosage modification is not routinely necessary. Although olanzapine clearance is about 30% lower in women than in men, no apparent difference in effectiveness or adverse effects were found; therefore, dose modification is probably unnecessary. However, because the mean elimination half-life of olanzapine is 1.5 times greater in subjects >65 years of age, caution should be used in dosing the elderly. The combined effects of age, smoking status and gender could lead to substantial pharmacokinetic differences in populations; therefore, it may be necessary to modify the dose in patients who exhibit a combination of factors that may results in a slower metabolism of olanzapine.[9]

Dose adjustment of OFC in renal impairment is not required. Olanzapine is highly metabolized prior to excretion with only 7% excreted unchanged. Additionally, a fluoxetine study in dialysis patients produced plasma concentrations comparable to those in patients with normal renal function. In hepatic impairment, however, the pharmacokinetics of OFC might be altered and the lowest starting dose should be considered in these patients.[9]

CLINICAL TRIALS

Five clinical studies were conducted to evaluate OFC as a treatment strategy for TRD, three of which are included in the official label. These studies have observed mixed results, complicated by inconsistent definitions of TRD. A small pilot study conducted between April 1997 and June 1998 found that patients with a history of TRD treated with OFC showed a significantly greater reduction in depressive symptoms than patients treated with olanzapine ($p=0.03$) or fluoxetine ($p=0.006$) monotherapy.[11] In this study, TRD was defined retrospectively as a history of failure to respond to antidepressants of two different classes, (one of which was not an SSRI), after at least four weeks of therapy at an acceptable therapeutic dose. A failure to respond was then confirmed during a screening period where fluoxetine was given.

These results were not duplicated in two larger trials in which initial antidepressant failure was not required during the current depressive episode. With the intent of replicating the results of the pilot study with a larger sample size, Shelton et al. studied OFC in 500 patients, but failed to find a statistically significant change in the primary outcome.[12] However, OFC versus olanzapine reached significance in a post hoc analysis of a subgroup of patients with SSRI failure during the current depressive episode ($p=0.005$). Unfortunately, this subgroup was not specified *a priori*. This study defined TRD as a failure to respond to an SSRI followed by failure to respond to nortriptyline during an open-label lead-in phase.[12] Corya et al. found a statistically significant improvement in the primary outcome, but only for OFC compared to olanzapine ($p<0.001$).[6] This study also performed a subgroup analysis similar to the Shelton et al. study and found a statistically greater improvement with OFC compared to both olanzapine ($p<0.001$) and fluoxetine ($p=0.006$). The investigators determined that the subgroup, this time specified a priori, represented a more conservative, real-world criteria under which TRD patients would likely present to clinicians. This study specified TRD as a historical failure to achieve satisfactory SSRI antidepressant response for at least 6 weeks at an acceptable dose, and prospective failure to achieve satisfactory partial response to venlafaxine during the 7-week lead-in phase.[6]

In the two most recent studies, TRD was defined as a documented history of failure to achieve a satisfactory response to an antidepressant (except fluoxetine) after at least 6 weeks of therapy at a therapeutic dose as well as a prospective failure on fluoxetine during the current depressive episode. These also generated conflicting results as one found a significant improvement in the primary endpoint ($p<0.001$) and the other did not. The pooled results, however, revealed significant differences for OFC versus fluoxetine ($p<0.001$) and olanzapine ($p<0.001$).[13,14]

Table 2. Summary of Clinical Trials for OFC.[6,11-15]

TRIAL	DESIGN	1° OUTCOME MEASURE	RESULTS
Shelton, et al. Pilot Study (2001)[11] (n=28)	8-week R, DB study comparing: • OFC (n=10) • OLZ (n=8) • FLX (n=10)	Mean Δ from baseline in MADRS	Primary analysis: OFC -13.6 vs • OLZ -2.8 (p=0.03) • FLX -1.2 (p=0.006)
Shelton, et al. (2005)[12] (n=500)	8-week R, DB, MC study comparing: • OFC (n=146) • OLZ (n=144) • FLX (n=142) • NTP (n=68) Subgroup analysis (n=314)	Baseline-to-endpoint mean Δ in MADRS	Primary analysis: OFC -8.71 (0.70)[a] vs: • OLZ -6.95 (0.71) [p=0.077] • FLX -8.51 (0.70) [p=0.841] • NTP -7.46 (0.98) [p=0.298] *Post-hoc* analysis (SSRI failure during current depressive episode): OFC -9.1 vs: • OLZ -5.6 (p=0.005) • FLX -7.9 (p=0.33) • NTP -7.1 (p=0.18)
Corya, et al. (2006)[6] (n=483)	12-week R, DB, MC study comparing: • OFC (n=243) • OLZ (n=62) • FLX (n=60) • VNL (n=59) • OFC 1/5[b] (n=59) Subgroup analysis (n=334)	MADRS mean total Δ score at endpoint	Primary analysis: OFC -14.06 (0.59)[a] vs: • OLZ -7.71 (1.17) [p<0.001] • FLX -11.70 (1.14) [p=0.062] • VNL -13.73 (1.16) [p=0.795] • OFC 1/5 -11.97 (1.13) [p=0.095] Subgroup analysis (SSRI failure during current depressive episode): OFC -14.6 vs: • OLZ -9.4 (p<0.001) • FLX -10.7 (p=0.006) • VNL -14.7 (p=0.98)
Thase, et al. (2007)[13] (n=605)	2 parallel 8-wk R, DB studies comparing: • OFC (n=200) • OLZ (n=199) • FLX (n=206)	Baseline-to-endpoint mean Δ in MADRS	Study 1: OFC -11.0 (10.0)[c] vs: • OLZ -10.5 (9.5) [p=0.739] • FLX -9.4 (10.0) [p=0.253] Study 2: OFC -14.5 (10.4) vs: • OLZ -7.0 (8.5) [p<0.001] • FLX -8.6 (9.6) [p<0.001] Pooled analysis: OFC -12.7 (10.3) vs: • OLZ -8.8 (9.1) [p<0.001] • FLX -9.0 (9.8) [p<0.001]
Corya, et al. (2003)[15] (n=560)	76-week, MC, open-label study of safety & efficacy of OFC in MDD patients Without TRD n=415 (74%) With TRD: n=145 (26%)	Mean Δ from baseline in MADRS & CGI-S	Entire cohort: • MADRS -21.8 (p=0.0001) • CGI-S -2.2 (p=0.0001) Without TRD: • MADRS -22.3 (p=0.0001) • CGI-S -2.3 (p=0.0001) With TRD: • MADRS -19.2 (p=0.0001) • CGI-S -2.0 (p=0.0001)

Δ = change; CGI-S = Clinical Global Impressions-Severity of Illness Scale; DB = double-blind; MADRS = Montgomery-Asberg Depression Rating Scale; FLX = fluoxetine; MC = multicenter; NTP = nortriptyline; OFC = olanzapine/fluoxetine combination; OLZ = olanzapine; pts = patients; R = randomized; SD = standard deviation; Stat sig. = statistically significant; TRD = treatment-resistant depression; VNL = venlafaxine; w = with.

[a] Mean change (SE).

[b] OLZ 1/5 was included as a "pseudoplacebo" arm.[7]

[c] Mean change (SD).

An integrated analysis of the five studies found the same pattern of results for OFC in each study and attributed the previously mixed results to inconsistencies in the definitions of TRD, study designs and measures.[14] This analysis examined the efficacy of OFC in all five clinical trials using only the Montgomery-Asberg Depression Rating Scale (MADRS) and a standardized definition of TRD: 2 documented antidepressant failures in the *current* depressive episode, including ≥ 1 prospective antidepressant failure. After methods standardization and exclusion of patients that no longer met the new inclusion criteria, the analysis found that patients treated with OFC experienced significantly greater improvement in depressive symptoms than those treated with olanzapine ($p<0.001$) or fluoxetine ($p<0.001$) monotherapy.[14] This was based on a mean change in MADRS from baseline to endpoint, response and remission rates, and the percentage of days spent in response and in remission. The advantage of OFC depressive symptom improvement was apparent early in treatment. There was a statistically significant separation between patients treated with OFC and those treated with fluoxetine ($p<0.001$) or olanzapine ($p<0.001$) at week 1. The baseline demographics for the 1,146 patients included in the integrated analysis from the five trials did not significantly differ between treatment groups. The mean age was 44 years; slightly over half were female, and a majority were Caucasion.[14] These five clinical trials along with a 76-week open-label safety and efficacy trial are summarized in Table 2**.**

SAFETY & MONITORING

The benefits of OFC for TRD should be weighed against the potential adverse effects. The most common treatment-emergent adverse events (≥ 5% and at least twice that for placebo) are summarized in Table 3**.** OFC was generally similar to olanzapine monotherapy regarding adverse events.[14] In a 76-week safety and efficacy study of OFC in patients with MDD, the most commonly reported adverse events leading to study discontinuation were weight gain (N = 45; 8%) and somnolence (N = 27; 4.8%).[15] In the integrated analysis that examined the safety and efficacy data from 1,146 patients, the mean change in weight for the OFC group was +4.42 kg and 40.4% of OFC patients had a weight gain of ≥ 7% of total body weight. This was significantly higher than the fluoxetine group ($p<0.001$), but not the olanzapine group ($p=0.515$).[14]

Laboratory findings for OFC were also generally similar to those for olanzapine monotherapy except for random total cholesterol. The mean change was significantly greater for OFC than for fluoxetine ($p<0.001$) and olanzapine ($p<0.001$) alone.[14] The mechanism of this finding is unclear. Clinically significant elevations in triglyceride levels have been observed with OFC use. Hyperglycemia has been reported in patients treated with atypical antipsychotics including olanzapine as well as OFC. Some cases were associated with ketoacidosis, coma or death. Olanzapine's metabolic effects must be considered carefully in those with cardiovascular risk factors,

Table 3. Treatment-Emergent Adverse Events Occurring in ≥ 5% of OFC patients *and* at least twice that of placebo[9,14]

					p-value	
Event	**OFC (%)**	**Fluoxetine (%)**	**Olanzapine (%)**	**Overall**	**OFC vs Fluoxetine**	**OFC vs Olanzapine**
Weight Increased	27.9	7.1	33.5	<0.001	<0.001	0.091
Increased appetite	24.3	6.3	29.2	<0.001	<0.001	0.128
Dry mouth	18.6	6.5	21.2	<0.001	<0.001	0.376
Somnolence	15.6	6.5	13.5	<0.001	<0.001	0.426
Fatigue	14.0	9.4	16.0	0.024	0.051	0.428
Peripheral edema	11.2	1.1	7.4	<0.001	<0.001	0.074
Tremor	9.7	6.3	5.4	0.047	0.075	0.026
Sedation	8.5	2.8	10.6	<0.001	<0.001	0.333
Hypersomnia	6.1	2.0	8.3	<0.001	0.005	0.270
Attention disturbance	5.5	3.4	6.6	0.142	0.181	0.553

OFC = olanzapine/fluoxetine combination.

Table 4. OFC Drug Interactions[9]

DRUG/CLASS	INTERACTION	RECOMMENDATION
MAO-I	Reports of serious, sometimes fatal reactions in patients receiving fluoxetine and an MAOI	Concomitant use C/I; do not use OFC within 14 days of DC an MAOI; allow ≥ 5 weeks after DC OFC before starting an MAOI
Pimozide	Potential for drug interactions or QT_c prolongation	Concomitant use C/I
Thioridazine	QT_c prolongation or potential for elevated thioridazine plasma levels	Concomitant use C/I; do not use thioridazine within 5 weeks of DC OFC
Tryptophan	Serotonin syndrome	Concomitant use not recommended
Triptans, linezolid, lithium, tramadol, St. John's Wort	Serotonin syndrome	Use caution

C/I = contraindicated; DC = discontinuing; MAOI = monoamine oxidase inhibitor; OFC = olanzapine/fluoxetine combination.

established diabetes mellitus, or prediabetes.[16]

As with all antipsychotic medications, a potentially fatal condition, Neuroleptic Malignant Syndrome (NMS), has been reported with olanzapine. Immediate discontinuation is warranted upon signs and symptoms of NMS such as hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability. Other signs may include elevated creatinine phosphokinase, myoglobinuria and acute renal failure. Antipsychotic treatments also carry the risk of Tardive Dyskinesia (TD). As the duration of treatment and the total cumulative dose increase, the risk of developing TD and the likelihood that it will become irreversible are believed to increase as well. Fortunately, the incidence of dyskinetic movements in OFC-treated patients has been infrequent.[9,16]

Fasting blood glucose, A_1c, and lipid profiles should be monitored at the beginning of treatment and periodically thereafter.[9] Clinicians should monitor for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness.[16] Due to the high incidence of weight increase, baseline weight and BMI should be recorded and monitored periodically.[17]

DRUG INTERACTIONS

Table 4 summarizes serious potential drug interactions along with the strength of recommendation regarding concomitant use of OFC.

COST

The average retail price and range for each strength of Symbyax® from 3 pharmacies in Gainesville, FL is included in Table 5. In general, the cost of olanzapine and fluoxetine separately was not cheaper than the combination. At times the combination was actually cheaper. Also, the exact strengths of the combination product are not available for the individual components.

SUMMARY

Untreated depression often results in social, physical, psychological and economic consequences and up to 15% of individuals with Major Depressive Disorder die by suicide.[4] Olanzapine/fluoxetine combination is the first FDA-approved drug for the acute treatment of treatment-resistant depression as defined

Table 5. Symbyax® Retail Price

STRENGTH (OLAN/FLUOX)	AVERAGE COST*	RANGE
3mg/25mg	$272.55	$265.72 – $283.95
6mg/25mg	$371.13	$359.46 – $376.99
6mg/50mg	$368.87	$352.68 – $376.99
12mg/25mg	$542.80	$525.46 – $557.99
12mg/50mg	$542.80	$525.46 – $557.99

*Cost data based on 30-day supply at 3 Gainesville community pharmacies

by nonresponse to two separate trials of different antidepressants of adequate dose and duration during the current depressive episode.[1-2] Future guidelines will likely include OFC in their armamentarium of agents to battle TRD.[8] Clinical trials evaluating OFC have had mixed results, but an integrated analysis that standardized five studies found that patients treated with OFC experienced significantly greater improvement in depressive symptoms than those treated with olanzapine ($p<0.001$) or fluoxetine ($p<0.001$) monotherapy.[14] Except for random total cholesterol, the adverse effect profile of OFC resembles that of each agent alone.[9,14] Fasting blood glucose, A_1c, lipid profiles, weight, and BMI should be monitored at baseline and periodically thereafter.[9,17] For patients in whom the benefits of OFC therapy outweigh the risks of adverse effects, OFC provides another option when first-line antidepressant therapies have failed.

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DRUG UPDATES

Prasugrel (Effient®) - *Eli Lilly and Company*

In July, 2009, the FDA approved prasugrel, an oral thienopyridine platelet aggregation inhibitor, for use in patients with unstable angina or myocardial infarction who undergo percutaneous coronary intervention (PCI). Prasugrel is the third drug in its class to be approved, following ticlopidine and clopidogrel; however, prasugrel is believed to be a more effective adenosine diphosphate (ADP) receptor inhibitor than its counterparts owing to a more efficient metabolism resulting in greater levels of active metabolite delivery to the platelet. Although this may translate into improve efficacy, significant concern has been raised over the potential for a corresponding increase in bleeding rates. Data from the TRITON-TIMI 38 trial suggests three subgroups at a particularly elevated risk: elderly, underweight and those with a previous history of stroke/TIA Consequently, the FDA has required a black-box warning regarding the risk of bleeding. In those weighing > 60kg, the recommended dose is 10 mg once daily in combination with aspirin. A dose of 5 mg once daily has been recommended (but not prospectively studied) for those weighing < 60 kg.

Levonorgestrel (Plan B®) Going Generic

The FDA recently approved the first generic version of Plan B, an emergency contraceptive containing 0.75 mg levonorgestrel given within 72 hours of intercourse. The approval comes nearly two years after the approval of an over-the-counter Plan B product for women aged ≥ 18 years of age; however, those aged < 18 years still require a prescription.

The recent approval allows marketing of a prescription-only generic product. A generic over-the-counter product is not expected to be available until approximately September when marketing exclusivity held by Duramed Pharmaceuticals for the nonprescription use expires.

Dronedarone (Multaq®) - *sanofi-aventis*

Dronedarone, a benzofuran derivative with an electropharmacologic profile similar to amiodarone, was approved in July of this year for use in paroxysmal or persistent atrial fibrillation or atrial flutter. Structurally, dronedarone differs from amiodarone by the removal of iodine and the addition of a methane-sulfonyl group which decreases lipophilicity and shortens the half-life (~24 hours), thereby reducing tissue accumulation which occurs with amiodarone use due to its exceedingly long half-life. Dronedarone is believed to offer similar efficacy as amiodarone but with an improved safety/tolerability profile. However, limited long term (>12 month) data is available to adequately assess the safety and toxicity of dronedarone. Moreover, available data only compares dronedarone to placebo rather than amiodarone. In the DIONYSOS trial, dronedarone was reportedly less effective than amiodarone in reducing atrial fibrillation following electrical cardioversion but significantly better tolerated; however, the full report of this trial has not been published. One phase III study, ANDROMEDA, was halted early after an interim safety analysis revealed an excess risk of death in the dronedarone group (as compared with placebo). These results were not duplicated in several other large-scale clinical trials.

The recommended dose for dronedarone is 400 mg by mouth twice daily. Administration with meals is recommended.

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