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CYMBALTA®: A DUAL APPROACH TO TREATING DEPRESSION

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Introduction

The World Health Organization recognizes depression as one of the most debilitating diseases. It affects almost 340 million people worldwide, including 18 million Americans. The majority of patients with major depression (MD) have other comorbid conditions such as anxiety or substance abuse disorders. The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) defines depressive symptoms as both physical and emotional.[2] Depression is thought to be mediated by the neurotransmitters serotonin (5HT) and/or norepinephrine (NE). They exert actions centrally within the raphe nucleus and locus ceruleus which project to the cerebral cortex and the limbic system in the forebrain. Deficiency of 5HT and NE neurotransmission is considered to be the substrate for symptoms associated with depression; consequently, pharmacologic agents that inhibit reuptake of one or both of these transmitters are expected to improve symptoms of depression.[6]

Duloxetine (Cymbalta®, Eli Lilly), a dual reuptake inhibitor of 5HT and NE, was approved in August 2004 for the treatment of depression and September 2004 for the management of pain associated with neuropathy. This review will evaluate the current evidence of duloxetine's efficacy and safety for the treatment of depression

Mechanism of action

Duloxetine inhibits the reuptake of both 5HT and NE,[1] but its affinity for 5HT receptors is greater. Duloxetine inhibits the reuptake of NE at doses greater than or equal to 60 mg/day; compared to venlafaxine, it is a more balanced inhibitor of 5HT and NE. Duloxetine does not exert significant activity at dopaminergic, histaminergic, muscarinic, alpha$_1$, opioid, $5HT_{1A}$, $5HT_{1B}$, $5HT_{1D}$, $5HT_{2A}$, or $5HT_{2C}$ receptors.[2] The metabolites of duloxetine are pharmacologically inert. Although both duloxetine and tricyclic antidepressants (TCA) are dual inhibitors of NE and 5HT, duloxetine may be better tolerated than TCA's since it is devoid of cholinergic, muscarinic, and adrenergic activity.[1]

Pharmacokinetics

Duloxetine is administered orally with a recommended starting dose of 20 mg twice daily. It adheres to a one compartment model with first order kinetics. The volume of distribution (Vd) is 1943 liters, and the half-life is 12.5 hours.[3] The drug reaches steady state after 3 days.[8] Compared to SSRIs, duloxetine has a shorter onset of action

INSIDE THIS ISSUE:

Table 1. Mean changes (standard error) after the end of therapy in depression

Studies	N	HAMD 17	HAMD 10	Anxiety/somatization subfactor	HAMA (total)	Results
Placebo	115	-6.1	-0.5	-2.0	-	P≤0.01 for HAMD 17 vs. placebo; p<0.01 for HAMD 10 and A/S vs. placebo
Duloxetine 60 mg/d[2]	121	-10.9	-0.9	-3.0	-	
Placebo[2]	136	-8.3	-0.6	-2.3	-	p≤ 0.05 for HAMD17 vs. placebo
duloxetine 60 mg	123	-10.5	-0.8	-2.6	-	
Placebo[10]	89	-5.0	-0.4	-1.4	-4.3	Primary Endpoint: HAMD 17
Duloxetine 40 mg/d	86	-7.4	-0.8	-2.1	-5.5	p≤ 0.01 vs. placebo
Duloxetine 80 mg/d	91	-8.6	-1.0	-2.9	-6.6	p≤ 0.001 vs. placebo
Paroxetine 20 mg/d	87	-6.2	-0.8	-2.1	-5.2	p= 0.150 vs. paroxetine

N = number of patients with at least 1 post baseline observation

because of its effects on both 5HT and NE.[1] Duloxetine is highly protein bound (>90%),[8] and is metabolized to several inactive metabolites in the liver via CYP1A2 and CYP2D6.[4] Bioavailability of duloxetine is decreased by 66% in smokers due to the induction of CYP1A2. However, no formal dose alterations are recommended in this population. Duloxetine is not recommended in patients with hepatic impairment or moderate to severe renal disease. Population pharmacokinetic studies do not support a need for dosage adjustment in patients with mild renal disease. Duloxetine can be administered without regard to meals. Safe and effective use of duloxetine in the elderly and in children has not been established.[8]

Clinical trials

Several studies have investigated the efficacy of duloxetine on depressed mood and physical symptoms associated with depression. Two randomized, double-blind, placebo-controlled trials have been conducted.[2] (Table 1) In both studies, patients taking duloxetine reported a significantly greater reduction in painful symptoms associated with MD (e.g., back pain, shoulder pain) within 2 weeks of therapy compared to placebo. The reduction in the Hamilton depression scores and the Somatic Symptom Inventory scores from baseline to end of follow up were higher in the duloxetine group versus the placebo group ($p<0.02$, $p<0.05$, respectively), indicating improvement. The authors concluded that duloxetine showed significant improvement in Hamilton depression and pain scores compared to placebo.[2]

A randomized, multicenter, double bind trial compared the efficacy of duloxetine 20 mg twice a day, 40 mg twice a day, placebo, and paroxetine 20 mg once daily in patients with MD during 8 weeks of treatment.[10] The efficacy measures included HAMD 17 (17-item Hamilton Depression rating scale), HAMA (Hamilton depression total score), anxiety/somatization subfactor (A/S) and HAMD 10 (10-item Hamilton depression rating scale). The primary efficacy analysis used a mixed effects model repeated measures method of analysis. The patients were classified into lower and higher strata depending on their baseline severity of anxiety. Paroxetine 20 mg showed significant improvement in HAMD 10 and the A/S subfactor when compared to placebo but there was no difference in the HAMD total score between paroxetine and placebo. Duloxetine 40 mg/day showed significantly greater improvement vs. placebo in HAMD item 10 but there was no difference in the A/S subfactor or HAMA total score. Duloxetine 80 mg was significantly better than placebo in all three measures. When compared to paroxetine, duloxetine 40 mg showed significant improvement in the A/S subfactor only. Duloxetine 80 mg showed significantly greater improvement than duloxetine 40 mg/day on the A/S subfactor.[10] These results suggest that duloxetine is more effective than placebo for the treatment of MD, including physical symptoms. The effects of duloxetine are dose-dependent. At the highest dose, duloxetine improved some measures to a greater extent than paroxetine.

Table 2: Adverse reactions* (%) of among patients treated with duloxetine or placebo[9]

Adverse reaction	Duloxetine 20 mg/day N = 138	Duloxetine 40 mg/day N = 137	Duloxetine 80 mg/day N = 140	Placebo N = 138
Headache	7	10	8	9
Nausea†	9	9	13	2
Constipation	4	4	6	1
Diarrhea	5	4-	4	3
Fatigue†	1	8	10	3
Dizziness	2	6	7	2
Insomnia†	2	7	7	1
Dry mouth	4	5	7	1
Sinusitis	4	4	4	6
Upper respiratory infection	2	2	1	5
Nasopharyngitis	8	4	6	4

*All occurred in ≥5% of subjects in any treatment arm. †$P < .05$, for overall treatment effect (Pearson's $\chi 2$ test).

Adverse effects

Table 2 depicts adverse effects reported in a placebo-controlled, dose-ranging study of patients with urinary incontinence.[9] Nausea, insomnia, and fatigue were more likely to occur with duloxetine than placebo, and are dose dependent.

Dosing and administration

Duloxetine may be administered orally without regard to meals. The dosing criteria for duloxetine varies based on its indication. For depression, an initial dose of 40-60 mg/day given as a single or divided dose by mouth is effective in adults. Doses greater than 60 mg/day may not provide additional benefit.[8] The safe and effective use of duloxetine is not established in adolescents and children. The maximum dose of duloxetine in adults is 120 mg/day, although no advantage over lower doses has been identified. Duloxetine should not be used in patients with hepatic impairment, ESRD or severe renal impairment.[8]

Drug interactions

Duloxetine should not be used concurrently with monoamine oxidase inhibitors, drugs with MAOI activity like furazolidone, linezolid and procarbazine due to the high risk for serotonin syndrome. Also, centrally-acting medications such as TCAs, SSRIs, St. John's wort, Hypericum perfotum, amphetamine and dextroamphetamine, buspirone, cocaine, dexfenfluramine, fenfluramine, lithium, phentermine, sibutramine, nefazodone and trazodone should not be used concurrently with duloxetine. A drug-free interval of 5 days is recommended following the cessation of duloxetine and the intitiation of an MAOI and an interval of 14 days is recommended after the cessation of an MAOI and intitiation of duloxetine.[8] Duloxetine, when used concurrently with tramadol, may decrease the analgesic effect of tramadol by inhibiting the formation of tramadol's active metabolite. Disorientation, delusions, and hallucinations have been reported in patients treated with zolpidem and duloxetine concurrently.

Cost

The average retail cost of Cymbalta® for one month of therapy based on retail cost at 3 local pharmacies is $97.30 at 20 mg/d; $111.21 at 30 mg/d; and $111.21 for 60 mg/d.

Summary

Depression is a major health problem affecting millions of people. Duloxetine inhibits the reuptake of NE and 5HT, both of which are believed to play an important role in depression. It is also effective in stress urinary incontinence and for the management of pain associated with neuropathy. Duloxetine has a quick onset of action, which

offers a unique advantage compared to SSRIs. Its side effect profile appears to be favorable compared to TCAs and similar to other antidepressants. It is not clear whether duloxetine has the same effect as other antidepressants on suicidality, but caution should be used in patients at risk for this complication.

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XIFAXAN™: A NEW TREATMENT FOR TRAVELER'S DIARRHEA

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Introduction

Diarrhea is the most common medical problem among people traveling within and to developing countries. Mortality due to typical traveler's diarrhea is uncommon; however, the morbidity of untreated traveler's diarrhea is significant with at least 1% of sufferers requiring hospitalization, 20% confined to bed and nearly 40% changing their itinerary.[1] Classic traveler's diarrhea is usually defined as the passage of three or more unformed stools in a 24-hour period plus at least one symptom of enteric disease such as abdominal pain or cramps, nausea, vomiting, fever, or tenesmus. Traveler's diarrhea is a self-limited disease but may last longer than one week in 10% of patients and up to one month or more in 2%. The most common cause of traveler's diarrhea is contaminated food and water in which 80% of cases are caused by bacterial enteropathogens.[2]

At present, options for the prevention of traveler's diarrhea include education and chemoprophylaxis with either bismuth subsalicylate (BSS)-containing compounds or antibiotics, usually sulfonamides or fluoroquinolones. Antibiotics prevent approximately 80% of cases as long as they have reliable activity against enteropathogens in the destined regions.[1] Antibacterial therapy is generally recommended after the passage of the third stool in a 24 hour period; for diarrhea associated with moderate-to-severe abdominal pain or cramps, fever, or dysentery; and for symptoms that recur when drugs are discontinued.[2] The major benefits of antibiotics are a significant reduction in the total duration of diarrhea from 60-100 hours to approximately 30 hours and earlier relief of the accompanying gastrointestinal symptoms.[2] Currently, the drug of choice for the treatment of traveler's diarrhea is a fluoroquinolone. Trimethoprim and sulfamethoxazole (TMP/SMX) was once the drug of choice, but due to increasing resistance it is no longer recommended as empiric therapy. The use of a non-absorbable antibiotic, such as rifaximin (Xifaxan™, Salix Pharmaceuticals), is an attractive choice for the treatment and prophylaxis of traveler's diarrhea due to the potential of fewer adverse effects, safety in children, pregnant women, and possibly less impact on antibiotic resistance. The U. S. Food and Drug Administration (FDA) granted marketing approval for rifaximin in May 2004 for

Table 1. Rifaximin studies in patients with traveler's diarrhea [4, 5]

Study	Design (N)	Regimens	Results
R. Steffen et al[4]	Randomized, double-blind (254) placebo-controlled study conducted in Mexico, Guatemala, and Kenya	Rifaximin 600 mg/day x 3d versus placebo	Median time to last unformed stool: rifaximin 32.5 hours; placebo 60 hours. P-value=0.001
HL Dupont et al[5]	Randomized, double-blind, double-dummy (187) conducted in Mexico and Jamaica	Rifaximin 400 mg BID x3d versus ciprofloxacin 500 mg BID x3d	Median time to last unformed stool: rifaximin 25.7 hours; ciprofloxacin 25 hours. P-value=0.006

the treatment of patients (≥ 12 years of age) with traveler's diarrhea caused by noninvasive strains of *Escherichia coli*. This article will examine the safety, efficacy, and tolerability of rifaximin.

Pharmacology and Pharmacokinetics

Rifaximin, a derivative of rifamycin, is a semi-synthetic, non-systemic antibiotic. Rifaximin acts by binding to the beta-subunit of bacterial DNA-dependent RNA polymerase resulting in inhibition of bacterial RNA synthesis.[3] Rifaximin is not suitable for treating systemic bacterial infections because less than 0.4% of the drug is absorbed after oral administration. Absorption is not affected by food. Rifaximin's mean peak plasma concentration (C_{max}) is minimal and is reached approximately 1.25 hours after oral administration. Animal studies demonstrate that 80% to 90% of orally administered rifaximin is concentrated in the gut. Rifaximin induces cytochrome P450 3A4 (CYP 3A4). Despite limited oral bioavailability, its effects on P450 in the gut wall may produce clinically relevant drug interactions. Rifaximin is excreted primarily in the feces. Because of the limited systemic absorption, no specific dosing adjustments are recommended for patients with hepatic insufficiency. The pharmacokinetics of rifaximin in patients with impaired renal function have not been studied.

Drug-Drug Interactions

In an *in vitro* hepatocyte induction model, rifaximin was shown to induce cytochrome CYP3A4, an isoenzyme which rifampin is also known to induce. Two clinical drug-drug interaction studies were conducted using midazolam and an oral contraceptive containing ethinyl estradiol and norgestimate to assess the effect of rifaximin on the pharmacokinetics of these drugs.

The midazolam study was an open-label, randomized, crossover, drug-interaction trial designed to assess the effect of rifaximin 200 mg administered orally (PO) every 8 hours (Q8H) for 3 days and Q8H for 7 days on the pharmacokinetics of a single dose of either midazolam 2 mg intravenously or midazolam 6 mg PO. No significant difference was observed.[3] Rifaximin did not have clinically significant effects on midazolam.

An open-label, crossover study in 28 healthy female subjects examined whether rifaximin 200 mg PO administered Q8H for 3 days altered the pharmacokinetics of a single dose of an oral contraceptive containing 0.07 mg ethinyl estradiol and 0.50 mg norgestimate.[3] The pharmacokinetics of single doses of ethinyl estradiol and norgestimate were not altered by rifaximin.

Microbiology

Rifaximin has a relatively broad antimicrobial spectrum that includes aerobic and anaerobic gram-positive and gram-negative bacteria.[3] Rifaximin is effective against *E. coli* (enterotoxigenic and enteroaggregative strains). In *in vitro* studies, *E. coli* was capable of developing microbiological resistance to rifaximin. Organisms with high rifaximin minimum inhibitory concentration (MIC) values also have elevated MIC values against rifampin. Cross-resistance between rifaximin and other classes of antimicrobials has not been studied. The emergence of resistance to rifaximin underscores the importance of surveillance in preserving the drugs activity.

Clinical Trials

The efficacy of rifaximin was demonstrated in a limited number of controlled clinical trials in-

Table 2. Adverse events occurring in ≥ 2% of patients receiving rifaximin 600 mg/day, in placebo-controlled studies

Adverse Effect	Number (%) of Patients	
	Rifaximin 600 mg/day (N = 320)	Placebo (N = 228)
Flatulence	36 (11.3%)	45 (19.7%)
Headache	31 (9.7%)	21 (9.2%)
Abdominal Pain	23 (7.2%)	23 (10.1%)
Rectal Tenesmus	23 (7.2%)	20 (8.8%)
Defecation Urgency	19 (5.9%)	21 (9.2%)
Nausea	17 (5.3%)	19 (8.3%)
Constipation	12 (3.8%)	8 (3.5%)
Pyrexia	10 (3.1%)	10 (4.4%)
Vomiting NOS	7 (2.2%)	4 (1.8%)

volving several hundred patients with traveler's diarrhea caused by noninvasive strains of *E. coli* (Table 1). Clinical efficacy in these studies was primarily based upon the time to return to normal, formed stools and resolution of symptoms. Study results show that the duration of diarrhea is significantly shorter in patients treated with rifaximin compared to placebo, and significantly more patients receiving rifaximin demonstrate a clinical cure.[4] Rifaximin appears to be similar in efficacy to ciprofloxacin for the treatment of traveler's diarrhea.[5] One advantage is that rifaximin is nonadsorbable and, thus, may have a lesser impact on antimicrobial resistance among non-targeted pathogens (i.e., minimal collateral damage). The two published clinical trials summarized in Table 1 were conducted in traveler's diarrhea caused predominantly by *E. coli*.

A separate study, conducted in 72 US adults traveling to Mexico evaluated four separate outcomes: the most effective dose of rifaximin for the treatment of traveler's diarrhea; the effectiveness of rifaximin for eradication of causative bacterial enteropathogens; the relative safety and tolerability of rifaximin; and the efficacy of rifaximin versus TMP/SMX (which is effective in Mexico).[6] Results from that study suggest that 5 days of rifaximin treatment is as effective as therapy with trimethoprim/sulfamethoxazole (TMP/SMX) However due to the decreased efficacy of TMP/SMX worldwide, these results may no longer be applicable in all areas.

Dosage and Administration

Rifaximin can be administered orally with or without food. For traveler's diarrhea, the recommended dose is one 200 mg tablet taken three times a day for 3 days. No specific information is available on the treatment of overdosage with rifaximin. In clinical studies, at doses higher than the recommended dose (>600 mg/day), adverse effects were similar to the recommended dose (200 mg three times a day). In the case of overdose, discontinue rifaximin, treat symptomatically, and institute supportive measures as necessary. Rifaximin is indicated for the treatment of patients (≥ 12 years of age) with traveler's diarrhea caused by noninvasive strains of *E. coli*. Rifaximin should not be used in patients with diarrhea complicated by fever or blood in the stool or diarrhea due to pathogens other than *E. coli*.

Warnings and Precautions

Rifaximin is not effective in patients with diarrhea complicated by fever and/or blood in the stool or diarrhea due to pathogens other than *E. coli*. Rifaximin is not effective in cases of traveler's diarrhea due to *Campylobacter jejuni*. The effectiveness of rifaximin in traveler's diarrhea caused by *Shigella spp*. and *Salmonella spp*. has not been proven. Rifaximin should be discontinued if diarrhea symptoms worsen or persist more than 24-48

Table 3. Cost Comparison of Treatment for Traveler's Diarrhea[7]

Drug	Dosage	US Cost[1]
Azithromycin	1000 mg once or 500 mg once/d x 3d	$31.24 $46.86
Ciprofloxacin (generic)	500 mg bid x 3d	$30.42
Ciprofloxacin (brand)	500 mg bid x 3d	$33.60
Ciprofloxacin XR/XL (brand)	1000 mg once/d x 3d	$28.17
Levofloxacin	500 mg once/d x 3d	$31.50
Rifaximin	200 mg tid x 3d	$32.76

Cost based on the most recent data (July 31, 2004) from retail pharmacies nationwide available from NDCHealth, a healthcare information services company.

hours after treatment is started; alternative antibiotic therapy should be considered. Pseudomembranous colitis has been reported with nearly all antibacterial agents and may range in severity from mild to life-threatening. It is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents. The safety and effectiveness of rifaximin has not been established in pediatric patients less than 12 years of age. It is not known whether rifaximin is excreted in human milk. Rifaximin is teratogenic in rats at doses of 150 to 300 mg/kg and in rabbits at doses of 62.5 to 100 mg/kg. There are no adequate, well controlled studies in pregnant women. Rifaximin should only be used during pregnancy if the potential benefit outweighs the risk to the fetus. Rifaximin is contraindicated in patients with a hypersensitivity to rifaximin or any of the rifamycin antimicrobial agents, including rifampin.

Adverse Reactions

The safety of rifaximin 200 mg taken three times a day (TID) was evaluated in 320 patients in two placebo-controlled clinical trials with 95% of patients receiving at least three days of treatment with rifaximin. All adverse events that occurred at a frequency ≥ 2% in the two placebo-controlled trials combined are depicted in Table 2.

The most common adverse effects of rifaximin is flatulence, headache, abdominal pain, and rectal tenesmus. The following events have been reported from postmarketing experience: hypersensitivity reactions, including allergic dermatitis, rash, angioneurotic edema, urticaria, and pruritus.

Cost

A comparison of the cost of antibacterial agents frequently used to treat traveler's diarrhea appears in Table 3.

Summary

Rifaximin should be considered as a non-systemic treatment option for patients with traveler's diarrhea caused by noninvasive strains of *E. coli*. This drug has not been studied in cases of traveler's diarrhea caused by *Shigella spp* and *Salmonella spp.* and has been shown to be not ineffective in cases due to *C. jejuni*. Rifaximin has pharmacologic and safety advantages over the existing drugs for traveler's diarrhea. Rifaximin may have a favorable safety profile compared to systemically absorbed options. Rifaximin is a good alternative for patients allergic to sulfonamides or in areas where resistance to TMP/SMX is prevalent. Resistance has been reported to the quinolones due to widespread use and selective pressure. Thus, rifaximin represents a viable alternative to the fluoroquinolones for the treatment of traveler's diarrhea.

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New Dosage Forms

- Gatifloxacin (Tequin®) is now available in an oral suspension that is fruit-flavored. It is supplied in 1-, 2-, 3-, and 4-g unit-of-use bottles. After constitution with water, the suspension contains 200 mg of drug per 5 mL.
- Omeprazole (Zegerid®) is available in 20 and 40 mg as an immediate-release powder for oral suspension. The oral powder is approved for the treatment of heartburn and other symptoms related to gastroesophageal reflux, short-term treatment and maintenance of healing erosive esophagitis, and treatment of duodenal ulcers.
- Carbidopa and levodopa orally disintegrating tablets (Parcopa™) are indicated for the treatment of Parkinson's disease. The immediate-release formulation can be taken without water and is designed to facilitate dosing in this population. The recommended dose is the same as for conventional carbidopa/levodopa tablets. Parcopa is available in tablets containing phenylalanine, citrus or mint flavoring, 10 or 25 mg of carbidopa, and 100 or 250 mg of levodopa.
- Digoxin elixir is a lime flavored liquid, with 10% alcohol, indicated for the treatment of mild to moderate heart failure and the control of a resting ventricular response rate in patients with chronic atrial fibrillation.

Labeling Changes

- The antidepressants citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, and venlafaxine each now carries a warning regarding the potential for suicidal ideation and suicide attempts during therapy.
- The following adverse effects have been reported with ezetimibe (Zetia®) and are now included in the labeling under adverse events: cholelithiasis, cholecystitis, pancreatitis, nausea, angioedema, and rash. Also, the label was modified to reflect an interaction with cyclosporine that significantly increases systemic exposure to ezetemibe.

New Drug Approvals

- Acamprosate (Campral®) is approved for use as maintenance therapy in recovering alcoholics who are presently abstinent to increase the likelihood of persistent abstinence. The recommended dose is 666 mg three-times daily It is available as a delayed-release tablet that contains 333 mg. The dose should be decreased in patients with renal insufficiency.

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