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Fluticasone Furoate/Vilanterol: A New Inhaled Corticosteroid/ Long-Acting Beta Agonist

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Fluticasone furoate/vilatnerol (100mcg/25mcg) was FDA approved in May 2013 for once daily treatment in patients with chronic obstructive pulmonary disease (COPD) and for reducing exacerbations.[1] This is the first once daily long acting beta agonist/inhaled corticosteroid (LABA/ICS) COPD maintenance medication on the market. COPD is characterized as a disease of persistent airflow limitation due to chronic inflammation and airway constriction.[2] (Table 1) Both inflammation and constriction of airways are triggered by noxious stimuli with a high incidence of patients that are chronic cigarette smokers. A COPD exacerbation is an acute worsening of airflow limitations away from the day-to-day norm.[2] COPD exacerbations are uncontrolled and associated with increased mortality and decreased quality of life. There is a direct correlation that increasing number of COPD exacerbations per year lead to increased risk of death.

Treatment options are aimed at reducing COPD symptoms, reducing the frequency and severity of exacerbations and improving the quality of life.[2] Treatment should be tailored to the patient based on severity, risk of exacerbation, cost and availability. Treatment options include: beta2 agonists, anticholinergics, inhaled corticosteroids, combination of bronchodilator and inhaled corticosteroids, methylxanthines, systemic corticosteroids, and phosphodiesterase-4 inhibitors.

The objective of this article is to review the pharmacology, pharmacokinetics, clinical trials, precautions and adverse drug reactions, dosing and administration, and cost associated with fluticasone furoate/vilanterol.

Table 1 | Classification of Severity of Ariflow Limitation in COPD[2]

Gold Classification	Severity	FEV1 % predicted
GOLD 1	Mild	FEV1 ≥ 80%
GOLD 2	Moderate	50% ≤FEV1≤80%
GOLD 3	Severe	30% ≤ FEV1 ≤ 50%
GOLD 4	Very Severe	FEV1 ≤ 30%

Pharmacology[1]

Fluticasone furoate is an inhaled corticosteroid designed to decrease airway inflammation. Vilanterol is a long-acting beta agonist acting as a vasodilatory to increase airflow.

Fluticasone furoate is a synthetic corticosteroid with increased affinity at glucocorticoid receptors as compared to other corticosteroids. It has 29.9 and 1.7 times the affinity compared to dexamethasone and fluticasone propionate respectively. The glucocorticoid effect is responsible for inhibiting pro-inflammatory factors and antigen-induced lung eo-

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sinophilia. Corticosteroids have activity on multiple types of inflammatory mediators such as histamine, leukotrienes, cytokines and cells of the immune system (mast cells, eosinophils, and neutrophils).

Vilanterol, has selectivity for beta-2 adrenoreceptors similar to that of salmeterol. Binding to beta2- adrenoreceptors, lined on bronchial smooth muscle, causes an increase in cyclic AMP levels, which leads to airway relaxation. An increase in cyclic AMP also helps to inhibit mast cell degranulation, which if uninhibited would release mediators of hypersensitivity to noxious stimuli such as cigarette smoke.

Pharmacokinetics[1]

Fluticasone furoate has linear pharmacokinetics with peak plasma concentrations reached in 0.5-1 hour and steady state after six days. After six inhalations, there was a 2.6 times increase in plasma concentration as compared to one inhalation. Absolute bioavailability after inhalation was 15.2%, with 1.3% due to oral bioavailability after being swallowed.

Vilanterol also possesses linear pharmacokinetics but plasma levels are not associated with clinical effects. Peak concentrations are reached in 10 minutes with an absolute bioavailability of 27.3%, with less than 2% due to oral bioavailability after being swallowed.

COPD patients demonstrate a 46% decreased systemic exposure to fluticasone furoate and a 24% higher systemic exposure to vilanterol, compared to healthy controls.

Fluticasone furoate and vilanterol are cleared from the circulation through hepactic metabolism. This is accomplished through CYP3A4 metabolism to products with decreased activity at the glucocorticoid receptor and beta2-adrenoreceptors. When administered with strong CYP3A4 inhibitors, AUC increased by 36% and 65% for fluticasone furoate and vilanterol, respectively.[3]

Elimination of fluticasone furoate and its metabolites is mainly through feces with 1% of the oral dose recovered in the urine. Vilanterol and its metabolites (approximately 70% of dose) are recovered in the urine.

Clinical Trials

Currently all published trials on fluticasone furoate/vilanterol are placebo controlled or comparison with vilanterol alone. Three phase 3 trials have evaluated multiple doses of fluticasone fluticasone furoate (50, 100, 200mcg) with 25mcg of vilanterol on lung function (weighted mean FEV_1 and change from baseline trough FEV_1).[4-6] (Table 2) One phase 3 trial studied the impact of the addition of multiple strengths of fluticasone to vilanterol on decreasing the rate of COPD exacerbations.[7] Fluticasone furoate/ vilanterol is the only once daily combination LABA/ICS for maintenance treatment of COPD on the market. Medications that are administered with less frequency are thought to have increased adherence however there is a paucity of data supporting this .[8]

Measuring annual rate of COPD exacerbation per year is one of several tools clinicians have of assessing effectiveness of treatment. Dransfield et al. conducted two replicate, double blind, parallel group, randomized controlled trials looking at the primary endpoint of yearly rate of moderate to severe exacerbations in a COPD population.[7] Patients were over the age of 40, had COPD, and no recent exacerbations within the last month but within the last year. Patients were randomly assigned to one of four treatment arms: vilanterol 25mcg, fluticasone furoate/ vilanterol 50/25; 100/25; 200/25mcg. To assess the data collected, statistical analysis assumptions were made. To detect a 25% reduction in exacerbations with a 90% power, and a p-value of .05 the study needed a sample size of 390 patients per treatment arm. To account for patients that would drop out an intention to treat analysis was used for any patients who at least received one dose of therapy.

The replicate studies should have minimized inter-variability and produced similar results however, the results were different between the two studies (Table 3). The first study did not show a statistically significant reduction in yearly rate of exacerbations with the 200mcg/25mcg fluticasone furoate/ vilanterol group. (Table 3) However, because a hierarchal method was used when analyzing data, the smaller dosages of fluticasone furoate cannot be evaluated for statistical significance. The least squares mean yearly rate of COPD exacerbations in the vilanterol only group was 1.05 compared to 0.90 in the active treatment group of fluticasone furoate/vilanterol 200mcg/25mcg, representing a 14% reduction (p=0.1093; 95% CI 0.70-1.0). Study two did show statistical significance in the 200 mcg fluticasone furoate group with the least squares mean yearly rate of exacerbations being 0.79 compared to 1.14 in the vilanterol only group, a reduction of 35% (p=0.0004; 95% CI 0.6-0.9). Only when data for both studies were pooled did the 100mcg fluticasone furoate group have a statistically significant reduction in least squares mean yearly rate of exacerbations per year of 27% (p <0.0001; 95% CI 0.6-0.8). (Table 3)

Table 2 | Primary Endpoints of Clinical Trials Involving Fluticasone Furoate/vilanterol

Reference	Patients	Treatment Arms	1° Endpoints	Results	Author's Conclusions
Boscia[4], 2012	N=87 ≥ 40 yrs Hx of COPD	PL 50/25mcg FF/VI 100/25mcg FF/VI 200/25mcg FF/VI	Time adjusted (wm) 0-24 hr FEV1 after 28 days at end of each treatment arm	***Difference vs. PL*** 50/25mcg FF/VI=0.233 (p<0.001; 95%CI 0.179 -0.287) 100/25mcg FF/VI=0.220 (p<0.001; 95%CI0.165 -0.275) 200/25mcg FF/VI=0.236 (p<0.001; 95%CI 0.181-0.291)	Improvements in FEV_1 vs. PL were achieved at each time point & with each strength of FF/VI over the time period indicating rapid onset of action and sustained bronchodilation
Martinez[5], 2013	N=1224 ≥40 yrs Hx of COPD No Hx of exacerbations	PL 100mcg FF 200mcg FF 25mcg VI 100/25mcg FF/VI 200/25mcg FF/VI	(wm) FEV1 (0 -4h post dose) on day 168	***200/25mcg*** Vs. PL = .209 (p<.001 95%CI 0.157-0.261) Vs. VI=0.024 (95%CI -.027-.075) Vs. 200mcg FF=0.168 (p<.001 95%CI 0.117-0.219) ***100/25mcg*** Vs. PL=0.214(95%CI 0.161-0.266) Vs. VI = .029 (95%CI 0.023-0.081) Vs. 100mcgFF=0.168(95%CI=0.116-0.220)	Statistically significant ↑ in 1° endpoint with FF/VI 200/25mcg vs. PL but statistical significance was not seen in the FF/VI 100/25mcg
Kerwin[6], 2013	N= 1030 ≥40 yrs Hx of COPD Hx of 10PPy	PL 100mcg FF 25mcg VI 100/25mcg FF/VI 50/25mcg	(wm) FEV1 (0 -4h post dose) on day 168	***100/25mcg*** Vs. PL=0.173(p<.001 95%CI 0.123-0.224) Vs. VI=0.071 (95%CI 0.021=0.121) Vs. 100mcg FF=0.120(p<0.001 95%CI 0.070-0.170) **50/25mcg** Vs. PL=0.192 (95%CI 0.141-0.243) Vs. VI=0.090(95%CI0.039-0.140)	FF/VI 100/25mcg on post dose FEV1 was statistically significant vs. PL; due to statistical hierarchy, no significance with the VI 50/25mcg dose

FF= fluticasone furoate VI= vilanterol PL = placebo BL= baseline Hx: history
COPD: chronic obstructive pulmonary disease WM: weighted mean FEV1= Forced expiratory volume after 1 min

Table 3 | Individual and Pooled Data from Fluticasone Furoate/Vilanterol in COPD[7]

Study	25 mcg VI	50 mcg/25 mcg FF/VI	100 mcg/25 mcg FF/VI	200 mcg/25 mcg FF/VI
Study 1 LS mean yearly rate Ratio to VI (95%CI) P-value	1.05	0.92 0.9 (0.7-1.1) N/A	0.70 0.7 (0.5-0.8) N/A	0.90 0.9 (0.7-1.0) 0.1093
Study 2 LS mean yearly rate Ratio to VI (95%CI) P-value	1.14	0.92 0.8 (0.7-1.0) 0.0398	0.90 0.8 (0.6-1.0) 0.0244	0.79 0.7 (0.6-0.9) 0.0004
Pooled LS mean yearly rate Ratio to VI (95%CI) P-value	1.11	0.93 0.8 (0.7-1.0) 0.0141	0.81 0.7 (0.6-0.8) <0.0001	0.85 0.8 (0.7-0.9) 0.0003

VI: viltanerol FF: Fluticasone furoate LS: least squares N/A: not available

Toy et al. evaluated the relationship between daily dosing frequency and adherence to COPD treatment.[8] This study was a retrospective review of an administrative claims database documenting the history of prescription drug dispensing. Claims were chosen if they met three criteria: commonly used long-acting beta agonist or anticholinergic therapy in naïve users, diagnosis of COPD, and at least two pharmacy claims. Primary endpoint was the measure of the proportion of days covered (proportion of days in a given time interval the patient had drug available). There was a 6% absolute difference in the primary endpoint between the once daily and twice daily dosing of 43.3% and 37.0% respectively. These numbers should be evaluated with caution since all patients' baseline characteristics were statistically significantly different and the drugs used in the comparison were also different. This is also a retrospective review and not a randomized control and thus conclusions cannot be drawn about the difference because there is an increased risk of selection bias.

Precautions and Adverse Drug Reactions

Clinical trials have not studied subjects who were experiencing acute episodes of exacerbations therefore fluticasone furoate/vilanterol should not be used for relief or rescue of these episodes. Healthcare providers should provide patients with prescriptions for short-acting beta2-agonists therapy as needed. Patients should be instructed on proper use of this agent; and that increased use of a short-acting formulation is a sign of deterioration and should seek medical attention. Fluticasone furoate/ vilanterol should not be used in combination with other long-acting beta agonists due to risk of increased potassium levels and increased heart rate.[1]

Patients who were previously maintained on systemic corticosteroids can experience adrenal insufficiency if they are switched to fluticasone furoate/vilanerol due to decreased systemic concentrations in inhaled doses. When transferring a patient from systemic corticosteroids to fluticasone furoate a wean dose should be initiated if the patient was previously maintained on 20mg or more of prednisone or equivalent.[1]

Most types of adverse reactions seen with study patients related to increased infections both local and systemic. Patients receiving fluticasone furoate/ vilanterol had an increased risk of nasopharyngitis and oral candidiasis. Patients should be instructed to rinse their mouth, after each inhalation, with water, and to not swallow the water. Patients receiving fluticasone furoate/vilanterol also had an increased rate of pneumonia in clinical trials as compared to vilanterol alone. (Table 4)

Since vilanterol is a long acting beta agonist (LABA) its use as monotherapy in asthma is not recommended since there is a class effect of increased asthma-related deaths compared to placebo. Fluticasone furoate/vilanterol has not been evaluated for safety and efficacy for use in asthma and bronchospasm and therefore is not indicated.

Fluticasone furoate/ vilanterol is considered Pregnancy Category C in which therapy should be used if the benefits outweigh the risk. Due to the newness of the drug, there is insufficient safety data of its use in pregnancy and lactation.

Fluticasone furoate/vilanterol is not indicated for use in children as safety and efficacy has not been established. All phase II and III trials included only patients greater than 40 years old.

Dose and Cost[1]

Fluticasone furoate/vilanterol comes in a dry powder inhaler dosage of 100mcg/25mcg with 30 doses per inhaler. Each plastic inhaler contains 30-blister strips each of fluticasone furoate and vilanterol. There is a 14-day course pack that is only

Table 4|Rate of Common Adverse Drug Reactions with Fluticasone Furoate/Vilanterol Seen in Clinical Trials[1,4-6]

Adverse Event (%)	100/25mcg FF/VI	25mcg VI	100mcg FF	Placebo
Nasopharyngitis	9	10	8	8
URTI	7	5	4	3
Oropharyngeal Candidiasis	5	2	3	2
Study A[4]	<1	<1	<1	0
Study B[5]	2	2	2	1
Study C[6]	6.3	3.3	N/A	N/A

VI: vilanterol FF: fluticasone furoate URTI: upper respiratory tract infection N/A: not available

available for institutional use.

Fluticasone furoate/vilanterol should be inhaled orally once daily at the same time each day. After each inhalation the mouth should be rinsed with water but not swallowed. Dosages should not exceed one inhalation per day.

No dosage adjustment is needed in patients with renal impairment. In patients with severe renal impairment, (creatinine clearance <30ml/min) there was a 56% increase in AUC (0-24) but this increase did not increased systemic effects. Additionally, there is no recommended change in dosing for geriatric patients.

Patients with moderate to severe hepatic impairment should be monitored closely if starting on fluticasone furoate/vilanterol. Study subjects with severe hepatic impairment had a 75% increase in fluticasone furoate systemic exposure. This increase was correlated with a 14% increase in serum cortisol levels (0-24 hours). There was no increase in systemic exposure of vilanterol following repeat-dose administration for 7 days of fluticasone furoate/ vilanterol 200mcg/25mcg.

Fluticasone furoate/vilanterol is now available at many pharmacies. Three community pharmacies were called and the average cash price for a single inhaler which provides a one months supply was $315.99.

Summary

Fluticasone fuorate/vilanterol is the only once daily-inhaled corticosteroid/long acting beta agonist for the maintenance treatment of moderate-severe COPD and reducing COPD exacerbations. Fluticasone furoate/vilanterol 100/25mcg inhaled once daily reduced COPD exacerbations by 27% per year. There is no dose reduction necessary for patients with renal or hepatic impairment but therapy should be monitored closely for signs of increased systemic exposure to both components. As with other inhaled corticosteroids there is an increased rate of local infections such as orapharyngeal candidiasis and thus patients should be instructed to rinse their mouth with water but not swallow after each inhalation to decrease this risk. Fluticasone furoate/ vilanterol hopes to find its niche in the market as the only once daily COPD medication, however, there currently is a lack of evidence showing that once daily administration will increase adherence compared to twice daily. [8]

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Levomilnacipran: New SNRI for the Treatment of Major Depressive Disorder

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Depression is a major health problem and a leading predictor of functional disability and mortality.[1] Major depressive disorder (MDD) is a serious illness that affects more than 16% of adults at some point during their lifetime.[1] It is estimated that the United States' economic burden of depressive disorders is roughly $83 billion annually[2]. MDD is diagnosed using the Diagnostic and Statistical Manual of Mental Disorders, Fifth addition (DSM-V).[3] Risk factors for MDD include socioeconomic disadvantage, low quality of life, being female, minority status, disability and being middle-aged.[4] The onset of depression is usually around the 20 year mark.[4]

Pharmacotherapy is one of the primary choices for treatments of MDD.[5] First-line treatment options include selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), bupropion and mirtazapine. Tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) can also be used to treat MDD;

however these medications are usually not first-line agents. As of 2005, approximately 27 million people in the U.S had taken a form of anti-depressant therapy.[5]Levomilnacipran (Fetzima®) is a new SNRI which was approved by the FDA in July 2013 for the treatment of MDD in adults.[6] Levomilnacipran was developed by Forest Laboratories and Pierre Fabre Laboratories. It is the fourth SNRI to enter the US market for MDD, and currently that is its only indication. Levomilnacipran is an enantiomer of milnacipran, an SNRI approved for the treatment of fibromyalga. The objective of this article is to discuss the pharmacology, pharmacokinetics, clinical trials, adverse events, drug interactions, and dosing of levomilnacipran.

PHARMACOLOGY

The exact mechanism of action of antidepressants, including levomilnacipran, is unknown.[6] Levomilnacipran is a highly selective serotonin (5-HT) and norepinephrine (NE) reuptake inhibitor (Table 1). Neurotransmitters such as serotonin (5-HT) and norepinephrine (NE) play an important role in normal brain neurochemistry. It is hypothesized that the inhibition of the reuptake transporters in the presynaptic neuron will increase the amount of neurotransmitters in the synaptic cleft and increase serotonergic/noradrenergic neurotransmission. With chronic administration, this increase of neurotransmitters in the synaptic cleft causes the down regulation or desensitization of the autoreceptors on the neurons. This down regulation of autoreceptors is how antidepressents exert their clinical effect. The desensitization of the autoreceptor to "normal levels" is a time sensitive issue, there is general consensus that treatment of major depressive disorder requires several months or longer of sustained pharmacologic therapy.[7] Levomilnacipran is very potent reuptake inhibitor, NE (IC50 = 10.5 nM) and 5-HT (19.0 nM) in vitro, but lacks monoamine oxidase inhibiting activity.[6, 11] Levomilnacipran does not have significant affinity for alpha and beta adrenergic, muscarinic or histaminergic receptors.[11]

PHARMACOKINETICS

The pharmacokinetics of levomilnacipran were established through clinical trials and are summarized in Table 2. The relative bioavailability of levomilnacipran (ER formulation) after oral administration is 92% compared with oral solution.[6]The concentration of the drug is not significantly affected by food. Levomilnacipran is widely distributed with an apparent volume of distribution of 387-473 L.[6] Levomilnacipran has low protein binding (22%) in the serum, thus few protein binding drug interactions are expected.[6] The metabolism of levomilnacipran is predominantly via CYP3A4; however CYP2C8, 2C19, 2D6 and 2J2 also play a small role. These enzymes perform a desethylation of levomilnacipran. Levomilnacipran can also undergo hydroxylation. Both metabolites still undergo further phase II metabolism to form glucuronide conjugates. About 58% of the drug is excreted in the urine unchanged, 18% is excreted as N-desethyl levomilnacipran, and 9% accounts for other identifiable metabolites.[6] The half-

Table 1 | Binding Affinity of SNRIs to Reuptake Transporters [6-9]

Antidepressant	Ki[a] for SERT[b] site (nM[c])	Ki for NERT[d] (nM)
Levomilnacipran	11	91
Venlafaxine	9.1	1060
Desvenlafaxine	40	558
Duloxetine	1.6	11.2
Milnacipran	123	200

a.Ki= inhibition constant is a way to measure binding affinity of the drug to receptor, in this case the transporters. The smaller the K_i the higher the affinity of the drug is to its target therefore, the more potent it is. It should be noted that this is based on in-vitro studies with human cells.
b. SERT= Human transporter for serotonin
c. nM = nanoMolar, d. NERT= Human transporter for norepinephrine

Table 2 | Pharmacokinetic Properties of Levomilnacipran[6]

Property	Levomilnacipran
Tmax	6-8 hours
AUC	5196 ng.h/mL
Cmax	341 ng/mL
Terminal ½ life	12 hours
Bioavailability	92%
Volume of distribution	387-473L
Protein binding	22%

Tmax = time to peak concentration, AUC = Area under the Curve, Cmax = maximum concentration

life of levomilnacipran is about 12 hours. In patient with renal impairment, dose adjustment is recommended for patients with moderate renal impairment, (creatinine clearance of 30-59 mL/min); the maintenance dose should not exceed 80 mg daily. For patients with severe impairment (creatinine clearance of 15-29 mL/min), the maintenance dose should not exceed 40 mg daily. In patient with any degree of hepatic impairment, no dose adjustment of levomilnacipran is needed.[6] Elderly patients studied showed a slightly higher Cmax and AUC however, no dose adjustment is recommended based on age. There have been cases of clinically significant hyponatremia in elderly patients who were taking SSRIs and SNRIs, elderly patients taking levomilnacipran maybe at greater risk for this adverse event.[6]

Clinical Trials

The efficacy and safety of levomilnacipran was evaluated in four Phase III studies in the United States. All four studies were double-blinded, randomized, placebo-controlled studies. All four studies had an induction phase, treatment phase, a taper-down phase, and usually lasted between 10-11 weeks total. Treatment phase was the same duration (8 weeks) for all four studies. All four studies used a modified intention to treat group that was defined as a randomized population who received ≥ one dose of double-blinded study medication and ≥ 1 post baseline Montgomery Asberg Depression Rating Scale (MADRS) score.

Levomilnacipran was evaluated in two flexible-dose studies[13, 15] (dose can be increased based on patient tolerability within treatment period) and two fixed dose studies (patient had defined target treatment goals of 40mg, 80mg or 120mg). [12,14] Inclusion criteria were 18-80 years of age, current DSM-IV-TR criteria for major depressive disorder, current ongoing depressive episode ≥ 8 weeks, score ≥ 30 on MADRS at baseline, score ≥ 26 on the self-rated MADRS and body mass index (BMI) ≥ 18 and ≤40. Exclusion criteria were pregnant or breastfeeding women, higher risk for suicide, history of mania, hypomania, schizophrenia or any other psychotic disorder classified by DSM-IV-TR, obsessive-compulsive disorder or seizure disorders, substance abuse/ dependence within 6 months of the study and clinically significant abnormalities on physical exam.[12-15]None of the studies had exactly the same inclusion/ exclusion criteria but the differences were not significant.

The primary endpoint for all four studies was change from baseline to end of the study (week 8) in the MADRS total score; Table 3 includes all four trials and primary outcome scores. All four studies also included a secondary endpoint which was change from baseline to end of study (week 8) in the Scheehan Disability Scale (SDS) total score. MADRS is a validated method to assess symptoms outcome and is frequently used in MDD studies, it is scored from 0 to 60.[17] A total score of 35 or greater in the MADRS is suggestive of severe depression.[15] A 2-point difference between drug effect and placebo is considered to be a clinically significant improvement.[13] The Sheehan Disability Scale (SDS) is a validated scale that measures emotional disturbance in patient function in three different aspects of life: work/school, social life and family life, with each item receiving a score of 0 to 10.[13]

Of the flexible dose studies, levomilnacipran SR 40 -120 mg/day, one did not show a statistically significant difference from placebo in any of the outcomes.[15] The three remaining studies did show statistical difference in primary and secondary outcomes.[12-14] A limitation to the clinical trials was that the duration of treatment was shorter than what is typically seen in practice for antidepressant therapy, usually 6-12 months. Also the studies did not assess response, remission or recovery which is a goal of antidepressant therapy for MDD.[13] Another limitation with all the studies is use of strict exclusion criteria. Most patients treated for depression have other DSM-IV-TR comorbidities such as anxiety, obsessive compulsive disorder, suicidal ideation etc. According to the STAR*D trial only 1/3 of patient studied in clinical trials for antidepressants therapy actually convey MDD patients that present in day-to-day clinical practice.[4]

Gommell et al studied 362 patients in a flexible dose study with 184 patients receiving placebo and 178 placed in a flexible-dosing levomilnacipran SR group. After induction phase patients assigned to the levomilnacipran SR group's dose could be increased from 40mg to 80mg/day based on patient response and tolerability; at the end of Week 4, dosage could again be increased 40 to 80 or 80 to 120mg/day. This study failed to show any statistically significant differences between placebo and treatment group (Table 3) in both primary and secondary outcomes. Study limitation includes suboptimal dosing and using twice the number of capsules for dose increases which could have increased the placebo effect.[15]

Asnis et al included a total of 704 patients in a fixed dose study where179 patients received placebo, 181 patients received 40mg, 181 patients received 80 mg, 183 patients received 120 mg dose of levomilnacipran once daily for an 8-week treatment period. The least squares mean difference (LSMD) in MADRS total score at the end of week 8 was signifi-

cant vs placebo for all dose groups[13] (Table 3). Note there was statistically significant difference vs placebo at week 4 for the 80-mg (-11 vs -9, $p < 0.05$) and 120-mg (-13 vs -9, $p < 0.01$) doses. A LSMD from baseline to week 8 on secondary efficacy measure, SDS total score change, was significantly greater for only the 80-mg (-9.7, [standard error of 0.77]) and 120-mg/d (-9.7 [standard error of 0.78]) doses of levomilnacipran vs. placebo.[13]

Contraindications, Precautions and Warnings

Consistent with most antidepressants, the FDA placed a Black Box Warning in the levomilnacipran package insert concerning suicide with antidepressants in the treatment of young adults age 18-24. Serotonin syndrome is pronounced with SSRIs and SNRIs if they are combined with other drugs that might increase serotonin levels. Examples

Table 3 | Summary of Results from the Primary Efficacy Endpoint MADRS [12-16]

Study	Treatment Group	Mean Baseline Score (SD)	LSMD (SE)	Placebo-subtracted Difference[a] (95% CI)	Authors conclusions
Gommell, et al	Levomilncipran (ER 40 -120mg/ day) n= 178	35.9 (4.1)	-15.7	1.5 no confidence interval reported P-value =0.260	Study failed to demonstrate statistically significant improvement for levomilnacipran SR relative to placebo. Drug was well tolerated
	Placebo n= 184	35.5 (4.0)	-14.2	--	
Asni, et al (fixed Dose)	Levomilncipran (SR 40mg/day) n=181	36.0 (4.1)	-14.8 (1.0)	-3.2 (-5.9, -0.5)	Study showed that levomilnacipran demonstrated efficacy and generally good tolerability in this clinical trial for primary outcome.
	Levomilncipran(SR 80mg/day) n=181	36.1 (3.9)	-15.6 (1.0)	-4.0 (-6.7, -1.3)	
	Levomilncipran (SR 120mg/day) n=183	36.0 (3.9)	-16.5 (1.0)	-4.9 (-7.6,-2.1)	
	Placebo n=179	35.6 (4.5)	-11.6 (1.0)	--	
Bakish, et al (fixed Dose)	Levomilncipran (SR 40mg/day) n=185	30.8 (3.4)	-14.6 (0.8)	-3.3 (-5.5,-1.1)	Treatment with both doses showed statistical and clinical significance with primary outcome and both doses were generally well tolerated
	Levomilncipran (SR 80mg/day) n=187	31.2 (3.5)	-14.4 (0.8)	-3.1 (-5.3,-1.0)	
	Placebo n=185	31.0 (3.8)	-11.3 (0.8)	--	
Sambunaris et al (flexible-dose)	Levomilncipran (ER 40 -120mg/ day) n= 215	35.0 (3.6)	-15.3 (0.8)	-3.1 (-5.3,-0.9)	Levomilnacipran was superior to placebo in reducing MADRS scores from week 1 and response rates on the SDS and MADRS at week 8 were higher for levomilnacipran than placebo. Drug was well tolerated.
	Placebo n=214	35.2 (3.8)	-12.2 (0.8)	--	

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval unadjusted for multiplicity.
Difference (drug minus placebo) in least-squares mean change from baseline to endpoint (Week 8).

of such drugs are monoamine oxidase inhibitors and the antibiotic linezolid. There have been reports of increased blood pressure with the SNRIs as a drug class. Patients should have baseline blood pressure checked and periodically throughout treatment. Patients who have a preexisting condition of hypertension should be well controlled before initiation of treatment. Levomilnacipran is pregnancy category C with animal data showing no teratogenic effects. It is not known if levomilnacipran is present in human milk, however the drug does appear in the milk of lactating rats.

Adverse Events

Levominacipran's safety was evaluated by Thaseet al[16]in a pooled analysis of 5 clinical studies including 2,673 patients (18-78 years of age). Of the 2,673 patients exposed to at least one dose, 737 patients were given medication for 6 months and 367 were exposed for one year. Short-term, placebo-controlled studies were performed in 1,583 patients while the remainder of the patients continued in a one-year open label study. Attrition due to adverse events was seen in 9% of patients in the short-term, placebo controlled studies vs. 3% in the placebo group (1,040). The most common adverse event leading to discontinuation was nausea (1.5%). Other most commonly seen adverse events in the placebo-controlled studies with incidence above 5% are summarized in Table 4.[6,16]

Table 4 | Adverse reactions that occurred with Levomilnacipran-treated patients and were relatively common (≥ 5%)[16]

Adverse reaction	Placebo (n=1040) (%)	Levomilnacipran 40-120 mg/day (n=1583) (%)
Nausea	6	17
Headache	13	17
Dry mouth	7	10
Constipation	3	9
Hyperhidrosis	2	9
Dizziness	5	8
Heart Rate	1	6
Tachycardia	2	6
Vomiting	1	5
Palpitations	1	5
Erectile dysfunction	1	6
Ejaculation disorder	<1	5

Drug Interactions

There are some noteworthy drug interactions with levomilnacipran. Levomilnacipran is contraindicated with MAOI inhibitors[4] and should be used with caution with drugs that can increase serotonin levels such as TCAs, trazodone, ergot alkaloids, tramadol and linezolid.[10] These medications can act synergistically to increase serotonin levels and cause serotonin syndrome. Levomilnacipran can interact with ketoconazole, a CYP3A4 inhibitor, which may result in increased levels of levomilnacipran. The recommended maximum daily dose of levomilnacipran is 80mg/day in patients using ketaconazole. There is the possibility of other drug interactions through the CYP enzyme system but further evaluation into the significance of these interactions is ongoing.

Dosing

The recommended dose range for levomilnacipran is 40 mg to 120 mg once daily, with or without food. Levomilnacipran should be initiated at 20 mg once daily for 2 days and then increased to 40 mg once daily. Based on efficacy and tolerability, levomilnacipran may then be increased in increments of 40 mg at intervals of 2 or more days. The maximum recommended dose is 120 mg once daily. Levomilnacipran should be taken at approximately the same time each day. Levomilnacipran should be swallowed whole. Do not open, chew or crush the capsule. Levomilnacipran is expected to be available soon. However, after calling multiple local pharmacies none had the product or product pricing available.

Summary

Levomilnacipran is a new drug for the treatment of MDD. It will be the fourth SNRI to enter the US market for this indication. It is a potent inhibitor of NE and 5-HT reuptake. Its common side effects include erectile dysfunction, hypertension, nausea, and constipation. A Black Box Warning has been placed on all SSRIs and SNRIs for increased risk of suicide, therefore monitoring of patients on levomilnacipran is warranted. The drug is affected by ketoconazole, a CYP3A4 inhibitor, and the dose

of levomilnacipran should not exceed 80mg/day if used with ketoconazole. Caution should be used when combining levomilnacipran with other drugs that can increase levels of serotonin, due to serotonin syndrome. Patients that have renal insufficiency should be monitored and require a dose decrease if renal impairment is moderate to severe. Levomilnacipran has shown efficacy in the treatment of depression in multiple different clinical trials compared to placebo. It has not yet been compared to other second generation antidepressants. Clinicians mostly use tolerability to guide pharmacotherapy with antidepressant as seen in the STAR*D trial.[4] Levomilnacipran has been shown to be well-tolerated but its place in therapy remains to be seen.

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In October 2013 Dr. Curry stepped down as Chair of CHFM. He will remain a valuable faculty member of the department. PharmaNote® would like to thank Dr. Curry for his years of support to students, faculty, and staff, as well as his continued support of this publication.

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