Analysis of New Brand Name Drugs for MDD and Bipolar I Depression/Schizophrenia

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Fetzima

- Brand: Fetzima
- Generic: levomilnacipran (generic not available)
- Commonly Prescribed for: major depressive disorders in adults
- How the Drug works:
  - Active enantiomer milnacipran; potent inhibitor of neuronal serotonin and norepinephrine reuptake (SNRI); inhibits norepinephrine uptake with ~3-fold higher potency in vitro than serotonin without directly affecting the uptake of dopamine or other neurotransmitters
- How does it compare to other Drugs:
  - Moderate number adverse effects.
  - More threatening adverse effects such as Glaucoma.
  - Require Renal Dosing
  - Require monitoring of BP and Heart rate.
  - Similar Depression score improvement as other drugs.
- How long till it works:
  - approximately 2 weeks.
- If it works:
  - Patient will have less Depression based on mean reduction in MADRS score of 3.4 compared to placebo.
- If it doesn't work:
  - Increase dose, or consider different medication.
- Tests:
  - Blood pressure and heart rate should be measured prior to initiating treatment and periodically throughout FETZIMA treatment. Pre-existing hypertension should be controlled before initiating treatment with FETZIMA

Side Effects

- Side Effects:
  - (≥ 10% of any treatment group) were headache, nausea (17% compared to 6% in placebo), constipation (9% compared to 3% placebo), dry mouth, increased heart rate (6% compared to 1% in placebo), and hyperhidrosis (9% compared to 2% placebo), erectile dysfunction (6% compared to 1% placebo)
  - Abnormal Bleeding, Glaucoma, Trouble urinating (4-6% compared to 0% placebo), Hypomania, Seizures or convulsions, Discontinuation syndrome, Hyponatremia (When used with an SSRI in combination therapy).

- Notable Side Effects:
  - High blood pressure and/or increased heart rate
  - Urinary hesitation occurred in 4%, 5% and 6% of FETZIMA-treated patients receiving doses of 40, 80, and 120 mg, respectively.
- Life Threatening or Dangerous Side Effects:
  - Serotonin Syndrome
  - Narrow Angle Closure Glaucoma

Weight Gain: Very Low
Sedation: Not sedating.

Dosing and Use

- Usual Dose Range
  - Dosage Forms: Extended release Capsules 20mg, 40mg, 80mg, 120mg.
- How to Dose:
  - Recommended dose of 40mg – 120mg/daily
  - Swallow whole, do not open, chew, or crush.
- Dosing Tips:
  - Initiate dose at 20mg/daily for 2 days then increase to 40mg/daily. Able to increase dose by 40mg at intervals of every 2+ days.
- Overdose:
  - In clinical studies , cases of ingestions up to 360 mg daily were reported with none being fatal.
- Long-Term Use:
  - No tolerance noted. Efficacy was not established beyond 8 weeks.
  - Over 1 year of use, the mean increase BP from initiation of treatment in systolic BP was 3.9 mm Hg and diastolic BP was 3. 1 mm Hg.
- Habit forming: No
- How to Stop:
  - Gradually titrate down before stopping.

Pharmacokinetics and interactions:

- Other than CYP3A4 drug interactions, FETZIMA is predicted, based on in vitro studies, to have a low potential to be i nvolved in clinically significant pharmacokinetic drug interactions.
- Excretion: 58% unchanged in urine; 18% N-desethyl metabolite in urine

Pharmacodynamics:

- An in vivo study showed a clinically meaningful increase in levomilnacipran exposure when FETZIMA was co-administered with the CYP3A4 inhibitor ketoconazole : Do not exceed 80 mg once daily.

Precautions:

- Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term studies. These studies did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in patients over age 24

Do Not Use:

- Hypersensitivity
- Uncontrolled narrow-angle glaucoma
- Do not use MAOIs intended to treat psychiatric disorders with levomilnacipran or within 7 days of stopping levomilnacipran due to an increased risk of serotonin syndrome
- Do not initiate levomilnacipran within 14 days of stopping an MAOI

Special Populations:

- Renal Impairment:
  - Mild (CrCl 60-89 mL/min): No dosage adjustment required
  - Moderate (CrCl 30-59 mL/min): Do not exceed 80 mg/day
  - Severe (CrCl 15-29 mL/min): Do not exceed 40 mg/day
  - End-stage renal disease: Not recommended
- Hepatic Impairment:
  - Hepatic elimination is low, no dosage adjustment required with mild, moderate, or severe hepatic impairment
- Cardiac Impairment:
  - Heart rate increase in FETZIMA - treated patients receiving doses of 40 mg , 80 mg and 120 mg was 7. 2 , 7.2, and 9.1 bpm in 6 out of 1583 patients.
- Elderly: Approved.
- Children and Adolescent: not approved for use in patients under 18
  - There were 14 cases of suicidality in <18, and 5 cases in <24 years old per 1000 patients.
- Pregnancy: Pregnancy Category: C
  - Neonates exposed to SSRIs or SNRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding; such complications can arise immediately upon delivery.
  - Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying
- Breast Feeding:
  - Unknown if distributed in human breast milk, but was found to be present in milk of lactating rats.

Brintellix

- Brand: Brintellix
- Generic: vortioxetine hydrobromide (generic not available on market)
- Commonly Prescribed for: Major Depressive Disorder
- How the Drug works:
  - The mechanism of the antidepressant effect of vortioxetine is not fully understood, but is thought to be related to its enhancement of serotonergic activity in the CNS through inhibition of the reuptake of serotonin (5-HT)
- How long till it works: 2 weeks.
- If it doesn't work:
  - One randomized study on Jan 2014 found Brintellix show no improvement over placebo up to 10mg/daily. Dosage higher than 10mg/day is recommended if no improvement seen in 2 weeks.
- How does it compare to other Drugs:
  - High rate adverse effects especially Nausea (23% to 32% at highest dose).
  - No special population dosing required.
- Tests: None needed.

Side Effects

- Side Effects: nausea, constipation, vomiting, and sexual dysfunction
- How Drug Causes the side effects:
- Notable Side Effects:
  - Nausea occurs with 21%-32% of patients with dosage from 5mg-20mg in the first week. About 10% of patients who continue to 6-8 weeks will have nausea.
- Life Threatening or Dangerous Side Effects:
  - Serotonin Syndrome.
- Weight Gain: No significant effect found.
- Sedation: Not found at 10mg/day dose. Low.
- Best Augmentation for Side Effects: None noted.

Dosing and Use

- Usual Dose Range: 10mg -20mg once daily.
- Dosage Forms:
  - Film coated 5 mg, 10 mg, 15 mg, and 20 mg immediate release tablets
- How to Dose:
  - The recommended starting dose is 10 mg administered orally once daily without regard to meals
  - The dose should then be increased to 20 mg/day, as tolerated. Consider 5 mg/day for patients who do not tolerate higher doses
  - The maximum recommended dose is 10 mg/day in known CYP2D6 poor metabolizers.
- Overdose:
  - 40 to 75 mg was associated with increased rates of nausea, dizziness, diarrhea, abdominal discomfort, generalized pruritus, somnolence, and flushing.
- Long-Term Use:
  - Open label studied up to 64 weeks at 10mg/day shows improved MADRS scores compared to placebo.
  - At 52weeks Side effects include occurred in 70.6% of patients involving: nausea (15.2%), headache (12.4%), nasopharyngitis (9.8%), diarrhea (7.2%), and dizziness (6.8%)
- Habit forming: No
- How to Stop:
  - BRINTELLIX can be discontinued abruptly. However, it is recommended that doses of 15 mg/day or 20 mg/day be reduced to 10 mg/day for one week prior to full discontinuation if possible
- Pharmacokinetics:
  - linear and dose-proportional when vortioxetine is administered once daily. The mean terminal half-life is approximately 66 hours, and steadystate plasma concentrations are typically achieved within two weeks of dosing.
  - Eliminated via urine (59%) and feces(26%).

Pharmacodynamics:

- Strong inhibitors of CYP2D6: Reduce BRINTELLIX dose by half when a strong CYP2D6 inhibitor (e.g., bupropion, fluoxetine, paroxetine, or quinidine) is coadministered
- Strong CYP Inducers: Consider increasing BRINTELLIX dose when a strong CYP inducer (e.g., rifampin, carbamazepine, or phenytoin) is coadministered for more than 14 days. The maximum recommended dose should not exceed 3 times the original dose

Precautions:

- Serotonin Syndrome has been reported with serotonergic antidepressants (SSRIs, SNRIs, and others), including with BRINTELLIX, both when taken alone, but especially when coadministered with other serotonergic agents (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John's Wort)

Do Not Use:

- Hypersensitivity to vortioxetine or any components of the BRINTELLIX formulation
- Monoamine Oxidase Inhibitors (MAOIs): Do not use MAOIs intended to treat psychiatric disorders with BRINTELLIX or within 21 days of stopping treatment with BRINTELLIX.
- Do not use BRINTELLIX within 14 days of stopping an MAOI intended to treat psychiatric disorders. In addition, do not start BRINTELLIX in a patient who is being treated with linezolid or intravenous methylene blue

Special Populations:

- Renal Impairment: No dose adjustment needed.
- Hepatic Impairment: not studied in severe hepatic impairment.
- Cardiac Impairment: No dose adjustment needed. Minimal effect on cardiac system.
- Elderly: No restrictions.
- Children and Adolescent: Not studied.
- Pregnancy: Pregnancy Category C
- Breast Feeding: not studied in humans. Drug present in milk of lactating rats.

Viibryd

- Brand: Viibryd
- Generic: vilazodone HCl (generic not available yet)
- Commonly Prescribed for: Major Depressive Disorder
- How the Drug works:
  - The mechanism of the antidepressant effect of vilazodone is not fully understood but is thought to be related to its enhancement of serotonergic activity in the CNS through selective inhibition of serotonin reuptake resulting in 5 Fold higher levels of Serotonin than other SSRIs.
  - Vilazodone is also a partial agonist at serotonergic 5 - HT 1A receptors (SPARI); however, the net result of this action on serotonergic transmission and its role in vilazodone's antidepressant effect are unknown.
- How long till it works:
  - Steady - state is achieved in about 3 days.
- How does it compared to other Drugs:
  - Low adverse effects profile.
  - Narrower therapeutic range.
- Tests: None needed.

- Side Effects:
  - Diarrhea (6.4%), nausea (5.3%), vomiting(1.1%), insomnia (1.4%), dizziness (2.0%), decrease libido (2.9%), hypomania (0.1%). (Seizure patients were excluded from studies)
- Notable Side Effects:
  - Nausea and Diarrhea.
- Life Threatening or Dangerous Side Effects:
  - Serotonin Syndrome
  - There is 1 case report of pediatric (23 month old) overdose resulting in recurrent seizures requiring intubation.
  - In mice: hepatocellular carcinomas was increased in males at 16.5 times the MRHD. Elevated prolactin levels were observed in a 2 - week study of vilazodone administered at 5.5 and 33 times the MRHD. Increases in prolactin levels are known to cause mammary tumors in rodents.
- Weight Gain: None found.
- Sedation: None found

Dosing and Use

- Usual Dose Range: 10mg – 40mg
- Dosage Forms:
  - 10 mg, 20 mg and 40 mg immediate release, film coated tablets
- How to Dose:
  - The recommended dose for VIIBRYD is 40 mg once daily.
  - VIIBRYD should be titrated to the 40 mg dose, starting with an initial dose of 10 mg once daily for 7 days, followed by 20 mg once daily for an additional 7 days, and then increased to 40 mg once daily
  - VIIBRYD should be taken with food.
  - Administration without food can result in inadequate drug concentrations and may diminish effectiveness
- Overdose:
  - Risk of Serotonin Syndrome
  - Adverse reactions associated with overdose of VIIBRYD at doses of 200 - 280 mg as observed in clinical trials included serotonin syndrome, lethargy, restlessness, hallucinations, and disorientation.
- Dosing Tips:
  - Administration of VIIBRYD with food (high fat or light meal) increases oral bioavailability
- Long-Term Use:
  - No tolerance detected. Main studies are up to 8 weeks, but open label studies have been done up to 52 weeks without increase adverse risks.
- Habit forming: None.
- How to Stop: When discontinuing treatment, reduce the dose gradually

- Pharmacokinetics:
  - Vilazodone is eliminated primarily by hepatic metabolism.
  - Terminal half - life of approximately 25 hours.
- Pharmacodynamics:
  - MAOIs: Do not use VIIBRYD concomitantly with an MAOI or within 14 days of stopping or starting an MAOI
  - CYP3A4 inhibitors: The VIIBRYD dose should be reduced to 20 mg when co - administered with CYP3A4 strong inhibitors
  - CYP3A4 inducers: Based on clinical response, consider increasing the dose of VIIBRYD up to 2 - fold when used concomitantly with strong CYP3A4 inducers (e.g., carbamazepine) for greater than 14 days. The maximum daily dose should not exceed 80 mg.
- Do Not Use:
  - Do not use MAOIs intended to treat psychiatric disorders with VIIBRYD or within 14 days of stopping treatment with VIIBRYD.
  - Do not use VIIBRYD within 14 days of stopping an MAOI intended to treat psychiatric disorders.
  - Do not start VIIBRYD in a patient who is being treated with linezolid or intravenous methylene blue

Special Populations:

- Renal Impairment: no dose adjustment is necessary
- Hepatic Impairment:
  - In mild, moderate, and severe hepatic impairment, no dose adjustment is necessary
- Cardiac Impairment: No dose adjustment needed.
- Elderly: no dose adjustment needed.
- Children and Adolescent:
  - Not specifically studied in children. Not recommended for patients <18 years old due to 14/1000 suicidality risk with SNRI/SSRI in general.
- Pregnancy: Pregnancy Category C
- Breast Feeding:
  - Not recommended. No human studies, but mice studies show presence of drug in milk of lactating mice.

Latuda

- Brand: Latuda
- Generic: lurasidone hydrochloride (generic not available yet)
- Commonly Prescribed for:
  - Schizophrenia
  - Depressive episodes associated with Bipolar I Disorder (bipolar depression), as monotherapy and as adjunctive therapy with lithium or valproate.
- How the Drug works:
  - The mechanism of action of LATUDA in the treatme nt of schizophrenia and bipolar depression is unknown. However, its efficacy in schizophrenia and bipolar depression could be mediated through a combination of cen tral dopamine Type 2 (D2) and serotonin Type 2 (5HT 2A) receptor antagonism.
- How does it compare to other drugs:
  - Bipolar Depression: Improved MADRS score with monotherapy compared to placebo (-4.6 compared to 0, respectively)
  - Schizophrenia: Worse BPRSd or PANSS Scores at 120mg/day compared to Olanzapine 15mg/day (-7.5 compared to -12.6 of Olanzapine) or Quietiapine ER 600mg/day (-16.2 compared to -17.5 of Quietiapine), but better than placebo (0.0 change).
  - No Tardive Dyskinesia or Neuroleptic Malignant Syndrome reported (but still possible) during studies including open label studies up to 52 weeks.
- If it doesn’t work: Add lithium or valproate for Bipolar depression.
- Tests: Check CBC, CMP, and HgA1C.

- Side Effects:
  - Cerebrovascular Adverse Reactions in Elderly Patients with Dementia-Related Psychosis: Increased incidence of cerebrovascular adverse events (e .g., stroke, transient ischemic attack).
  - **Neuroleptic Malignant Syndrome (None reported but still possible):** Manage with immediate discontinuation and close monitoring.
  - **Tardive Dyskinesia (Not reported in studies but still possible)**: Discontinue if clinically appropriate
  - Dystonia (3.5-6.5% compared to 0.8% placebo): Discontinue if clinically appropriate.
  - Hyperglycemia in Diabetes Mellitus (1.3% compared to placebo of 1.0%).
  - Dyslipidemia (minimal): Undesirable alterations have been observed in patients treated with atypical antipsychotics.
  - Weight Gain(2.4% of >7% weight gain compared to 0.7% placebo): Gain in body weight has been observed. Monitor weight.
  - Hyperprolactinemia (2.8% compared to 1.0% placebo affecting more in female compared to male): Prolactin elevations may occur. Mostly at doses of 120mg/day or higher.
  - Leukopenia, Neutropenia, and Agranulocytosis (Not reported with Latuda but is a risk factor in antipsychotic): Perform complete blood counts (CBC) in patients with a pre-existing low white blood cell count (WBC) or a history of leukopenia or neutropenia.
  - Orthostatic Hypotension and Syncope (0.6-0.8% compared to 0% in placebo): Dizziness, tachycardia or bradycardia, and syncope may occur, especially early in treatment. In patients with known cardiovascular or cerebrovascular disease, and in antipsychotic-naïve patients, consider a lower starting dose and slower titration
- How Drug Causes the side effects:
- Notable Side Effects:
  - Somnolence (15.5% at 20 mg, 15.6% at 40 mg, 15.2% at 80 mg, 26.5% at 120 mg and 8.3% at 160 mg/day compared to 7.1% in placebo)
  - Akathisia (13% compared to 3% placebo, 22% at 120mg/d),
  - Extrapyramidal symptoms (14% compared to 6% placebo, 22% with 120mg/day dose)
  - Nausea (10% compared to 5% placebo, 13% at 120mg/day)
  - Creatinine elevation from normal to high (3.0% compare to 1.6% placebo, Starts showing Cr elevation at 120mg/d and higher dose).
- Life Threatening or Dangerous Side Effects:
  - In Elderly with dementia-related psychosis: Mortality with drug is 4.5%, compared to a rate of about 2.6% in the placebo group in a 10 week randomized study. Most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature.
- Weight Gain: Low
- Sedation: High
- Augmentation to Improve effects:
  - Lithium or valproate has been shown to have mild to moderate improvement in Bipolar Depression by MADRS score reduction of 3.6-4.6 when used with Latuda compared to placebo with lithium or valproate.

Dosing and Use

- Usual Dose Range:
  - Schizophrenia: 40mg-160mg per day
  - Bipolar Depression: 20mg-120mg
- Dosage Forms: White to off-white tablets.
- How to Dose:
  - Start at 40mg/day for Schizophrenia
  - Start at 20mg/day for Bipolar Depression
  - No need for dose titration.
- Dosing Tips:
  - Administration with food increases the AUC approximately 2-fold and increases the Cmax a pproximately 3-fold.
  - Poorly absorbed with only 9-19% and peak serum at 1-3hrs.
- Overdose:
  - Risk of Neuroleptic Malignant Syndrome
- Long-Term Use:
  - No controlled studies beyond 6 weeks.
  - Data provided are from Open-label studies that have been done up to 52 weeks.
- Habit forming: No
- How to Stop: May discontinue without adverse effects.
- Pharmacokinetics:
  - LATUDA is predominantly metabolized by CYP3A4.
  - Excrete 80% through feces and 9% through urine.
- Pharmacodynamics:
  - No dose adjustment is needed for lithium, substrates of P-gp, CYP3A4 or valproate when coadministered with LATUDA.
  - Avoid Grapefruits as it inhibits CYP3A4.
  - Concomitant Use of a Moderate CYP3A4 inhibitor (e . g., diltiazem): LATUDA dose should be reduced to half of the original dose level.
  - Concomitant Use of a Moderate CYP3A4 Inducer: It may be necessary to increase the dose of LATUDA
- Precautions:
- Do Not Use:
  - Should not be used concomitantly with strong CYP3A4 inhibitors (increase up to 10x) (e.g., ketoconazole, clarithromycin, ritonavir, voriconazole, mibefradil, etc.) or strong CYP3A4 inducers (decrease by more than 50%) (e.g., rifampin, avasimibe, St. John’s wort, phenytoin, carbamazepine, etc.)

Special Populations:

- Renal Impairment
  - Mild: No dose adjustment
  - Moderate: Start at 20mg/day with max at 80mg/day
  - Severe: Start at 20mg/day with max at 80mg/day
- Hepatic Impairment
  - Mild: No dose adjustment
  - Moderate: Start at 20md/day with max at 80mg/day
  - Severe: Start at 20mg/day with max at 40mg/day
- Cardiac Impairment: No QTc changes up to 600mg/day dose.
- Elderly: no dose adjustment needed.
- Children and Adolescent
- Pregnancy: Pregnancy Category B.
  - No adequate and well controlled studies of LATUDA use in pregnant women. Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery.
- Breast Feeding: No human studies. Found in milk of lactating mice.