NEW AND UPCOMING PSYCHOTROPIC TREATMENT OPTIONS

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Disclosure

- I do not have a vested interest in or affiliation with a corporate organization offering financial support or grant monies for this presentation
- I do not have an affiliation with an organization that has a specific interest in the therapeutic areas under discussion

DEPRESSIVE DISORDERS

Levomilnacipran (Fetzima)

- FDA approved for depression in July 2013
  - Not FDA approved for fibromyalgia
- Serotonin and norepinephrine reuptake inhibitor
- Active enantiomer of milnacipran (Savella)
- Dose:
  - Initiate at 20 mg once a day for 2 days then increase to 40 mg
  - Increase dose by 40 mg at intervals of 2 or more days
  - Maximum recommended dose of 120 mg once a day
  - Maximum of 80 mg once a day if given with strong CYP 3A4 Inhibitor

Levomilnacipran (Fetzima)

- Contraindication
  - Uncontrolled narrow-angle glaucoma
- Adverse reactions
  - Nausea, constipation, hyperhidrosis, increase heart rate, erectile dysfunction, tachycardia, vomiting, palpitations, urinary hesitation

Olie JP et al. Encephale 2009;35(6):595-604.
Citrome L. Int J Clin Pract 2013 Sep 8. Epub ahead of print.

Vortioxetine (Brintellix)

- FDA approved for depression in October 2013
- Multimodal serotonergic drug
  - Serotonin reuptake inhibitor
  - Serotonin (5-HT) receptor 1B partial agonist agonist at 5-HT1A receptors
  - Antagonist at 5-HT3 and 5-HT7 receptors
- Dose
  - 10 mg/day for 1 week, then increase to 20 mg/day for maximum efficacy
  - Dose adjustment is recommended when Brintellix is co-administered with strong inhibitors of CYP 2D6 and strong CYP inducers

Vortioxetine (Brintellix)

- Contraindication
  - Use within 14 days of stopping an MAOI or concurrent use with linezolid or methylene blue
- Lower risk of sexual side effects compare to SSRIs
- Adverse reactions
  - Nausea, dizziness, diarrhea, dry mouth, headache, constipation and vomiting

Place in Therapy

- Unclear
  - Limited head to head comparison trials with existing antidepressants
  - Trials comparing milnacipran and venlafaxine showed similar efficacy and tolerability profiles
- Levomilnacipran maybe preferred for patients with neuropathic pain symptoms
- Vortioxetine may cause less sexual dysfunction
- Cost of medications may limit use

BIPOLAR AND RELATED DISORDERS

Atypical Antipsychotics

Generic	Brand
Olanzapine	Zyprexa (Zydis), Relprev
Olanzapine/fluoxetine	Symbyax
Quetiapine	Seroquel, Seroquel XR
Risperidone	Risperdal (Consta, M-tab)
Ziprasidone	Geodon
Aripiprazole	Abilify
Asenapine	Saphris
Lurasidone	Latuda

Atypical Antipsychotics for Bipolar Disorder

	Acute Mania /Mixed	Bipolar Depression	Bipolar Maintenance
Olanzapine	√		√
OLZ / FLX		√	
Quetiapine	√	√	√ (adjunct)
Risperidone	√		√ (Consta)
Ziprasidone	√		√ (adjunct)
Aripiprazole	√		√
Asenapine	√		
Lurasidone		√	

Lurasidone (Latuda)

- FDA approved for the treatment of schizophrenia in October 2010
- FDA approved for treatment of bipolar depression (monotherapy and adjunct) in July 2013
- Dosage
  - Schizophrenia: 40 to 160 mg once a day
  - Bipolar depression: 20 to 120 mg once a day
  - Take with food (min of 350 calories) to increase absorption
  - Renal and hepatic dose adjustment recommended
- Metabolize via CYP 3A4
  - Avoid grapefruit juice

Lurasidone (Latuda)

- Adverse effects
  - Somnolence, akathisia, extrapyramidal symptoms, nausea, vomiting, diarrhea, anxiety
- Metabolic changes
  - Average weight change: +0.29 to 1.28 kg
  - 2.4 to 3.1% of patients gain ≥ 7% baseline body weight
  - Similar to ziprasidone in comparison study
- Mild prolactin elevation
  - Incidence is dose-dependent and greater increase in women than men
  - No hyperprolactinemia related symptom was reported

	1st line	2nd line
Mania	• Lithium • Valproic acid • Atypical antipsychotic Combination if severe or psychotic features present	Carbamazepine
Mixed	• Valproic acid • Atypical antipsychotic	Any of above mania treatments
Depression	•Lithium •Lamotrigine* •Quetiapine • Olanzapine/fluoxetine	•Lurasidone •Valproic acid •Augmentation with SSRI or bupropion + lithium or valproic acid
Maintenance	• Lithium • Valproic acid •Atypical antipsychotic	• Lamotrigine – especially for preventing depression, limited efficacy preventing mania

*Lamotrigine – not for acute bipolar depression

KETAMINE

Ketamine

- Used as a dissociative anesthetic agent for more than 40 years
- Mechanism of action
  - NMDA (N-methyl-Daspartate) receptor antagonist
- Dose
  - 0.5 mg/kg given as IV infusion over 40 mins
- Adverse events
  - Anxiety, dissociative symptoms, increase blood pressure

Ketamine Clinical Studies

Author, years	Number of Pt	Result
Berman, 2000	9	Improvement observed within 72 hrs
Zarate, 2006	18	71% of patients responded after 1 day; 35% maintained a response for ≥ 1 week
Matthew, 2010	26	Response observed in 65% of patient at 24 hrs and 54% at 72 hrs
Ibrahim, 2012	42	62% of patients responded; Average time to relapse approx 17.2 days
Diazgranados, 2012	18	Response rate were 44% after 1 day and improvement seen through day 3
Zarate, 2002	15	Improvement seen through day 3
Murrough, 2012	24	70.8% of patents were responders; Median time to relapse was 18 days
Murrough, 2013	72	64% of patients responeded No difference in treatment outcome at day 7

Salvadore G, et al. CNS Neuroscience & Therapeutics 2013;19:428-436.
Murrough JW, et al. Am J Psychiatry 2013;170:1134-1142.

Ketamine

- Effect of ketamine on treatment-resistant depression appears to be both quick and substantial
- Patients with acute suicidal risk, history of psychosis, unstable general medical conditions, substance abuse in the last 2 years, abnormal ECGs, or various other features were excluded from clinicals
- Unknown whether ketamine is safe or effective in a wider, more representative group of patients

Ketamine

- Concerns
  - Abuse potential
  - Short duration of benefit and clinical studies
  - Feasibility of IV infusion for out-patient settings

NEW AGENTS IN PIPELINES

Cariprazine

- **Indication:**
  - Bipolar Mania, Schizophrenia, MDD Adjunctive
- **Phase III Completion Date:**
  - NDA filed for Schizophrenia/Bipolar Mania November 2012
  - FDA are requesting more information, including clinical trial data from the company
- **Mechanism of Action:**
  - Dopamine (D2 and D3) receptor partial agonist with high selectivity towards the D3 receptor

Cariprazine

- **Safety and Efficacy Data:**
  - Most common adverse events include akathisia, insomnia, and weight gain,metabolic syndrome, extrapyramidal symptoms and sedation
  - The efficacy and safety of Cariprazine have been so far investigated only in a few short-term (unpublished) clinical trials
  - Three studies in schizophrenia and three studies in bipolar mania/mixed episodes evidenced a statistically significant therapeutic effect compared to placebo for Cariprazine at doses ranging from 1.5 to 12 mg/d.

Suvorexant (MK-4305)

- **Indication:**
  - Insomnia
- **Current Status:**
  - Merck received a Complete Response Letter (CRL) from the FDA for Suvorexant in June 2013. The company is evaluating the requests in the CRL and plans to submit definitive data in response to the FDA in early 2014.
- **Mechanism of Action:**
  - Orexin receptor antagonist designed to inhibit the binding of the neuropeptide orexin to its receptor turning off wakefulness

Suvorexant (MK-4305)

- **Safety and Efficacy Data:**
  - Increased rate of suicidal ideation and daytime drowsiness with higher doses of 30 to 40 mg in Phase III trials
  - Generally safe and effective based on clinical trials. The efficacy of Suvorexant has been established at doses of 10 to 40 mg
  - Safety data do not support approval of doses at 30 and 40 mg

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