ADVANCES IN PSYCHOPHARMACOLOGY: 2011-2015

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Disclosures

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What’s New

- **Antidepressants**
  - Vilazodone (Viibryd) 2011
  - Levomilnacipran ER (Fetzima) 2013
  - Vortioxetine (Brintellix) 2013
  - NSI-189 (not approved)

- **Antipsychotics**
  - Lurasidone (Latuda) 2010, 2013
  - Cariprazine NDA resubmission 1/2015
  - Brexpiprazole submitted 2014
  - Inhalable loxapine (Adasuve) 2012
  - Amoxapine (Asendin)

- **Anticonvulsants**
  - Ezogabine (Potiga) 2011
  - Eslicarbazine (Aptiom) 2013

- **Other Agents**
  - Suvorexant (Belsomra) 2014
Vilazodone

- Marketed at Viibryd
- Approved for acute unipolar depression
- SRI + Partial agonist at 5HT1A
- Very high affinity
  - 5HTTR Ki = 0.2 nM
  - 5HT1A Ki = 0.5 nm
- 69% partial agonism

Effective in Depression: ES=0.5-0.54
(US study sites)

Levomilnacipran ER

- Marketed as Fetzima
- Approved for major depression
- L enantiomer of milancipran (Savella), which is approved for MDD overseas, and fibromyagia in the USA in 2009
- SNRI
- Affinity at norepinephrine reuptake pump is greater, but inhibition of serotonin reuptake is greater
Levomilnacipran: Effective in Depression

- Effective in depression at average dose of 73mg/day

Vortioxetine

- Marketed at Brintellix
- Approved for acute unipolar depression
- Very high multiple affinities, Ki’s are
  - $5HTTR = 1.6$
  - $5HT1A$ (agonist) = 15
  - $5HT3 = 3.7$
  - $5HT7 = 19$
  - $5HT1D = 54$
  - $5HT1B$ (partial agonist) = 33
Studies Submitted to FDA

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<tr>
<th>Study 1</th>
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<th>Study 3</th>
<th>Study 4</th>
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**Mean change from baseline**

- $-14.5$ to $-20.4$
- $-15.4$ to $-16.2$
- $-11.3$ to $-17.2$
- $-11.7$ to $-18.8$
- $-12.8$ to $-14.3$
- $-10.8$ to $-13.0$
- $-14.4$ to $-13.7$
- $-10.3$
- $-13.7$

*P < .025, †P < .01, ‡P < .001, §P < .0001 versus placebo after adjusting for multiplicity.
NSI-189: Only Phase I

- A growth factor–like chemical
- Stimulates neurogenesis in vitro and in vivo
- In animal models enlarges the hippocampus
- In small phase II studies effect size 0.9
- Effect maintained for 2 months after stopping drug
Lurasidone

- Initially approved for schizophrenia in 2010
- Approved for bipolar depression in 2013
- Effective in bipolar depression at sub-antipsychotic dose (around 20 – 30 mg/d, minimal antipsychotic dose = 40mg)
Lurasidone in Bipolar Depression

Studied in Monotherapy at 2 dose ranges (33mg/d and 85mg/d) and add-on therapy (66mg/d). Effect kicks in at 20mg/d, and dose increases do not increase effect.
Antidepressant Effect Via 5HT7

- Preclinical studies show that 5HT7 blockade is anxiolytic, antidepressant, and pro-cognition
- Preclinical studies show that 5HT7 stimulation is anxiogenic and pro-depressant
- Affinity at 5HT7 is very high ($K_i = 0.5 \text{nM}$) and 2 fold greater than D2 ($1.7 \text{nM}$)
Lurasidone: Absorption

• Should be taken with food to maximize absorption
• AUC doubles, but Cmax triples with food
Cariprazaine: Not Available

- NDA submitted
- Preclinical studies suggest antimanic efficacy
- Partial agonist at D2 receptor
Cariprazine in Schizophrenia

- Phase III studies completed and submitted to FDA
- Efficacy demonstrated

Cariprazine: Preclinical Studies

- In animal model of mania, cariprazine normalizes hyperactivity

Cariprazine in Mania

- 3-12mg/day
- Effective in at least 2 Phase III studies
- Being reviewed by US FDA

Brexipiprazole: Being Reviewed by US FDA

- Similar to aripiprazole
- A D2/5HT1A partial agonist
- Intrinsic D2 is only 8% of dopamine
- Akathisia lower than placebo
- Being reviewed for schizophrenia and adjunct for MDD
Brexpiprazole in Schizophrenia

- Effective at 4mg/day
- Performed at Colombia, Croatia, Mexico, Philippines, Russia, Slovakia, Taiwan and the USA
Brexpiprazole in MDD

- Examined as add-on treatment in people with MDD who failed retrospective, and blinded prospective antidepressant treatment for 8 weeks each.
- 2 studies one with 2mg/day and one with 1 or 3 mg/day; for 6 weeks.
- Both studies show statistically significant improvement.
Inhalable Loxapine

• New delivery system for old drug
• Thermally generated aerosol
• Indicated for acute agitation in psychotic or manic individuals
• Some concern in patients with asthma or COPD

Loxapine: Old ‘Atypical’

• The affinity of loxpine to 5HT2A > D2 (Ki 6.63 and 11 nM, respectively)
• This is definition of second generation antipsychotic (i.e., loxapine is unidentified ‘atypical’ antipsychotic)
• Affinity at D4 > D2 which may predict anti-aggression effect (Ki 8.4 and 11 nM, respectively)
Inhaled Loxapine: Agitation

- 314 manic/mixed patients in 17 centers
- Separation within 10 min of administration
- Similar outcome in schizophrenia

Amoxapine is an Antipsychotic

- 6 week, multi-site, double-blind, randomized, comparison study of risperidone (3-5mg/day) and amoxapine (150-250mg/day) in acute schizophrenia
- The 2 drugs are equivalent

Eslicarbazepine: Anticonvulsant

- Therapeutic dose 600 – 1200 mg/day (up to 2400mg)
- ½ life is around 24 hours
- Eliminated exclusively by kidney (91% of drug)
- Levels at therapeutic doses are 4 – 9 ug/mL
- Effective for complex partial seizures

Eslicarbazepine: 3 Equivocal Mania Studies

A

Mean ± SD relative change (%) in total YMRS score over time

B

Mean ± SD relative change (%) in total YMRS score from baseline to end of treatment

Ezogabine or Retigabine (Potiga): Novel Anticonvulsant

- First in class anticonvulsant
- Opens voltage-dependent K channels (i.e., hyperpolarizes cell membranes in excitable tissues)
- Approved for complex partial seizures
- In addition to typical anticonvulsant side effects, ezogabine may cause blue skin color and pigment changes in retina
Ezogabine in Bipolar Illness

• Preclinical studies of the amphetamine model in mice and rats generally suggestive of antimanic efficacy
• One open study in a small number of manic patients with modest effects with 3/10 people achieving at least a 50% improvement (response)

Suvorexant (Belsomra): Sleep Aid

- Suvorexant is an antagonist of orexin 1 and 2 receptors in the cortex
- Orexin is an activating neuropeptide that originates in neurons in the hypothalamus that radiate throughout the cortex. It is a key component of the wake-promoting system of the CNS
- Orexin abnormalities are causative of narcolepsy (people with narcolepsy have fewer orexin neurons and lower CSF orexin)

Suvorexant: Efficacy and Safety

- In short- and long-term trials improves onset of sleep and maintenance of sleep (early and middle insomnia).
- No rebound insomnia with abrupt discontinuation after long-term use.
- Some dose-related AM sedation.
- Problems with driving efficacy after suvorexant.
- Controlled substance.
- Dose related increased suicidal ideation (at > 40mg, twice recommended 20mg dose).
“Harry’s mood stabilized in ’78, and it hasn’t budged since.”