Update on Novel Agents in Resistant Depression

Charles DeBattista, MD
Professor of Psychiatry and Behavioral Sciences
Stanford University School of Medicine
Disclosures

- Research Support, Astra Zeneca, CNS Response, Takeda, St. Jude, Brain Resources, Assurex,
- Consultant: Pfizer, Genentech
New Strategies

- Ketamine
- Other glutamatergic agents
- Scopolamine
- Botulinum toxin
- Agomelatine
- Vortioxetine
- Opiate agents
- Triple reuptake blockers
Ketamine

- Anesthetic agent
- Used intravenously primarily
- Used for chronic pain
- N-methyl-D-aspartate antagonist
- Can cause psychotic-like symptoms
- Acute antidepressant efficacy not sustained
Change in the 21-item Hamilton Depression Rating Scale (HDRS) over 1 week (n = 18)

Zarate, CA et al. Arch Gen Psychiatry 2006; 63:856-864.
Response Rates

Response to Repeated Ketamine Infusions

*M p<.05

GLYX-13 in Major Depression

- U shaped dose response in rat models and in Phase 2A study
- No ketamine-like side effects
- Phase 2A study – 1,5,10 or 30 mg or placebo; i.v.
- 5 mg. and 10 mg. separated from placebo at day 7 but not at day 14; other doses did not
- Effect size for single dose 0.58

IV scopolamine

- Muscarinic agonist (i.e. physostigmine) is rapidly depressogenic in some
- Muscarinic antagonists (scopolamine) may be rapidly antidepressant in some
- IV scopolamine (4μg/kg over 15 minutes) produced 32% drop vs 6.5% drop for pcb
  Effects seen by day 3 and lasted 2 weeks
  (Drevets, Zarate, Furey: Biol Psychiat 2013)
OnabotulinumtoxinA (OBA) vs. Placebo in Major Depression: HDRS-17

(N=30)

Dose – women 29U
men 39U

OnabotulinumtoxinA (OBA) vs. Placebo in Major Depression: CGI

OnabotulinumtoxinA (OBA) and Frown Expression
(N=30)

Frown Expression before and after OBA treatment

before
( patient went into remission)

after

Dose – women 29U
men 40U

MADRS scores over time (mean ± standard error of the mean), in the OBA (33) and placebo (41) groups at 3 and 6 weeks versus baseline

Response and remission rates (as judged by MADRS scores) are presented as the percentage of participants in the OBA and placebo groups at the six week visit.
**Melatonin**

- Produced by pineal gland; controlled by SCN
- Increased in evening
- Serum levels may be low in major depression (Buckley and Schatzberg, J Psych Res, 2010)
- Melatonin may improve winter depression (Lewy et al., PNAS, 2006)
- Supports neurogenesis or cell survival in hippocampus (Ramirez-Rdriguez et al., Neuropsychoph, 2009)
- Melatonin/buspirone combination maybe effective as antidepressant (Barlow et al., ACNP, 2009)
Agomelatine

- M1 and M2 agonist
- 5HT2c antagonist
- Several positive European studies led to European licensure
- Elevated LFTs are a potential limiting factor for FDA approval
Vortioxetine

- 5HT1A agonist; 5HT reuptake blocker; 5HT1b partial agonist; 5HT3 antagonist; etc.
- Phase III monotherapy trials completed
- Positive trials reported in severe and non-severe MDD; dose is 10-20 mg per day
- Recent FDA approval and release
- 1st approval for cognitive sx of MDD in Europe
Triple Reuptake Inhibitors

- Amitifadine, bicifadine, indatraline, tesofensine (Cocaine)
- Possible indications in MDD, Parkinsons, Obesity, diabetes
- Potential advantages: rapid action, help with anhedonia and motivation, less sexual side effects, less weight gain
- Potential disadvantages: habit forming, psychotomimetic, withdrawal, rebound depression
- Experience with DA agents (nomifensine, amineptine) mixed
- Phase II trials in MDD have been mixed
Opiate Specific Agents

• Alkermes 5461 (Suboxone+samidorphan)
• Buprenorphine+ Mu opioid receptor (MOR) antagonist
• Decreases risk of addiction, Kappa antagonism decreases dynorphin level, increases DA
• Phase III trials to be completed 2015
• NDA for adjunctive treatment MDD in 2016?
• Phase two trials of add on to SNRI or SSRI showed 5-8 point MADRS drops
Plasma Infusions in the Treatment of MDD
Conclusions

- There is still a large unmet need in the treatment of depression
- We need faster acting agents, a better side effect profile, more efficacy in some patient
- Novel agents targeting glutamate, dopamine, and opiate receptors hold some promise in addressing some of these issues