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

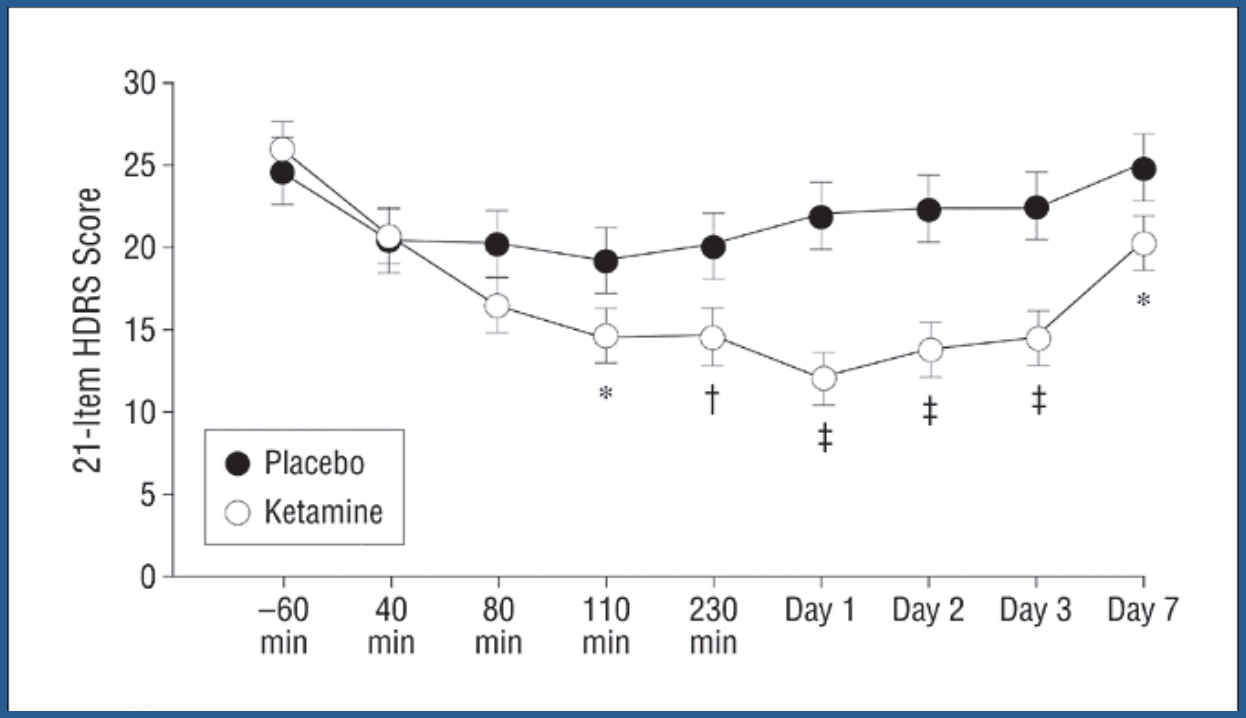
New Strategies

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

Ketamine

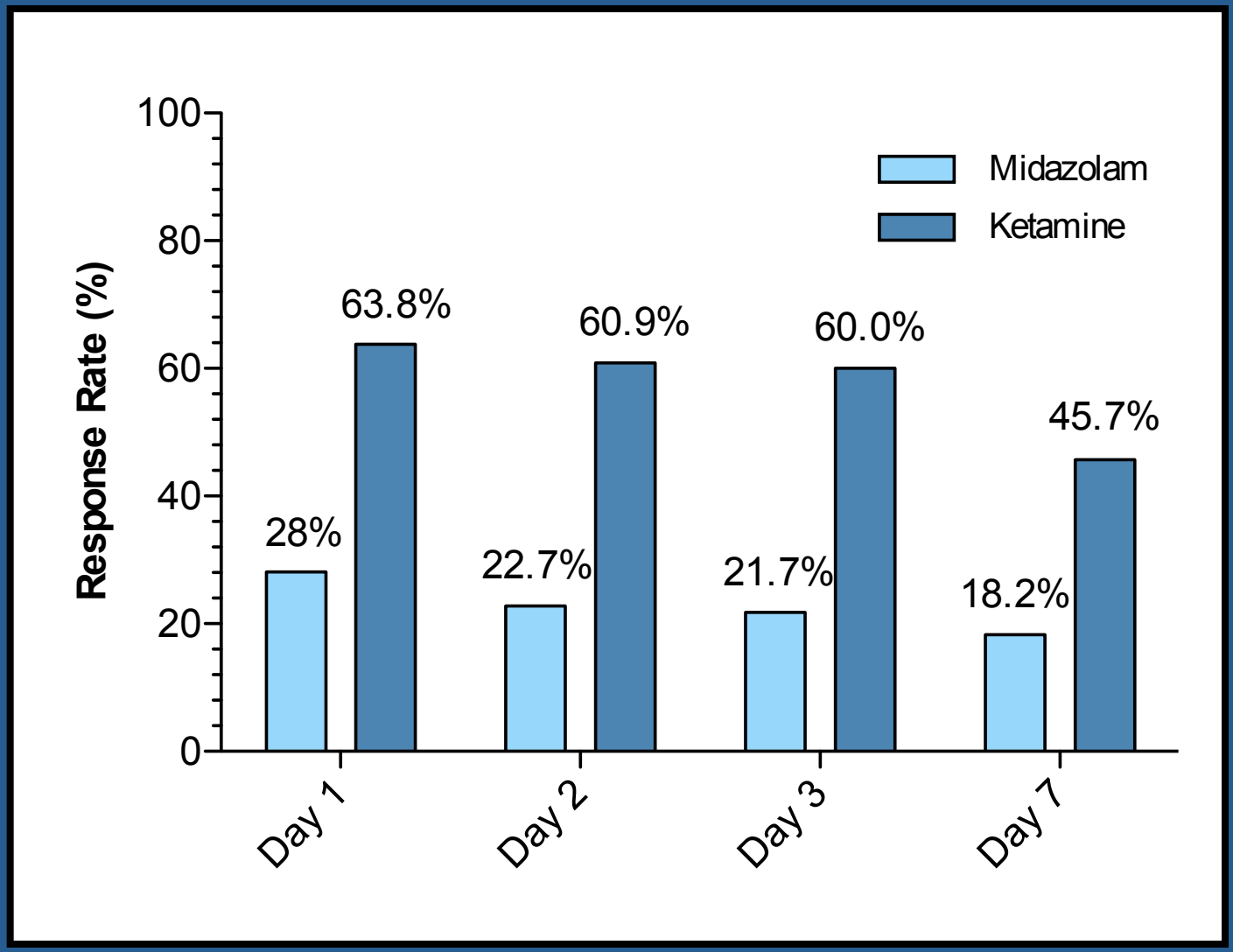
- Anesthetic agent
- Used intravenously primarily
- Used for chronic pain
- N-methyl-D-aspartate antagonist
- Can cause psychotic-like symptoms
- Acute antidepressant efficacy not sustained

Change in the 21-item Hamilton Depression Rating Scale28 (HDRS) over 1 week (n = 18)



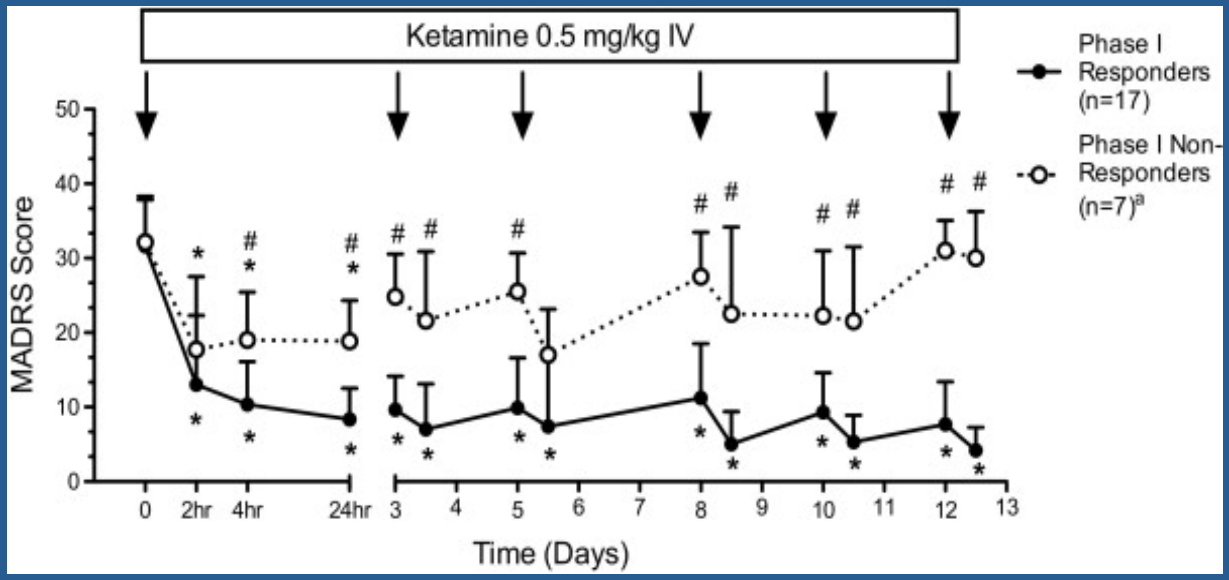
Zarate, CA et al. Arch Gen Psychiatry 2006; 63:856-864.

Response Rates



Murrough JW et al. Am J Psych, 2013.

Response to Repeated Ketamine Infusions



*p<.05

Murrough JW et al. Biol Psych, 2013.

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

Burch RM: ACNP Annual Meeting, Dec. 2012.

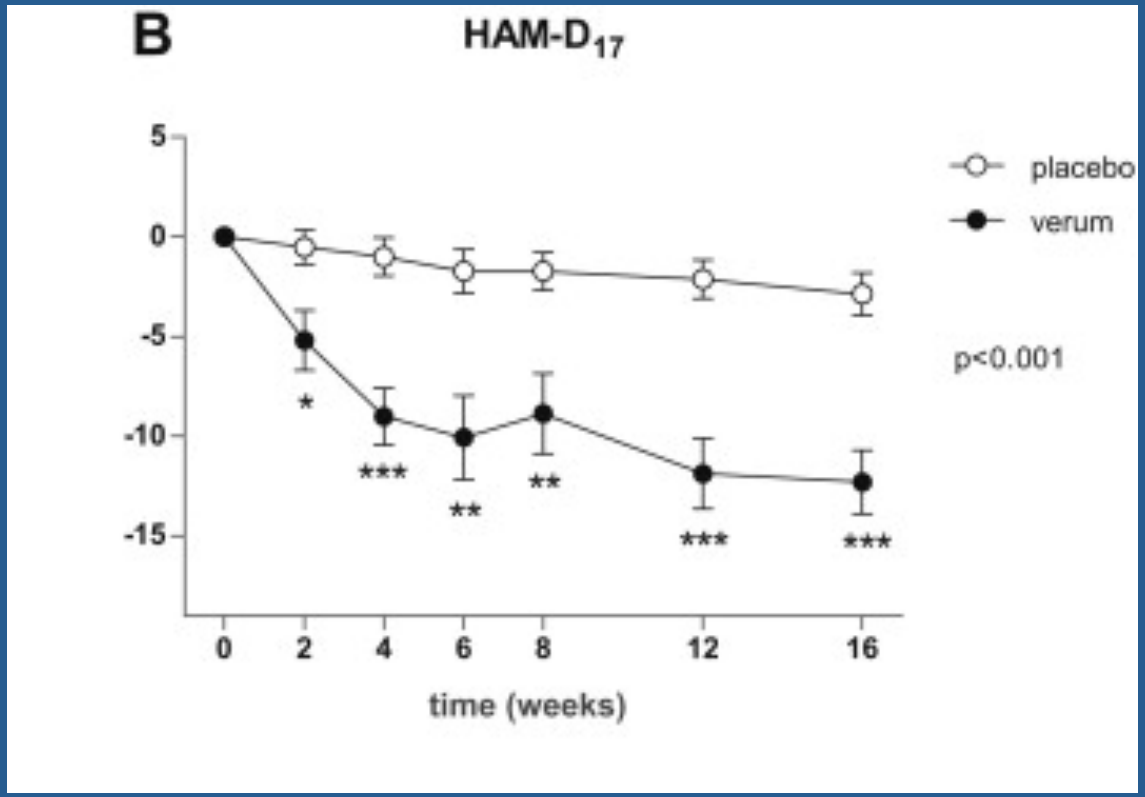
IV scopolamine

- 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

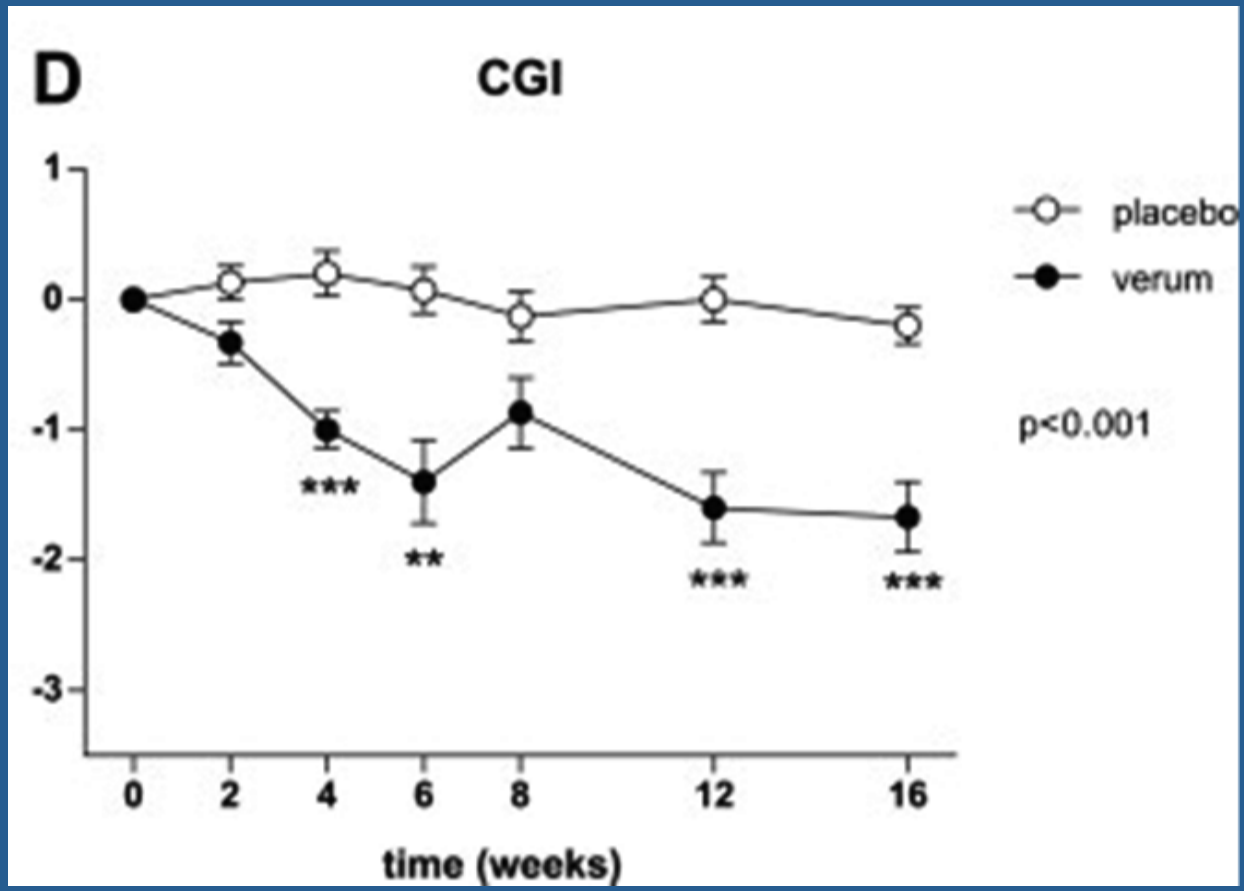
(N=30)



Dose – women 29U
men 39U

Wollmer et al. J Psychiatr Res 46: 574-581, 2012.

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



Wollmer et al. J Psychiatr Res 46: 574-581, 2012.

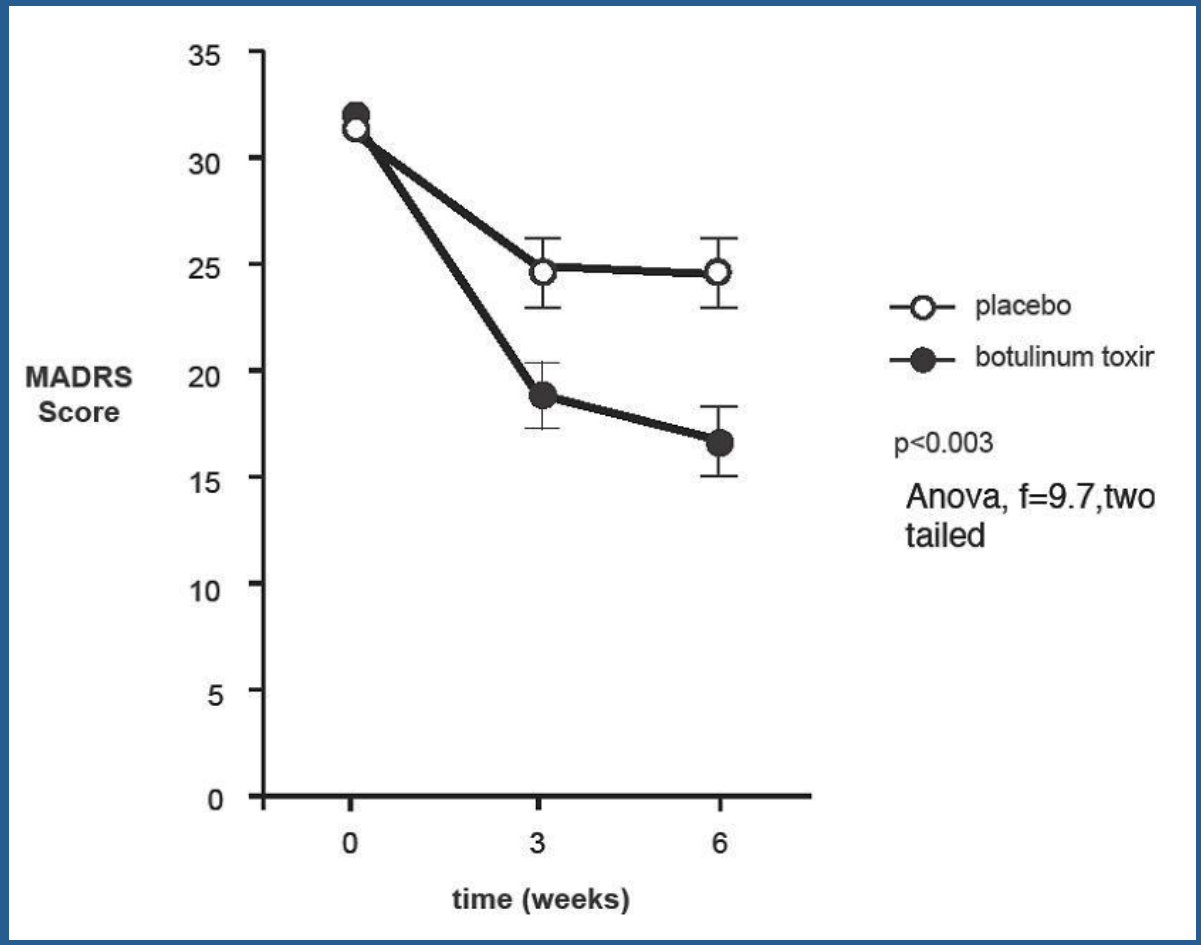
OnabotulinumtoxinA (OBA) and Frown Expression

(N=30)

Dose – women 29U
men 40U

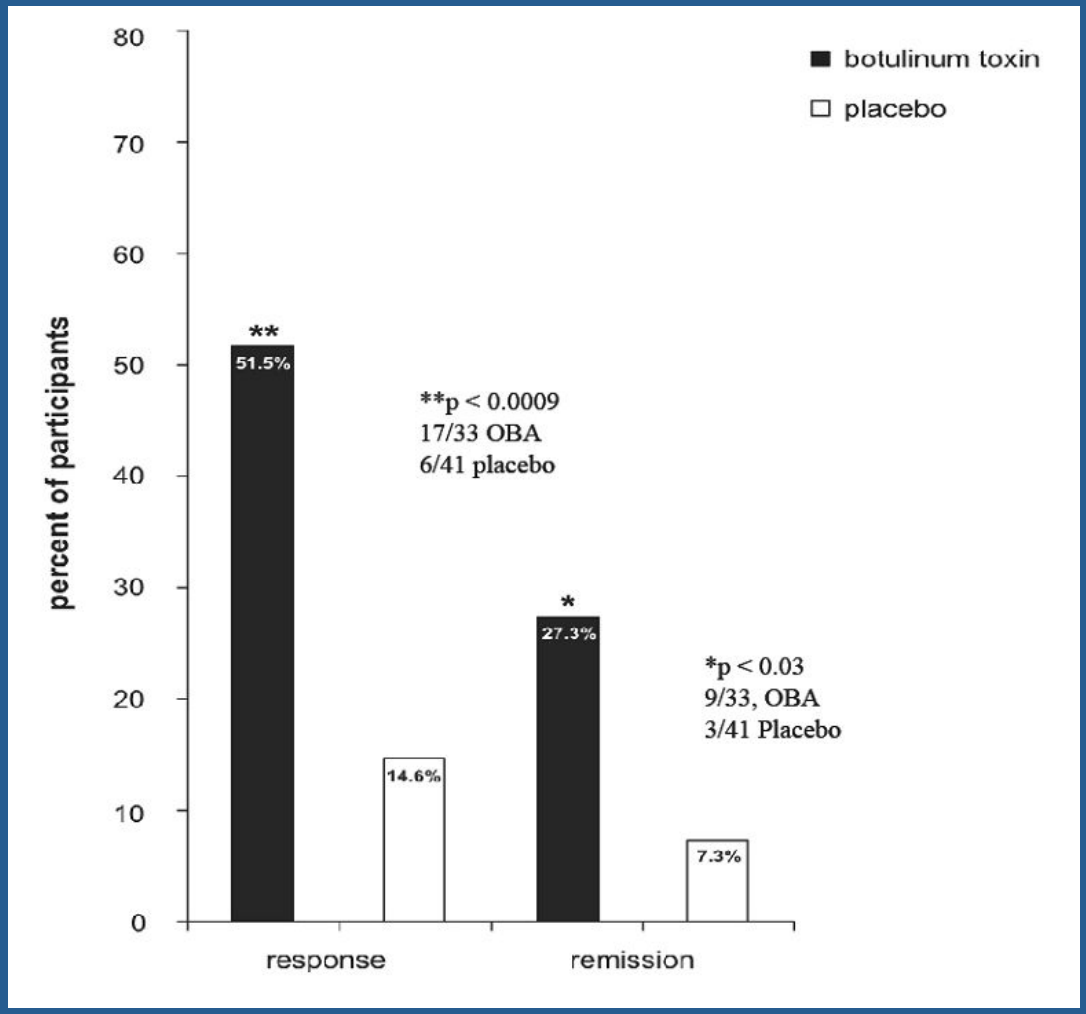
Finzi, Rosenthal: ACNP Annual Meeting, 2012.

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



Finzi, Rosenthal: ACNP Annual Meeting, 2012.

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



Finzi, Rosenthal: ACNP Annual Meeting, 2012.

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
- Phase III US program – 2 positive trials published (Zarecka et al J Clin Psychopharm 2010; Stahl et al J Clin Psychiatry 2010)
- 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 opiod 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

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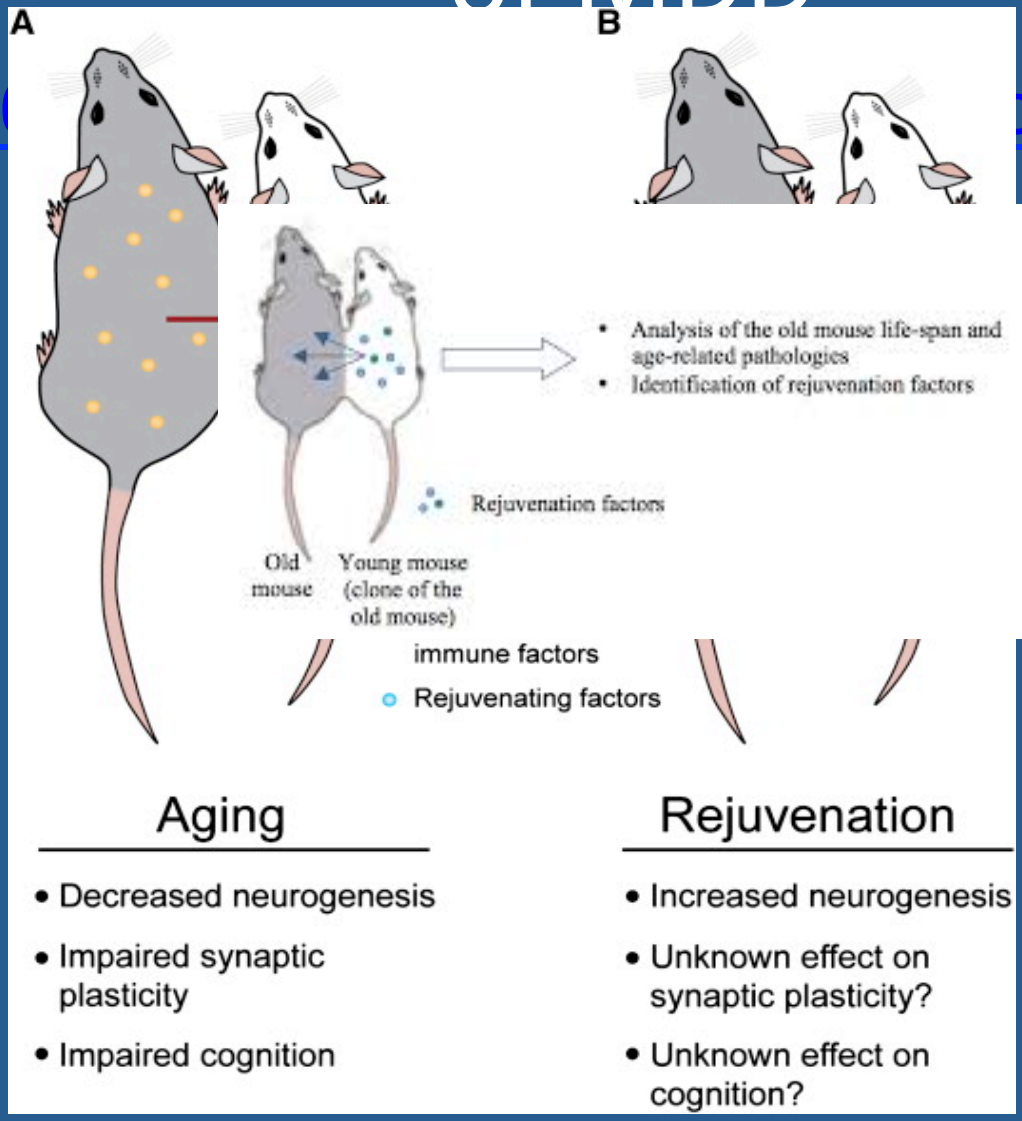

Conclusions

- 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