



Novel Treatments for Mood Disorders

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Disclosures

My spouse/partner and I have the following relevant financial relationship with a commercial interest to disclose:

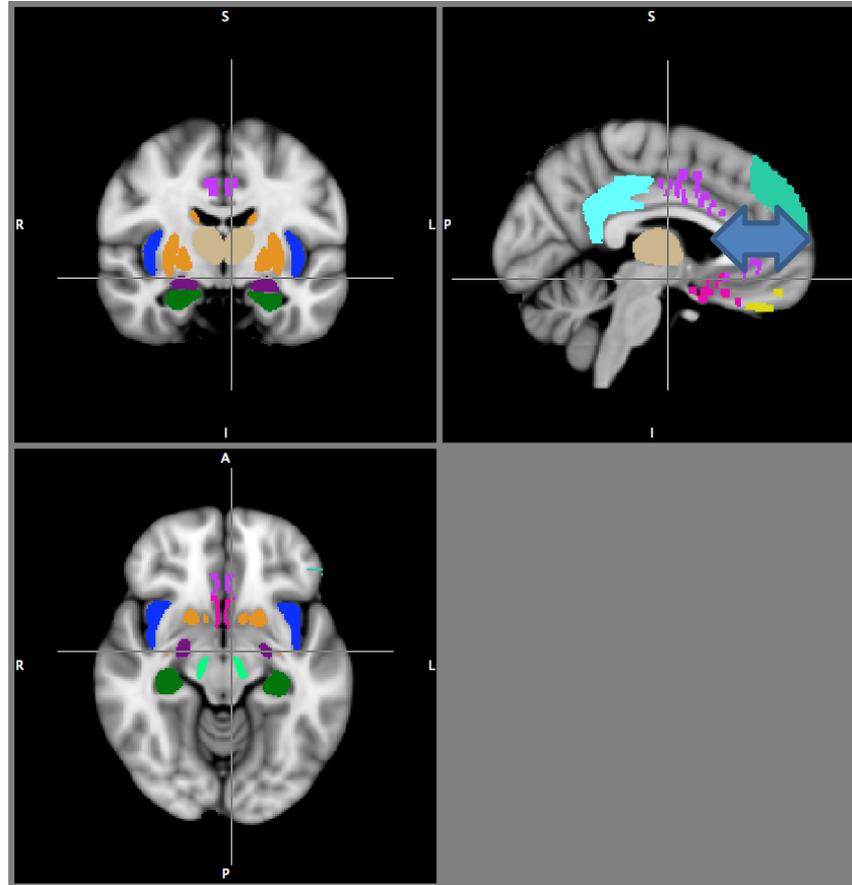
Spouse is an employee of Roche
Pharmaceuticals

MDD Statistics

- 12 month prevalence U.S.: 9%
- Mortality from Suicide: 20+ x gen pop
- Increased risk of CV death.
- Economic Costs to U.S: \$36.6 Billion

Lepine JP, Briley M. Neuropsychiatr Dis Treat 2011; 7(suppl 1) 3-7.

Depression Model

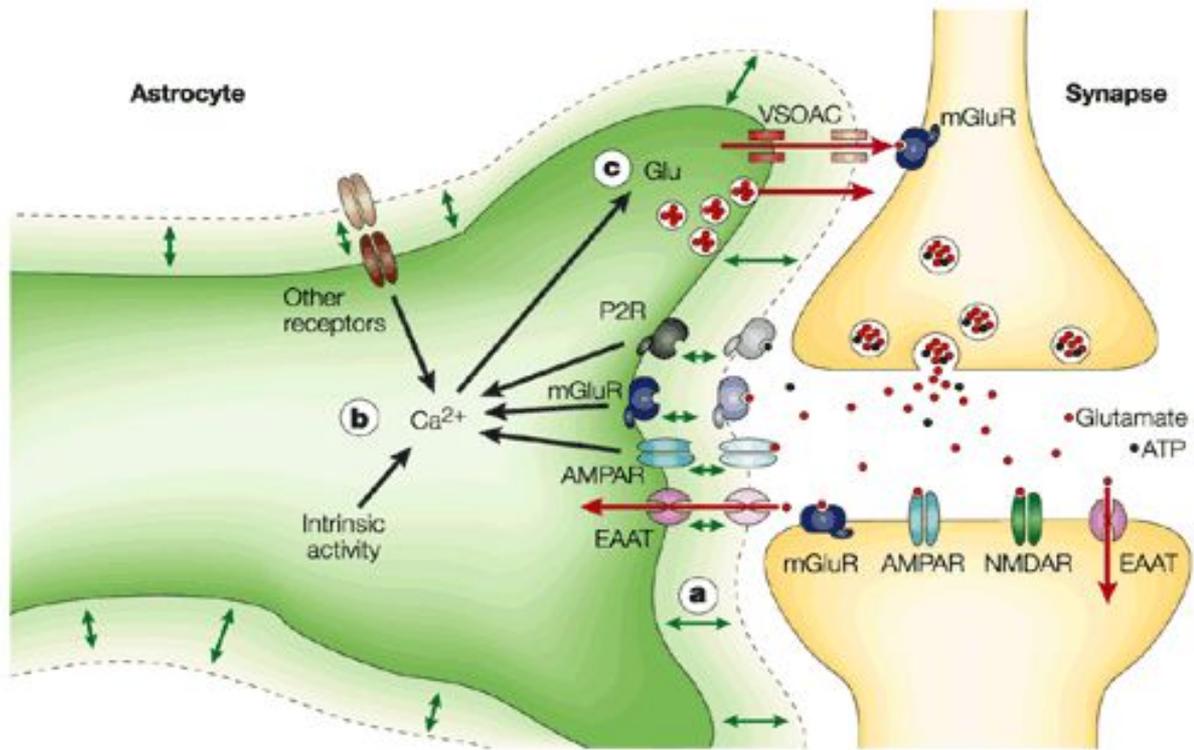


Adapted from Mayberg, 2003

Targets

- Glutamate
- GABA
- Monoamines
- Opiates
- Inflammation
- Neurosteroids
- Mood Stabilizers
- Neuromodulation
- Non-Pharmacologic Tools

Glutamate Synapse



Nature Reviews | Neuroscience

Glutamate

- NMDA
- AMPA
- Metabotropic
- Allosteric Modulators
- EAAT augmentation

NMDA

- R-Ketamine (PCN-101; HR071603)
 - Lower potency NMDAr antagonist (PCP site)
 - Lower potency DARI
 - Longer lasting AD effects in animal models.
 - Phase I trial underway in China

NMDA

BHV – 5000

- “Low trapping” NMDA antagonist
- Lanicemine – active metabolite
- Phase II – CRPS
- Plan MDD

Combination Medication

- AXS – 05
 - Bupropriion/dextromethorphan
 - DM: NMDA and sigma-1 agonist, TRI, Nicotinic receptor antagonist.
 - Breakthrough Therapy Designation for MDD, AD agitation
 - Fast Track: TRD
 - Currently in phase III

AMPA

- Perampanel – FDA approved anticonvulsant
 - AMPA antagonist
 - 8 mg/d and 12 mg/d: 12 and 20% hostility AE
 - Probe for ketamine.
- Org 24448 – potentiates AMPA subfamily GLUR
 - Study was withdrawn
- Rapastinel
 - 2016 Breakthrough Therapy designation from FDA
 - NR2B triggers influx of intracellular calcium
 - Increased AMPA
 - Phase III trials did not separate from placebo.

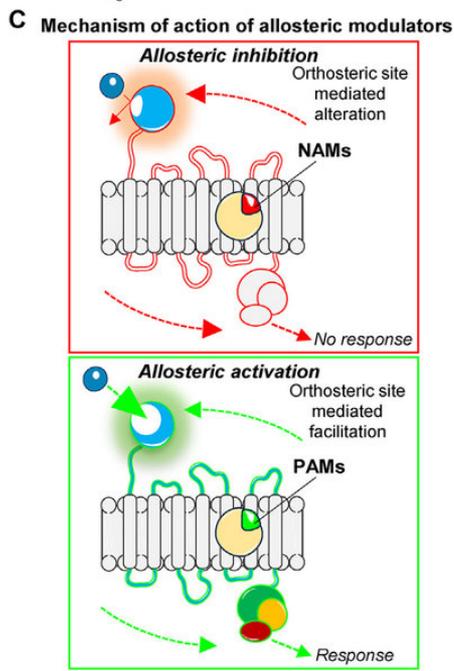
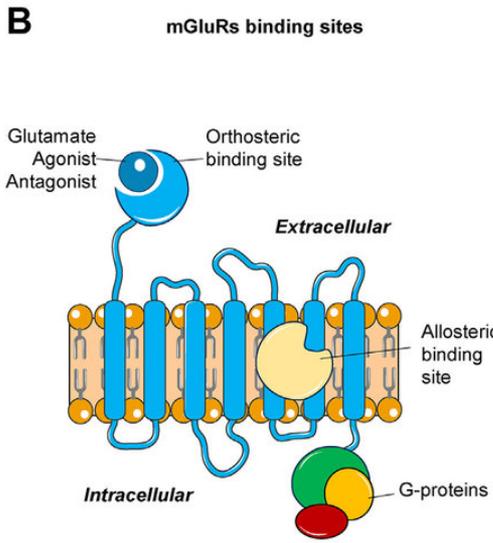
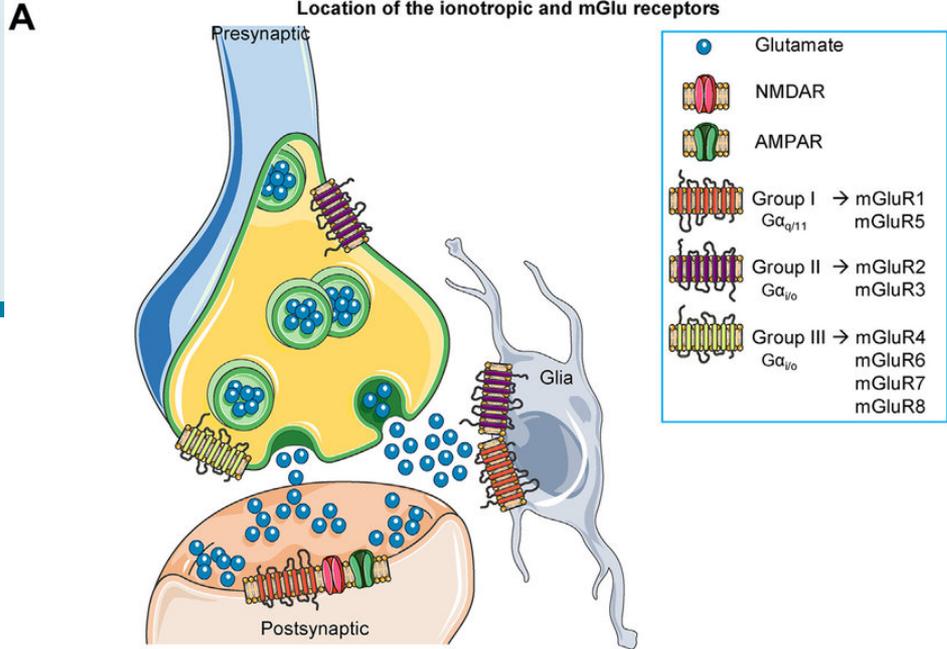
Metabotropic

- BCI-632
 - inhibits mGLU 2/3 presynaptic autoreceptor
 - Increases serotonin release
 - Chronic administration – hippocampal neurogenesis
 - “Ketamine without psychosis”
- BCI-838
 - Prodrug
 - Single and multiple escalating dose study completed

EAAT

- Troriluzole BHV-4157
 - Increases glial glutamate transporter-1

Location of the ionotropic and mGlu receptors



Allosteric Modulators of NMDA

- Positive
 - CAD-9303 – negative sx's of Schizophrenia
- Negative
 - CAD-9271
 - Treatment Resistant Depression
 - NMDAr 2B selective negative allosteric modulator
 - Currently in phase 2.

Glycine Modulators

- AV-101
 - Oral prodrug of 7-chloro-kynurenic acid
 - Potent glycine antagonist.
 - Fast-track status for adjunct treatment TRD
 - Phase II trials underway

Purine Antagonists

- JNJ-54175446
 - P2X7 receptor antagonist
 - Gene in area identified as susceptible to mood disorders
 - Receptor highly expressed in microglia. Mediates Glu release
 - IL-1 β
 - Phase II trial ongoing (12/21).

Neuroscience and Behavioral Reviews, 2018:192-205

GABA Modulators

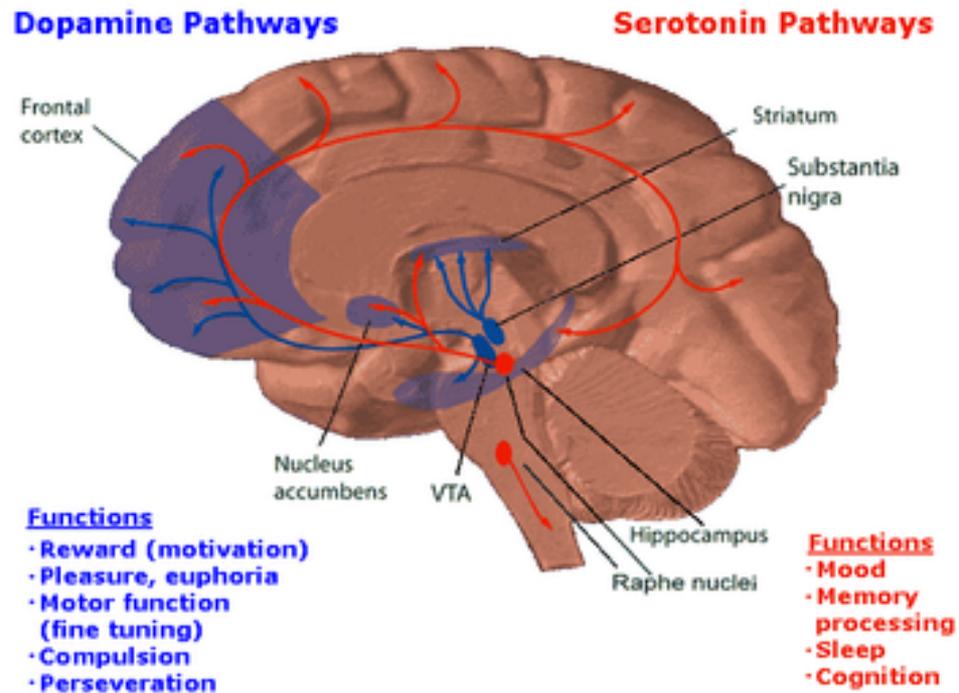
Alopregnanolone (Brexanolone)

- GABA-A receptor agonist
- Postpartum Depression
- Metabolites antagonize NMDA
- Men and Women with PTSD deficient alloprenanolone.
- Combined with extinction protocol.
- Study completion expected 2025.

GABA Modulators

- Ganaxolone
 - GABA-A Allosteric modulator-hyperpolarizes
 - Phase II for status epilepticus
- SAGE-217
 - GABA-A Allosteric modulator
 - Failed Phase III trial – suspended program

Monoamine Projections



Hallucinogens

- 5-HT_{2A} partial agonists
- Metabotropic Serotonin Receptor agonists
- PFC, Thalamus
- Raphe nuclei
- Three chemical classes
 - Tryptamines
 - Lysergamines
 - Phenethylamines
- Psychotherapy augmentation

Triple Reuptake Inhibitors (SNDRI's)

- Ideal Profile: Strong SERT; intermediate NET; and mild DAT inhibition. S. Stahl 2013
- Cocaine
- Phencyclidine
- Ketamine
- Ginkgo biloba extract (EGb761) Wikipedia 2017

SNDRI

Ansofaxine

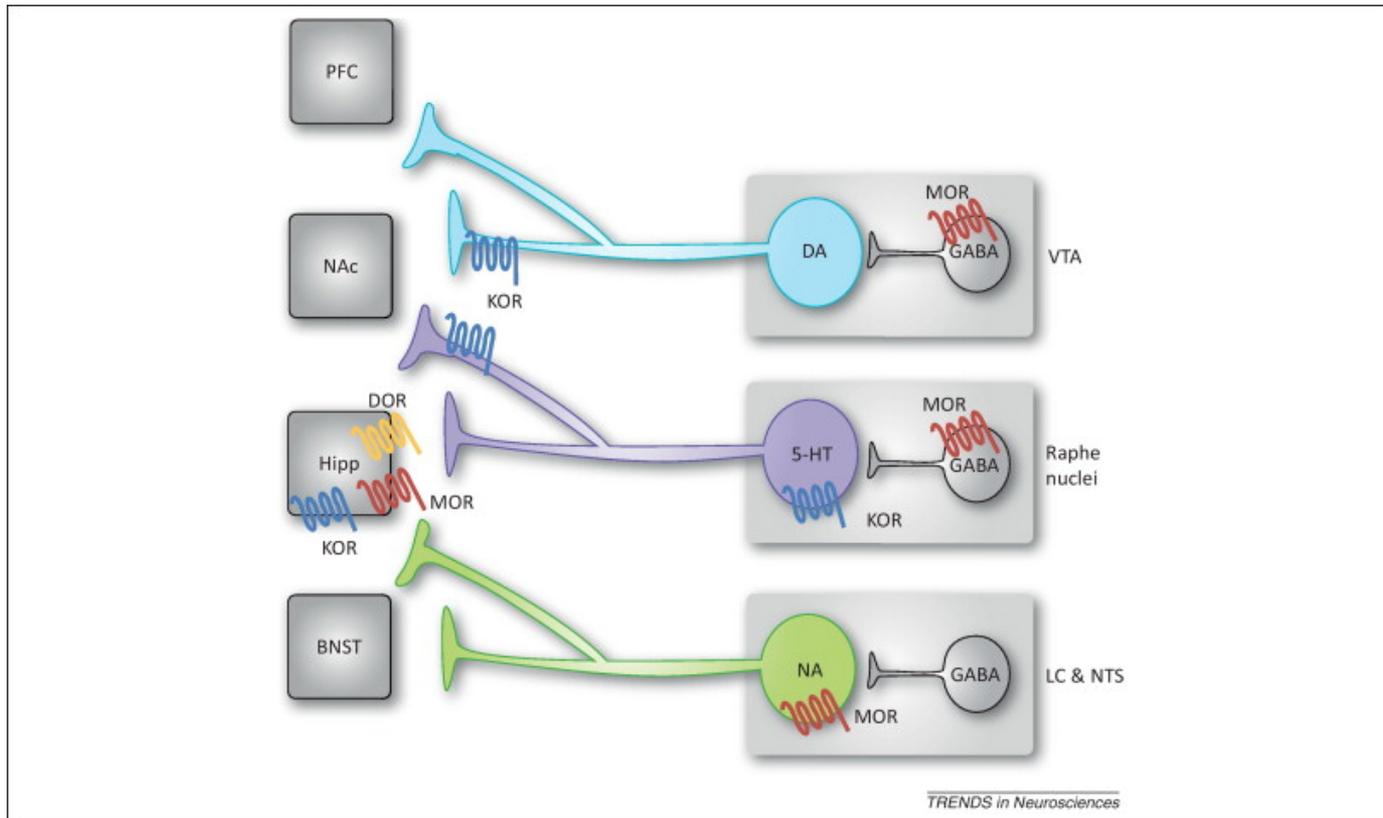
- Prodrug of desvenlafaxine
- SERT:NET:DAT: 4:5:3
- NDA filed with FDA, March 2020.

SNDRI

Mazindol

- IR previously marketed as obesity drug
- 2 Sustained release preparations in development
- NE reuptake inhibitor
- Blocks cocaine binding to DA receptors
- Phase II for Narcolepsy and ADHD

Opiates and Monamines



Lutz PE, Kieffer BL., Trends Neurosci 2013; 195- 206

Opiate Receptors

- Mu
 - Increased GABA tone on 5-HT neurons
- Kappa
 - Agonists are potent analgesics
 - Dysphoria, hallucinations, dissociation
 - Antagonists reverse learned helplessness.
 - Dynophan: decreases Glu and DA
 - BDNF
- Delta
 - BDNF
- Opioid Receptor Like 1 (ORL1)

Opiate Candidates

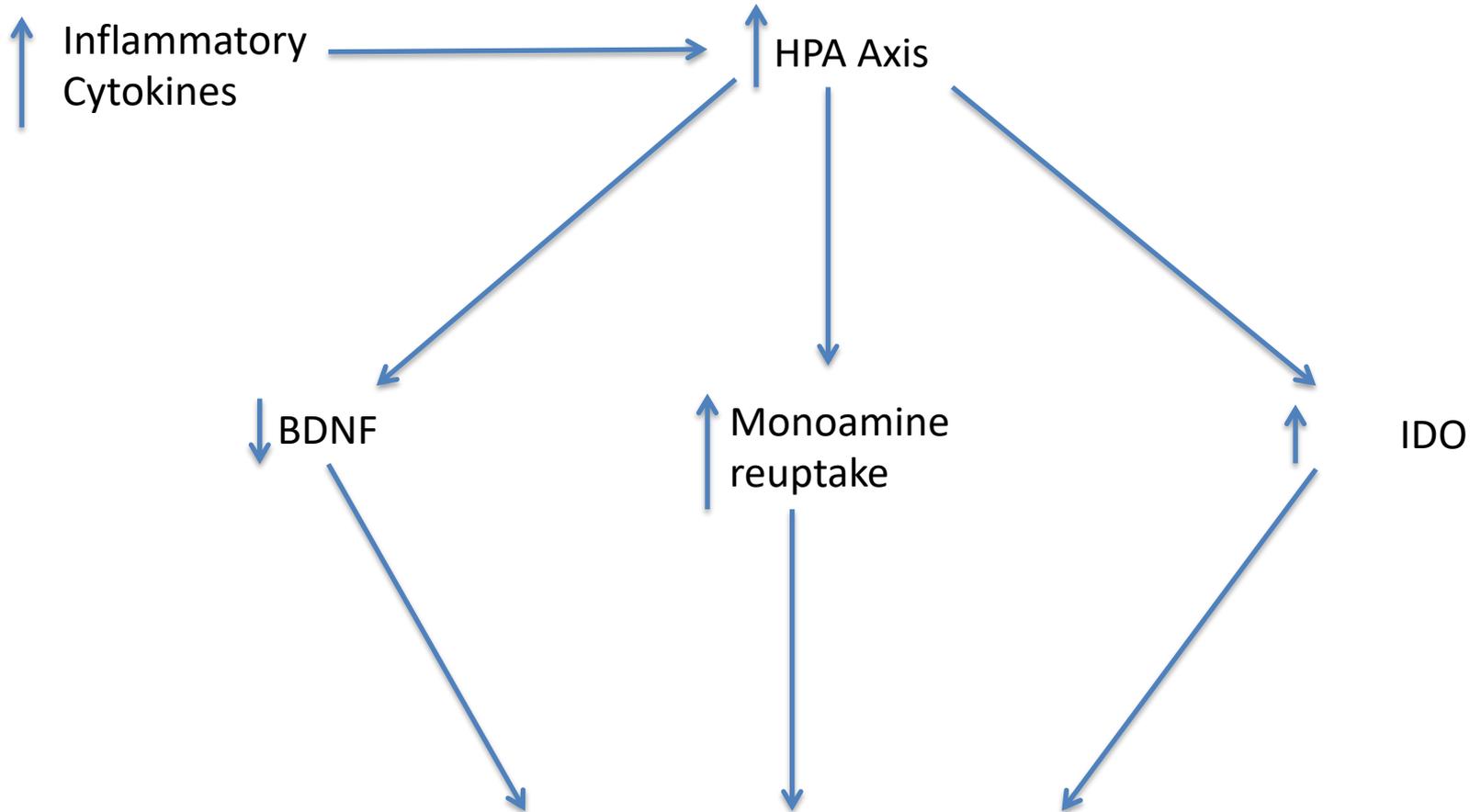
- Buprenorphine (MOR partial agonist; KOR antagonist)
 - Used off label for TRD
- ALKS-5461
 - buprenorphine/samidorphan
 - KOR antagonist
 - FDA rejected NDA.

Opiate Candidates

CERC - 501

- Short acting KOR antagonist.
- 30 fold selectivity for k receptors relative to mu and delta OR's.
- 2017 sold to Janssen - JNJ-67953964
- Phase IIA trial completed May 6, 2020.

Inflammation and Depression



Adapted from Nekovarova T. et al.,
Front Behav Neurosci 2014; 8:99 epub

Inflammatory Markers and Depression

Meta Analysis 1967 - 2008

- Interleukin-1
d=0.35 (95%CI:0.03-0.67) p=0.03
- Interleukin-6
d=0.25 (95%CI:0.18-0.31) p<0.001
- C-Reactive Protein
d=0.15 (95%CI:0.10-0.21) p<0.001

Howren M, et al. Psychosomatic Medicine 2009; 71:171-186.

Inflammation

Infliximab

- Tumor Necrosis Factor (TNF)
- 4 studies, 152 subjects.
- No Difference in HAM-D scores.
- Elevated TNF, CRP may define treatment responsive subtype.

Bavaresco DV et al., Pharmacol Biochem Behav 2020

Inflammation

- Exercise/weight loss
- Sertraline/ketoprofen – 2017
 - Interleukin
 - Results pending

Inflammation

ALKS-3831

- Olanzapine/Samidorphan
 - MOR antagonist
- NDA filed
- Samidorphan mitigates weight gain associated with olanzapine.

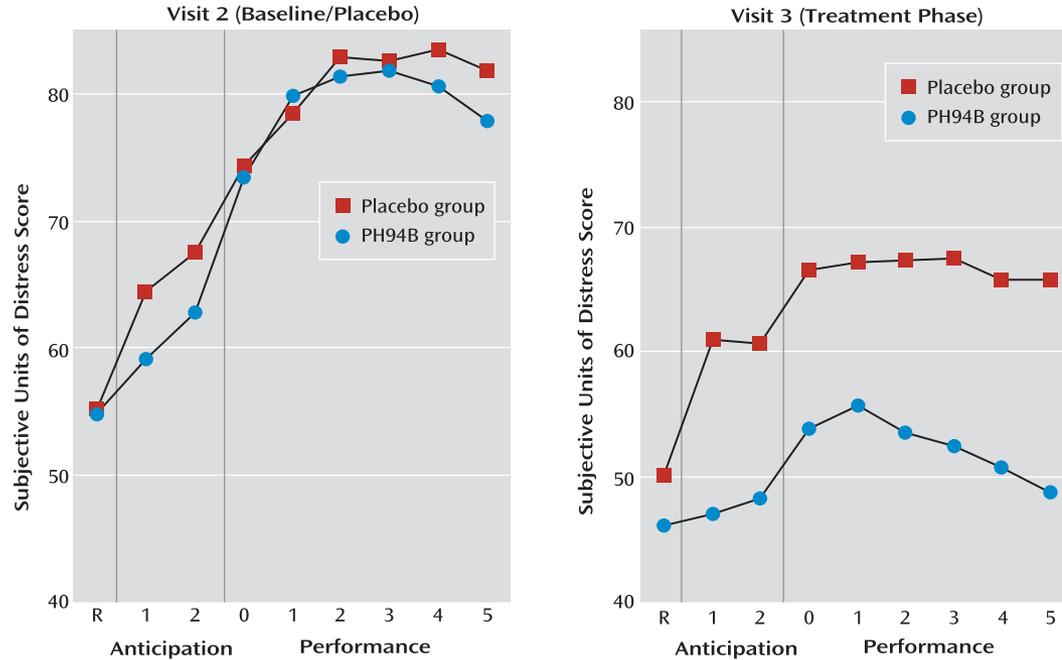
Neurosteroids

PH-10

- MDD
- Inhaled Neurosteroid
- Phase IIA: 8 week trial
- n=30; PBO, 3.2 ug, 6.4 ug
- 8 week HAMD: 6.4 ug-17.8 vs PBO -10.9
p=0.02
- **1 week HAMD: 6.4 ug-10.1 vs PBO -4.2**
p=0.03

PH94B

FIGURE 2. Public Speaking Challenge, Minute-by-Minute Subjective Units of Distress Scores for Women With Social Anxiety Disorder Receiving Intranasal Aerosol PH94B (N=45) or Placebo (N=46)^a

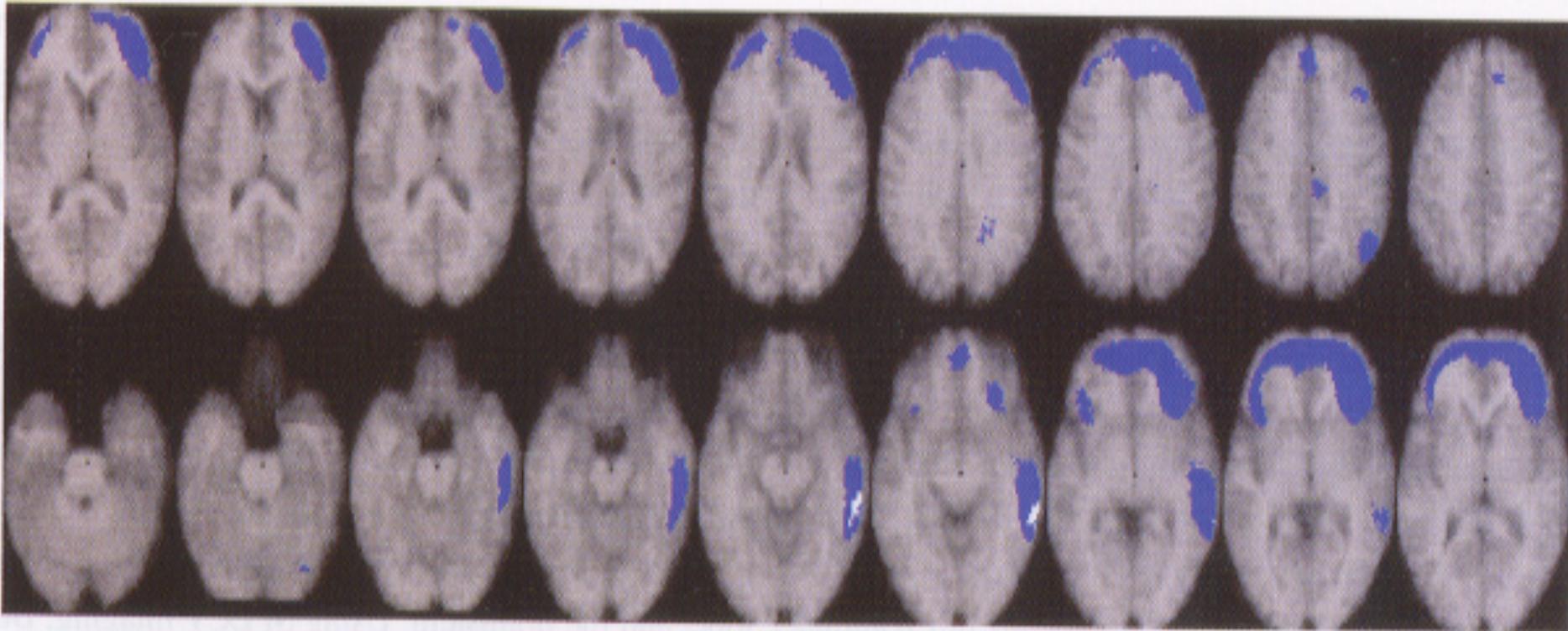


^a At visit 2, both groups received placebo. R=resting.

Inositol Monophosphate Inhibitor

- Ebselen (SPI-1005)
- “Lithium mimetic”
- Fast Track Status in Meniere’s Disease.
- Phase II study in bipolar disorder.

Neuromodulation



Neuromodulation

- **Deep TMS**
- **TMS: Theta burst**
 - 5 RCT's, 221 subjects
 - pooled RR 35.6% v 17.5% $p=0.005$ Berlim MT et al. , 2017.
- **ECT- Multifocal Stimulation**
- **Magnetic Seizure and iLAST Therapy**

Botox

- Corrugator and Procerus muscles injections
- Facial nerve signaling would shift.
- Phase II trial results were mixed.
- Postmarketing safety surveillance: Botox cohorts reported fewer depressive AE's.

Markunts T et al., Sci Rep. July, 2020

Physiotherapeutic Facial Massage

- 15 Minutes daily
- Relaxation of facial muscles associated with negative emotion.
- Strengthening of facial muscles associated with positive emotion.
- Study completion date June, 2021.

Adjunct Tools

- Teen Depression Module: online tool for PCP's to screen teens for Depression
- CBT augmented with text messaging: Individual and Group
- Depression Decision Aid (DDA) – Shared decision making tool.
 - Improved treatment initiation but not outcome.

Genotyping

PK:

- Cytochrome P450 Isoenzymes

PD:

- SERT (S)
- Antidepressant transport
- Individual Receptors -5-HT1A; 5-HT-2A
- BDNF – Val 66Met – decreased hippocampal volume
- IL-1b - mRNA levels higher in non-responders.
- IL-6 (rs 7801617) – escitalopram response.
- Polygenic Risk Scores

Genotyping

FDA: October 31, 2018:

- “... the relationship between DNA variations and the effectiveness of antidepressant medications has never been established.”
- “There are a limited number of cases for which at least some evidence does exist to support a correlation between a genetic variant and drug levels within the body, and this is described in the labeling of FDA cleared approved genetic test and FDA approved medications.”

Conclusions

- Glutamate system offers multiple targets. Avoiding the psychotomimetic effect while maintaining efficacy is the challenge.
- Addiction and fatalities from OD have slowed progress on opiates and hallucinogens.
- Metabolic consequences of illness/medications suggests some acute treatments may worsen long-term course of illness.
- Rational Polypharmacy?

References

1. Individual Company websites.
2. Clinical trials.gov
3. FDA.gov
4. Wikipedia; 9/23/2018 List of Investigational Antidepressants.
5. Mental Health Daily; 30+ New Antidepressants (2018): Drugs in Clinical Trials.