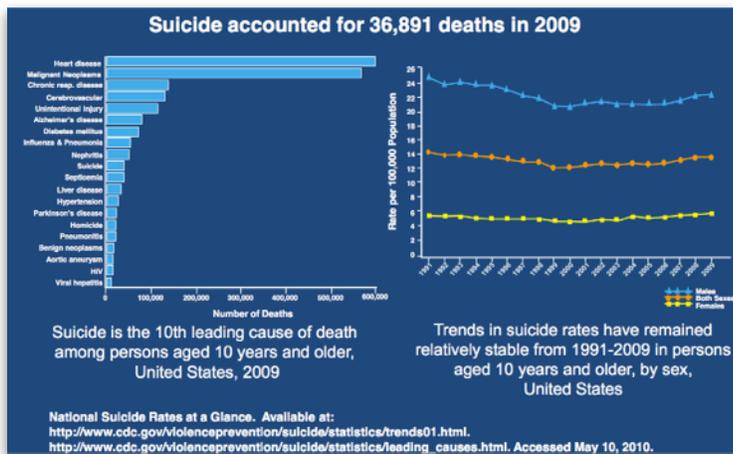


NEW FINDINGS IN DEPRESSION

Ketamine As A Treatment For Depression

From a presentation by Dr. Gerard Sanacora at the CANMAT Mood & Brain conference, 2014

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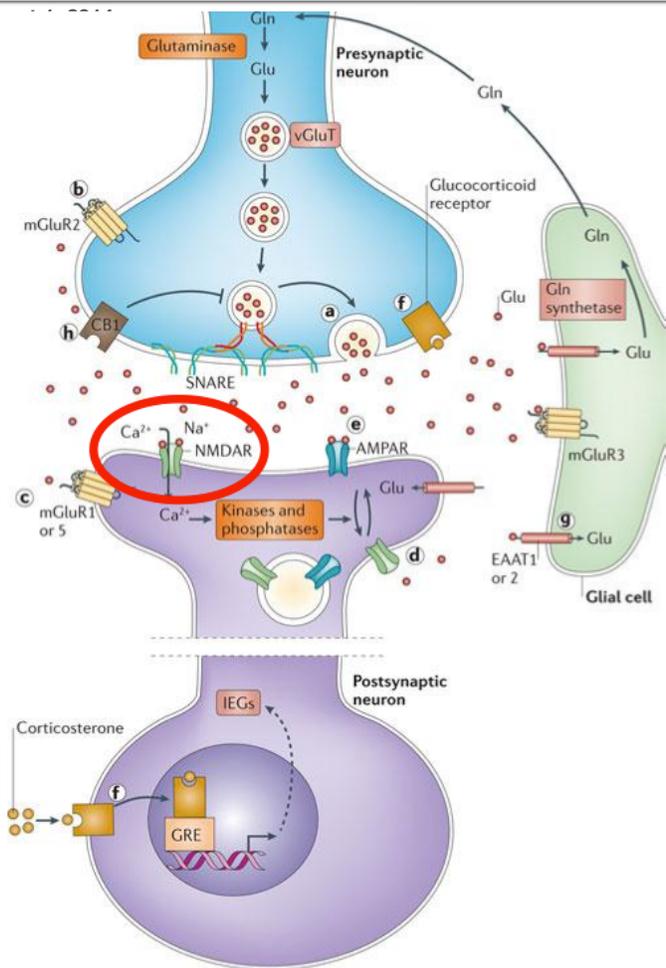
Dr. Sanacora (Yale University) began his talk by comparing the rates of **heart attacks** with those of **death by suicide**. According to the National Institute of Health, death from cardiovascular disease has steadily declined since the 1970s, while death by suicide, has remained comparatively unchanged over the last 50 years.

In terms of depression, there is a lack of pathophysiological knowledge, and the STAR-D study showed disappointing relapse rates of over 50% in one year when four levels of treatment were accumulated. Structural neuroimaging findings are also discouraging for depression as there is little definitive evidence for the same changes in brain regions occurring across large numbers of people.

It is known that stress has a part to play in the pathogenesis of the disorder and that stress-induced changes in prefrontal regions have been found (Liu, PNAS, 2008). The role of glutamate is under investigation and potential glutamate targets are NMDA receptors that has been associated with acute effects on mood have been recognized for many years (Crane, 1961). The Krystal study (2000) on ketamine had no adverse cognitive effects and had a rapid response (within 4 hours) in treatment resistant depressed patients. Since this paper there has been a wealth of literature on the use of ketamine in depression such as Zarate (2006) with a 73% response rate within one day and 33% remission within one day.

Potential Glutamate Targets

- a. Glutamate release
- b. Group II and III GluRs
- c. Group I mGluRs
- d. NMDARs**
- e. AMPARs
- f. Glucocorticoid receptors
- g. Excitatory amino acid transporters and exchangers
- h. Endocannabinoid receptors



Popoli, Yan, McEwen and Sanacora et al. *Nat Rev Neurosci.* 2012;13(1):22-37.

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Dr Sanacora outlined the limitations to the studies on ketamine thus far including:

- Ineffective blinding of patients, unknown duration of effect, little knowledge of the long-term effectiveness and safety of the treatment.
- It is unknown what the optimal dosing, or what the most beneficial route and frequency of administration are. There is a need for optimal dosing guidelines as there are dissociative effects with ketamine.
- It remains to be explored what are the moderators of response such as subtyping, genetics, endo-phenotypes, and whether there are any drug-drug interactions.

“Ketamine may reverse the effect of chronic stress”

-DR. SANACORA

- Finally there is little understanding of the mediators of response in terms of the proximal downstream effects of ketamine use.

The presentation included some of the recent evidence in the field of ketamine for treatment of depression:

- Murrough (2013) completed a trial of ketamine and midazolam and showed superior ketamine antidepressant effect for up to a two-week period with an administration of three times per week for three weeks.
- Shiroma (2014) showed a 60% response rate using the same paradigm of treatment.
- Blier (2012) found few long-term side-effects but some cognitive effects and risk of cystitis in long-term abusers.
- Liu (2012) suggested that brain-derived neurotrophic factor (BDNF) contributes to ketamine's antidepressant effects with the Met/Met homozygous group having no response but met carriers and non-met group having antidepressant effects.

Other NMDA drugs being developed were then discussed. CP-101-606 is a NR2B subtype of the NMDA antagonist found to be safe, generally well tolerated, and capable of producing an antidepressant response without also producing a dissociative reaction (Preskorn, 2008).

Lanicemine, a nonselective NMDA low trapping NMDA antagonist which may have minimal cognitive effects. **GLYX-13** a novel NMDAR glycine-site functional partial agonist, has an inverted U response with good antidepressant response at higher doses. Its mechanism of action appears to be over-excitation of NMDA receptor due to an oversupply of glutamate, which may involve diminished toxicity. **Scopolamine**, a cholinergic drug also appears to be associated with a rapid antidepressant effect.

Lastly Dr. Sanacora discussed the role of ketamine in plasticity and behavior. There may be a protein synthesis effect and ketamine may reverse the effect of chronic stress as there have been shown to be spine dendritic changes in those administered ketamine.