Fast-Fail Trials in Mood and Anxiety Spectrum Disorders (FAST-MAS): Using Brain Biomarkers vs Diagnoses for Improving CNS Trial Design

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Background for FAST-MAS Effort

- Existing treatments for mood and anxiety disorders have limited effectiveness.
  - Speaks to the need for a new generation of medications.
- Recent breakthroughs in basic and clinical science are ripe for application for development of new therapeutics
- Yet, CNS discovery pipeline is lean and FDA approvals of novel mechanism drugs for MAS rare in last 60 years
  - Nearly all drugs approved for depression and anxiety have been incremental changes of compounds available since the 1950s

National Advisory Council's Mental Health Workgroup. From Discovery to Cure. 2010; Paul et al., Nature Reviews. 2010; Krystal et al., Nature Rev Drug Discov. In Press. Denys and de Geus F, 2005; Trivedi et al., Am J Psych. 2006; Insel, Am J Psych. 2006

Background for FAST-MAS Effort

- Addressing need hampered by skyrocketing costs and failure rates
- Early-phase methods are key contributor
  - Frequently mislead companies to pursue extremely costly unsuccessful phase III studies.
- Examples:
  - Agomelatine. Melatonin receptor modulator, promising antidepressant; approved in Europe in 2009. Development halted after disappointing results from **phase 3** trials.
  - TC-5214. Nicotinic channel modulator for depression deemed a potential multibillion-dollar-a-year drug. Rights purchased for $1.24 billion. Had strongly positive results in a Phase II study. Failed to beat placebo in **4 phase 3** trials
  - Saredutant. Neurokinin 2 receptor antagonist with positive Phase 2 MDD study. Failed **Phase 3** clinical trials

National Advisory Council's Mental Health Workgroup. From Discovery to Cure. 2010; Paul et al., Nature Reviews. 2010; Krystal et al., Nature Rev Drug Discov. 2018.

Early Phase Trial Methodology Identified as a Key Problem: Focus on Phase 2a

- Phase 2a studies frequently underpowered, “mini” phase 3 trials
- Employ **Clinical Endpoints -** too variable to test potential with sufficient power at limited cost
  - DSM Problems:
    - Limited biomarker potential because of weak correspondence with neurobiology;
    - Many MAS Diagnoses have unacceptable test-retest reliability
      - DSMV Field Trials MDD-0.28; GAD-0.20
    - Dxs may not have a unique pathophysiology (e.g. MDD – 5/9 dx criteria)
- Often employ dose not established to engage target of interest (e.g. 5-HT2a antagonism)
- Do not test specific a priori hypothesis; test general hypothesis that the drug is effective
  - “All I care about is if it works and if it works I don’t care how”

Paul et al., Nature Reviews. 2010; Insel et al., Am J Psych. 2010; Kessler, British J Psych. 1996; Regier et al., Am J Psychiatry. 2013; Krystal et al., Nat Rev Drug Discovery. 2018.

Early Phase Trial Methodology Identified as a Key Problem: Focus on Phase 2a

- All these factors make outcomes:
  - Vulnerable to non-specific effects and bias
  - Greatly diminishes likelihood of replication
- Provides precarious basis for drug development and for “go/no go” decisions
  - Critical information coming from Phase 2a studies is of questionable utility:
    - Likelihood of improving FDA-accepted endpoints
    - Basis for designing pivotal trials, including dose
    - Commercial potential

Paul et al., Nature Reviews. 2010; Insel et al., Am J Psych. 2010; Kessler, British J Psych. 1996; Regier et al., Am J Psychiatry. 2013; Krystal et al., Nat Rev Drug Discovery. 2018

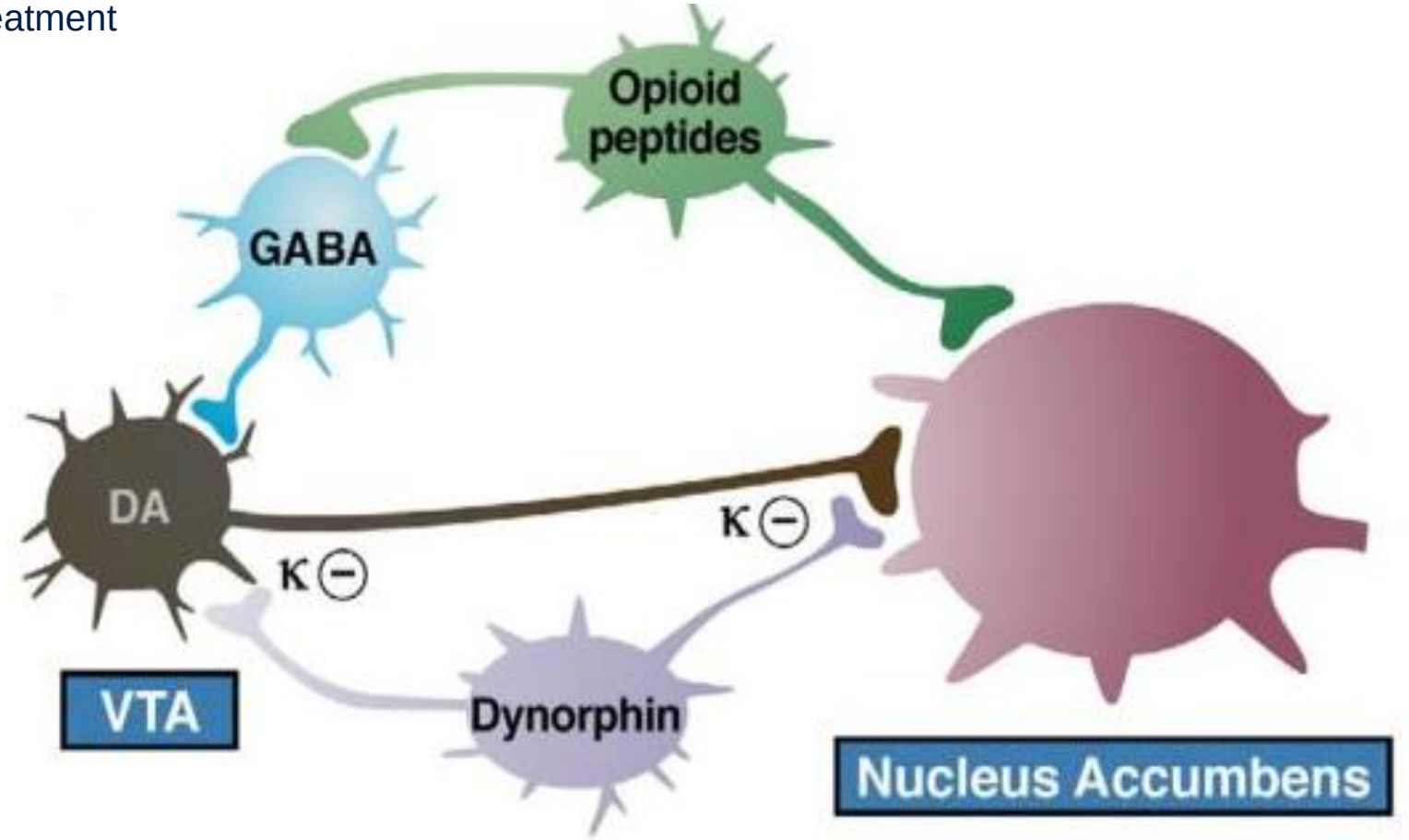
Background for FAST-MAS Effort

- To address problem NIMH funded **New Experimental Medicine Studies: Fast-Fail Trials in Mood and Anxiety Spectrum Disorders (FAST-MAS)** to provide more reliable early phase methods for evaluating compounds:
  - 1) Identify biomarker that reflects activity of the experimental compound at the neurobiological target;
  - 2) Use selective drug and use biomarker to find doses for Phase 2a that robustly engages target;
  - 3) In Phase 2a test specific “proof of mechanism” (POM) hypothesis that engaging target impacts brain circuitry that mediates anticipated clinical effect;
  - 4) proceeding to studies with clinical endpoints **only** if POM is established.
    - **Establishing POM should decrease likelihood that effects found in appropriately powered trials of KOR antagonists are due to non-specific effects or bias.**
    - **Ensures that negative findings in Phase III are interpretable, indicating that affecting the circuitry believed to mediate clinical effects is, in fact, not associated with those effects**

Krystal et al, Nat Rev Drug Discov. 2018

FAST-MAS POM Study of K Opioid Antagonism

- Sizable literature suggest that stress triggers Dynorphin release which inhibits VTA and NA Via K Opioid Receptors (KOR) and inhibits Reward-Related Function
- **<u>POM Hypothesis:</u> KOR Antagonism Increases NA Activation with Reward Anticipation**
  - POM Hypothesis test is basis for assessing if KOR antagonism has promise as Anhedonia Treatment



Bruijnzeel, 2009; Ebner et al., 2010; Muschamp et al., 2011; Carlezon et al., 2006; Maisonneuve et al., 1994; Tomasiewicz et al., 2008; Wee and Koob, 2010; Chartoff et al., 2012; Carlezon and Krystal, 2016; Krystal et al., Nat Med. 2020

Methods of FAST-MAS Study of KOR Antagonism

- 8-week double-blind, parallel-group, placebo-controlled, 2 arm study of high affinity, selective KOR antagonist JNJ-67953964 10 mg vs Pcbo
  - Toxicology, SAD, MAD completed, favorable pharmacologic and adverse effects profiles
  - Used 10 mg because it robustly engages the KOR in terms of PET receptor occupancy.
    - Lacking this information would have had to carry out PET study to determine dose with near complete receptor occupancy.
- **Key Inclusion Criteria**: Age 21 to 65; Snaith Hamilton Pleasure Scale (SHAPS) score ≥ 20, DSM-IV TR criteria for mood or anxiety disorder
- **Primary Outcome:** NA fMRI activation in anticipation of rewards in the monetary incentive delay (MID) task.
  - Study powered to detect effect size of 0.5; Targeted N=90 subjects but had sufficient power with N=72
- **Secondary Outcomes**: SHAPS, Probabilistic Reward Task (PRT)

Krystal et al., Nat Med. 2020. Zheng et al., 2013

Efficacy Results Based on Mixed Effects Models in ITT Population Means (SD) at End of Double-Blind Treatment Period N=89

Variable	Mean JNJ-67953964 (SD)	Mean Placebo (SD)	p	Effect Size (Hedges' g)
Primary Outcome Measure				
fMRI Ventral Striatal Activation in MID Task in Anticipation of Gain Contrasted with Non-Incentive Trials	0.72 (0.67)	0.33(0.68)	0.0095	0.57
Secondary Outcome Measures				
SHAPS	30.8 (3.7)	32.4 (3.6)	0.035	0.44
PRT Response Bias Block2-Block1 (N=46)	0.059 (0.15)	0.066 (0.15)	>0.10	N/A

-Post-hoc Correlation analyses suggest coherence of effects of treatment across units of analysis (neurobiology, clinical, behavioral)

- Change in primary outcome measure with treatment significantly correlated with change in key clinical secondary outcome (SHAPS) ($r=0.2$; $p<0.05$) and key behavioral outcome at a trend level ($r=0.24$; $p<0.10$)

Means are baseline corrected derived from mixed effects models

Krystal et al., Nat Med. 2020.

Conclusions

- We established POM for engaging our target (KOR Antagonism)
  - KOR Antagonism enhances activity in brain circuitry hypothesized to mediate a clinical therapeutic effect on anhedonia
    - Significant effects evident in all imaging measures included in this study assessing ventral striatal activity
    - SHAPS corroborative support; effect-size smaller as anticipated
- Based on FAST principles, “Go” criteria are met.
  - **Establishing POM decreases likelihood that significant effects found with clinical anhedonia endpoints in appropriately powered trials of KOR antagonists are due to non-specific effects or bias.**
  - **Negative Phase III studies carried out with JNJ-67953964 10 mg will be interpretable as indicating that engaging ventral striatal circuitry does not lead to improvement in anhedonia**
  - Findings also specifically support use of JNJ-67953964 10 mg in such studies.

Conclusions

- Serves as model for implementing Fast-Fail
  - Evaluating POM (testing if target engagement has hypothesized neural effect) before doing trials with clinical endpoints less closely related to direct biological effects of target engagement.
- Establishes a Fast approach early phase path for development of Anhedonia treatments
  - Validates RDoC Positive Valence System measures for assessing treatment outcome, at least related to the KOR mechanism
    - Primary Outcome: ventral striatal fMRI activation in anticipation of rewards in the monetary incentive delay (MID) task

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