ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Targeting Ventral Striatal Activation and Anhedonia in Early Phase Clinical Trials of Mood and Anxiety Spectrum Disorders: The NIMH FAST-MAS Perspective

Andrew D. Krystal, MD, MS

Professor of Psychiatry and Behavioral Sciences

Duke University School of Medicine

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Financial Relationships

- Consultant/Advisory Board:
  - Abbott, Astra-Zeneca, Attentiv, Bristol Myers-Squibb, Eisai, GSK, Lilly, Lundbeck, Merck, Novartis, Otsuka, Pfizer, Purdue, Roche, Sanofi-Aventis, Somaxon, Sunovion, Takeda, Transcept
- Grant Funding:
  - Grant support specifically related to this talk: NIMH Contract: HHS-N271-2012-000006-I
  - Abbott, ANS-St. Jude, Astellas, Brainsway, Duke Institute for Genome Sciences and Policy (IGSP), Duke Institute for Brain Sciences (DIBS), Lundbeck, Neosync, NIH, Novartis, Johnson and Johnson, Otsuka, Pfizer, Sunovion, Takeda, Teva, Transcept

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Overview

- Proposed solutions to the challenges facing CNS drug development:
  - Transform early phase study methodology ("Quick Win/Fast Fail")
  - Revolutionize how we think about mental illness (RDoC vs DSM)
- Example of Attempt at Implementing This Approach:
  - NIMH FAST-MAS: Study targeting anhedonia in terms of the ventral striatal response to reward

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Problems with Phase 2: Gate to Most Expensive Phase of Development

- Phase 2a clinical trial design\methodology thought to be biggest contributor to problems
  - Key Information relating to a drug candidate obtained from Phase 2a trials:
    - Likelihood of improving FDA-accepted endpoints
    - Information for designing pivotal trials such as dose
    - Likelihood of commercial potential
  - Phase IIa trials are frequently underpowered, “mini” phase 3 trials which are not long enough to demonstrate change
  - Usual **Clinical endpoints** too variable to test potential in Phase IIa study with sufficient power at limited cost
    - Vulnerable to bias problems
    - Basing go-no-go decision on getting statistical significance on a single clinical endpoint in such a study is highly risky

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Problems with DSM Diagnostic System

- Diagnostic categories based on consensus not science:
  - Based on clinician observation and patient symptom reports
    - Not informed by recent scientific developments
      - Fails to align with neuroscience and genetics findings
  - Not predictive of treatment response.
  - Does not capture fundamental underlying mechanisms.
  - Slow the development of new treatments targeted to underlying pathophysiological mechanisms.
    - Contribute to study failures:
      - Unlikely to be successful developing a drug for a condition that:
        - » Doesn't have a unique pathophysiology
        - » Is not reliably distinguishable from other conditions
        - » May subsume more than 1 condition

Insel et al., Am J Psych. 2010; Kessler, British J Psych. 1996

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Failure to Establish POC and Target Engagement at Doses Studied

- Companies often go to Phase III prior to establishing Proof of Concept (POC) in terms of efficacy/safety profile in Phase I-II
- Generally fail to establish target engagement with doses studied and that engaging target has effect on brain mechanisms relevant to clinical outcome
  - Leads to studies that do not test specific a priori hypotheses ("all I care about is if it works and if it works I don't care how")
    - Makes outcomes vulnerable to non-specific effects and bias
    - Greatly diminishes likelihood of replication

Paul et al., Nature Reviews. 2010

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Proposed Solution: "Quick-Win/Fast-Fail" Approach

- Since vast majority of candidates fail can we find a way to fail them faster and less expensively?
  - Requires shift of R&D investment from later to earlier stages
  - Design Phase I/IIa studies to definitively indicate potential
  - Pursue POC studies with biomarkers/surrogate endpoints early
    - Must establish early on whether or not a molecule engages its target and has desired pharmacological activity in humans
      - Biomarkers: Closer than clinical endpoints to pathophysiology and therapeutic mechanisms; thereby decrease variability and increase power
        - » Makes assessing efficacy potential possible in smaller/cheaper Phase IIa study which better predict Phase 3 results; decrease vulnerability to bias
      - Developing reliable biomarkers of both efficacy and safety for a variety of diseases will be necessary to make early 'go/no-go' decisions;

Paul et al., Nature Reviews. 2010

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Addressing Diagnostic Problems: NIMH Research Domain Criteria (RDoC) project

- Meant to replace DSM as new way of classifying psychopathology based on dimensions of observable behavior and neurobiological measures
  - Dimensional system: spans range from normal to abnormal
  - New framework for research on pathophysiology, especially genomics/neuroscience
    - Shift focus from refining clinically based classification to incorporating data on pathophysiology
  - Ultimately will inform future classification schemes.
    - Will help identify new treatment targets, detect treatment subgroups, improve match of research findings and clinical decision making.
    - Aimed at ensuring reliable and valid diagnosis.

Insel et al., Am J Psych. 2010

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

RDoC Constructs

- Identified key dimensions of function called “constructs”
  - Concept summarizing data about a specified functional dimension of behavior (and implementing genes and circuits) subject to continual refinement with advances in science.
  - Represent the fundamental unit of RDoC analysis
  - Central to psychiatric conditions, linked to underlying brain circuitry, and cut across current diagnostic boundaries
  - Constructs defined by associated:
    - Genes; Molecules Cells; Circuits; Physiology Behavior; Self-Reports; Paradigms
  - Related constructs are grouped into 5 major Domains of functioning: Negative Valence Systems (i.e., systems for aversive motivation), Positive Valence Systems, Cognitive Systems, Systems for Social Processes, and Arousal/Regulatory Systems.

Insel et al., Am J Psych. 2010

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Example Domain: Positive Valence Systems – Approach Motivation

Construct	Genes	Molecules	Cells	Circuits	Physiology	Behavior	Self-Reports	Paradigms
Reward Valuation		Dopamine; Serotonin		Cortico-limbic circuit: Anterior medial OFC; Ventral limbic striatum; Ventral tegmental area/Substantia Nigra			BAS reward sensitivity subscale; Sensitivity to reward subscale of the Sensitivity to Punishment: Sensitivity to Reward questionnaire	Kahneman-Spinner paradigm; Value-based decision making (e.g., preference test); can be explicit or implicit; Delay discounting; Counterfactual learning ("Armed bandit" task)
Effort valuation/ Willingness to work		Dopamine; GABA; Adenosine		Basolateral amygdala; Dorsal ACC; Ventral striatum (nACC), Ventral pallidum; VTA			Drive subscale of the Behavioral Activation Scale	Progressive ratio task; Effort-related choice behavior; Scheduleless key press to view or avoid pictures ; EEFRT Task
Expectancy/ Reward Prediction Error		Dopamine; Serotonin		Lateral habenula; Rostral medial tegmentum; Ventral striatum; Basal ganglia; Dorsal ACC; Substantia nigra/VTA; Orbital Frontal Cortex; Amygdala	Cortical slow waves; Heart rate change (e.g., HR deceleration in anticipatory period); Autonomic (e.g., skin conductance)	Reward-related speeding; Goal tracking; Sign tracking; Pavlovian approach	Affective forecasting; Self-report of craving; TEPS anticipatory scale; Generalized reward and punishment expectancy scale; Eating Expectancy Inventory; ASAM scale	Monetary Incentive Delay; Non-learning/passive gambling/guessing tasks; Cue reactivity
Action Selection/Preference Based Decision-Making				Amygdala				Modified Iowa Gambling Task; Card choice/gambling task per Sanfey (2003)

Positive Valence Systems = Reward/Habit

Construct	Genes	Molecules	Cells	Circuits	Physiology	Behavior	Self-Reports	Paradigms
Immediate Responsiveness to Rewards	DRD2; DAT; (TREK1)	Mu and delta opioid; Endocannabinoids; Orexin; Glutamate; Plasticity-related genes (CREB; FosB)		NACC; Medial OFC; Ventromedial PFC; Dorsal ACC; VTA; Ventral pallidum; Anterior insula; Lateral hypothalamus		Taste Reactivity	PANAS (state version); Consummatory subscale of TEPS	Monetary Incentive Delay; Gambling/guessing tasks; Taste reactivity
Sustained Longer-Termed Responsiveness to Reward Attainment		Serotonin; Opioids; Endocannabinoids; Orexin; Dopamine		Ventromedial hypothalamus; Medial preoptic area; Paraventricular hypothalamus; Arcuate nucleus; OFC; BA9/medial PFC	VNS (CCK); Peripheral endocannabinoids; PYY; GLP1; Gonadal hormones	Satiety sequence; Nipple refusal; Cessation consumption; Meal pattern analysis	Visual analog scales of satiety; Reward responsiveness subscale of BIS/BAS; Loss of control scale; Drug effects questionnaire	Devaluation task; Snaith Hamilton Pleasure Scale
Reward Learning	Various DA genes; Plasticity-related genes (CREB, FosB); Epi-genetic factors (HDAC, methyl transferases) ; DARP32; COMT; NMDA receptors on D1 neurons; Adenyl cyclase	dopamine & dopamine-related molecules; acetylcholine; Co-released neuromodular glutamate	medium spiny neurons ; dopaminergic neurons	dorsal striatum; Ventral striatum; Medial prefrontal; OFC; VTA/SN; Amygdala	Error/Correct /Feedback related negativity; Midline theta	Approach behaviors; Consummatory behaviors toward any goal object	Ecological momentary assessment; Ambulatory assessment and monitoring	probabilistic /deterministic reinforcement learning; Pavlovian conditioning; Instrumental conditioning and all its variants; Prediction error tasks
Habit	As above	As above				repetitive behaviors; stereotypic behaviors; compulsive behaviors	Measures of repetitive behaviors; Aberrant behaviors checklist	maze learning; knot tying; serial response; devaluation; response time acceleration; attention blindness; dual task; long-term probabilistic response learning; Perseveration tasks

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

NIMH Implementation of Solution: Funding Fast-Fail Trial Networks for Evaluating New Experimental Medicines

- Established networks for carrying out early phase trials of molecules engaging promising new **targets** embodying principles just discussed
  - Unique NIMH/private/academic partnership
- Meant to:
  - Provide a path for promising compounds currently not being developed
  - Establish a new standard for early phase drug development that will improve the cost/benefit of CNS drug development and rekindle pharma interest
  - Improve our understanding of mechanisms of psychopathology, treatments for psychiatric disorders, and optimal trial methodologies
- Awarded Grants in 3 Areas:
  - Mood and Anxiety Spectrum Disorders (FAST-MAS)
    - Grant Awarded to Duke (PI: A Krystal) HHS-N271-2012-000006-I
  - Psychotic Spectrum Disorders (FAST-PS)
    - Grant Awarded to Columbia (PI: J Lieberman)
  - Autism Spectrum Disorders (FAST-AS)
    - Grant Awarded to UCLA (PI: J McCracken)

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Key Steps in Implementing this Approach in Designing FAST-MAS Phase 2a Trial

- Choosing:
  - target
  - molecule which engages that target
  - dose of the molecule to study
  - appropriate RDoC construct(s)
  - outcome measures
  - patient population to study and how to select for that population
  - number of subjects to include in the trial

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Target Selection Process: Employing Proposed Novel Methods Relies Critically on CAREFUL Target Selection

- Working with committee including NIMH Program Officers and consultants to identify most promising targets to study and how to study them
  - Design trials based on the principles outlined earlier to optimize capacity to make a **definitive go/no-go decision** at end of Phase IIa.
    - Go/No-Go decision made based on whether **molecule engages target** not on whether have significant effect on a clinical scale
      - If we don't engage the circuitry it would not make sense to move forward even if there is a therapeutic effect on a clinical or self-report endpoint
      - This would be a setup for a failed phase III trial.

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

FAST-MAS Target Selection Process: Qualification Criteria

- Promising Pre-clinical/Clinical data
- Target of interest to the field
- Available means of assessing **target engagement**
- Available molecule for testing target hypothesis
  - Have to convince industry partner of the value of this approach
- Far along enough so that IND exists or IND-ready
- Not too far along in development
  - Phase II underway or beyond
- Established efficacy but target engagement not established
- Has not been found to lack efficacy in relevant clinical trial(s) or have prohibitive AE/tox profile
  - Or problem is molecule specific

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Challenge to Target Selection: What Do We Mean By Target Engagement?"

- Target engagement might mean demonstrating:
  - **Receptor occupancy with PET ligand**
  - That treatment affects a specific brain circuit with fMRI, or EEG measure
  - That treatment changes some relevant aspect of behavior in a laboratory task
  - That treatment leads to change in symptoms or behavior

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Process of Target Selection

- Exhaustive search led to identification of a target of interest
  - molecule was available that engaged that target and was at appropriate point in development
  - Means of establishing target engagement with PET available
    - Prior PET study allowed choice of dose that definitively engaged target
      - If PET study had not been available we would first have done a PET receptor occupancy vs dose study
  - Industry-partner willing to collaborate
  - Means of establishing POC in terms of effect on brain circuit during trial available

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Choice of RDoC Construct(s): We Chose to Study Anhedonia

- Because pre-clinical data strongly suggest that pharmacologically engaging the receptor target of interest should measurably affect key brain circuit so as to increase reward.
  - The inability to experience pleasure is a core symptom of major depression but also cuts across traditional diagnosis (anxiety disorders and schizophrenia)

Treadyway et al., 2009; Pizzagalli et al., 2005, 2009; Joiner et al., Psych Res. 2003; Snaith et al., BJP ,1995

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Choice of RDoC Construct(s): Challenge - Where in RDoC is the Function I want to Study?

- Need to find equivalent of anhedonia in RDoC and identify associated circuitry, behavior tests, clinical scales to employ in study
- The relevant RDoC Domain is Positive Valence Systems. <u>There are a number of relevant RDoC Constructs related to reward</u>:
  - Reward valuation, Expending Effort for Reward, Reward prediction/expectancy, Reward Responsivity, Effect of Reward on Learning
    - Reflects current best understanding of relevant neurobiology
  - Had to choose which is of primary interest but also decided to include measures to allow us to assess outcomes related to all of the key components
    - Circuits and measures overlap to a degree across Constructs of interest

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Domain: Positive Valence Systems – Approach Motivation

Construct	Genes	Molecules	Cells	Circuits	Physiology	Behavior	Self-Reports	Paradigms
Reward Valuation		Dopamine; Serotonin		Cortico-limbic circuit: Anterior medial OFC; Ventral striatum; Ventral tegmental area/Substantia Nigra			BAS reward sensitivity subscale; Sensitivity to reward subscale of the Sensitivity to Punishment: Sensitivity to Reward questionnaire	Kahneman-Spinner paradigm; Value-based decision making (e.g., preference test); can be explicit or implicit; Delay discounting; Counterfactual learning ("Armed bandit" task)
Effort valuation/ Willingness to work		Dopamine; GABA; Adenosine		Basolateral amygdala; Dorsal ACC; Ventral striatum (nACC), Ventral pallidum; VTA			Drive subscale of the Behavioral Activation Scale	Progressive ratio task; Effort-related choice behavior; Scheduleless key press to view or avoid pictures ; EEFRT Task
Expectancy/ Reward Prediction Error		Dopamine; Serotonin		Lateral habenula; Rostral medial tegmentum; Ventral striatum; Basal ganglia; Dorsal ACC; Substantia nigra/VTA; Orbital Frontal Cortex; Amygdala	Cortical slow waves; Heart rate change (e.g., HR deceleration in anticipatory period); Autonomic (e.g., skin conductance)	Reward-related speeding; Goal tracking; Sign tracking; Pavlovian approach	Affective forecasting; Self-report of craving; TEPS anticipatory scale; Generalized reward and punishment expectancy scale; Eating Expectancy Inventory; ASAM scale	Monetary Incentive Delay; Non-learning/passive gambling/guessing tasks; Cue reactivity
Action Selection/Preference Based Decision-Making				Amygdala				Modified Iowa Gambling Task; Card choice/gambling task per Sanfey (2003)

ISCTM Positive Valence Systems = Reward/Habit

Construct	Genes	Molecules	Cells	Circuits	Physiology	Behavior	Self-Reports	Paradigms
Immediate Responsiveness to Rewards	DRD2; DAT; (TREK1)	Mu and delta opioid; Endocannabinoids; Orexin; Glutamate; Plasticity-related genes (CREB; FosB)		NACC; Medial OFC; Ventromedial PFC; Dorsal ACC; VTA; Ventral pallidum; Anterior insula; Lateral hypothalamus		Taste Reactivity	PANAS (state version); Consummatory subscale of TEPS	Monetary Incentive Delay; Gambling/guessing tasks; Taste reactivity
Sustained Longer-Termed Responsiveness to Reward Attainment		Serotonin; Opioids; Endocannabinoids; Orexin; Dopamine		Ventromedial hypothalamus; Medial preoptic area; Paraventricular hypothalamus; Arcuate nucleus; OFC; BA9/medial PFC	VNS (CCK); Peripheral endocannabinoids; PYY; GLP1; Gonadal hormones	Satiety sequence; Nipple refusal; Cessation consumption; Meal pattern analysis	Visual analog scales of satiety; Reward responsiveness subscale of BIS/BAS; Loss of control scale; Drug effects questionnaire	Devaluation task; Snaith Hamilton Pleasure Scale
Reward Learning	Various DA genes; Plasticity-related genes (CREB, FosB); Epi-genetic factors (HDAC, methyl transferases) ; DARP32; COMT; NMDA receptors on D1 neurons; Adenyl cyclase	dopamine & dopamine-related molecules; acetylcholine; Co-released neuromodular glutamate	medium spiny neurons ; dopaminergic neurons	dorsal striatum; Ventral striatum; Medial prefrontal; OFC; VTA/SN; Amygdala	Error/Correct /Feedback related negativity; Midline theta	Approach behaviors; Consummatory behaviors toward any goal object	Ecological momentary assessment; Ambulatory assessment and monitoring	probabilistic /deterministic reinforcement learning; Pavlovian conditioning; Instrumental conditioning and all its variants; Prediction error tasks
Habit	As above	As above				repetitive behaviors; stereotypic behaviors; compulsive behaviors	Measures of repetitive behaviors; Aberrant behaviors checklist	maze learning; knot tying; serial response; devaluation; response time acceleration; attention blindness; dual task; long-term probabilistic response learning; Perseveration tasks

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Establishing POC in Terms of Effect on Brain Circuit

- Link to neural circuitry
  - Proof of Mechanism/Neural circuitry target engagement can be assessed with:
    - Task-associated fMRI Activation in ventral striatum during Monetary Incentive Delay Task
    - Resting state delta EEG current density in the rostral anterior cingulate

Wacker et al., 2009; Pizzagalli et al., 2004, 2009; Stoy et al., 2012; Ossewaarde et al., 2011

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Choice of Outcomes: Reverse of Traditional Approach

- Primary
  - Circuit measure of expected effect of drug on the brain Primary outcome is measure of engaging circuitry related to hedonic experience/response
- Key Secondary
  - Behavioral intermediate phenotype assessment (more closely linked to neural circuitry than clinical outcome but also linked to clinical outcome)
    - Probabilistic Reward Task assesses capacity to learn based on reward
  - Clinical Outcome: Measured with a clinical scale that has been demonstrated to be sensitive to treatment effects in depressed patients treated SSRI/SNRI
    - Snaith-Hamilton Pleasure Scale (SHAPS)
- Exploratory
  - Additional circuit measure
    - QEEG measure of cingulate activity
  - Additional Behavioral Measure
    - Effort Expenditure for Rewards Task assesses the degree to which one is motivated by reward as demonstrated by effort
  - Additional Self-report scale
    - Temporal Experience of Pleasure Scale (TEPS)
  - HAM-D, HAM-A

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Challenges in Process of Choosing Outcomes

- Started with clinical outcome
  - Agonizingly hard to give up:
    - HAM-D/HAM-A, DSM approach
    - Approach of seeking to find significant placebo vs drug effect on HAM-D/HAM-A or equivalent
  - Moved to Snaith-Hamilton
    - Clearly underpowered and risky
    - Hard to give up clinical outcome
- Finally settled on circuit outcome which was really the original intent and where we started
    - Go/No-Go decision will be made based on whether **molecule engages target** not on whether have significant effect on a clinical scale
      - If we don't engage the circuitry it would not make sense to move forward even if there is a therapeutic effect on a clinical or self-report endpoint;
      - This would be a setup for a failed phase III trial.

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Choice of Subject Population

- Dx mix:
  - DSM Dx mood and anxiety spectrum
    - One third must meet anxiety disorder criteria and not MDD
  - Anhedonia entry criteria (Snaith-Hamilton)
    - Circuit measure work insufficient to allow screening
      - This would ultimately be the goal.

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Challenges to Choice of Subject Population

- Novel endpoints may be unsuitable/unstudied for screening subjects
- Population choice affects regulatory (FDA) viability and clinical market potential
  - NIMH is having discussion with FDA about how RDoC approach can be applied to drug development/approval
  - Some FAST-MAS consultants have deep FDA experience
  - FDA approval will only be possible if can show that improvement of the RDOC endpoint does not represent improvement of one of the symptoms of a disorder; With anhedonia need to demonstrate:
    - 1) Treatment improves anhedonia but NOT depression scale (HAM-D/MADRS)
    - 2) Treatment improves anhedonia cross-diagnostically:
      - major depression; anxiety disorder who do not meet major depression criteria; and/or schizophrenia who do not meet major depression criteria.

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Challenges to Subject Population: Market Potential/Clinical Application

- "People don't have RDoC Constructs they have disorders."
  - MDD criteria (5/9) identifies heterogenous population (insomnia/sleepiness, weight loss/gain, etc)
    - No way to tell how useful/valid it is as it is its own "gold standard"; links to neurobiology suggest it is poor
  - We are treating symptoms now
    - No evidence or belief that treatments for schizophrenia address the entire syndrome. They address specific symptoms.
    - Treatment of depression is often similar. Outcome improved by targeting treatment to what we referred to as symptoms of MDD along antidepressants: insomnia (sleep aids), anergia (stimulants)
- "Won't everyone end up on multiple medications?"
  - People are on multiple medications now!
    - In clinical practice 60% of visits with 2 or more medications; 33% visits with 3 or more medications
    - Single agent therapy often fails across multiple disorders
- "Doesn't the DSM diagnosis matter?"
  - No data on whether MDD/anhedonia needs different treatment than schizophrenia/anhedonia
  - Our drugs are currently broad spectrum and dx really doesn't matter.
    - There is almost no disorder for which an "antipsychotic" is not used

Zigman and Blier, J Psychopharm. 2012; Mojtabai and Olfson, Arch Gen Psych. 2010;

Test-Retest Reliability of Diagnoses in DSM-V Field Trials

Target DSM-5 Diagnosis and Field Trial Site	Intraclass Kappa	95% CI	Interpretation	DSM-IV Prevalence	DSM-5 Prevalence (95% CI)
Schizophrenia					
CAMH	0.50	0.33–0.64	Good	0.53	0.37 (0.30–0.43)
UTSA	0.39	0.15–0.58	Questionable	0.16	0.13 (0.09–0.16)
Pooled	0.46	0.34–0.59	Good		
Schizoaffective disorder (CAMH)	0.50	0.30–0.65	Good	0.14	0.18 (0.14–0.24)
Bipolar I disorder					
Mayo	0.73	0.57–0.85	Very good	0.25	0.25 (0.21–0.30)
UTSA	0.27	0.08–0.44	Questionable	0.28	0.28 (0.24–0.33)
Pooledb[b]	0.56	0.45–0.67	Good		
Major depressive disorder					
Dallas VA	0.27	0.11–0.43	Questionable	0.49	0.37 (0.31–0.44)
Houston VA/Menninger	0.25	0.13–0.36	Questionable	0.34	0.36 (0.31–0.40)
UCLA	0.42	0.26–0.55	Good	0.26	0.28 (0.23–0.33)
UTSA	0.13	−0.06 to 0.30	Unacceptable	0.21	0.19 (0.15–0.24)
Pooled	0.28	0.20–0.35	Questionable		
Mixed anxiety-depressive disorder					
Penn	0.19	−0.07 to 0.42	Unacceptable	n/ac[c]	0.07 (0.05–0.10)
UCLA	−0.04	−0.13 to 0.08	Unacceptable	n/ac[c]	0.10 (0.07–0.13)
Pooled	−0.004	−0.10 to 0.09	Unacceptable		
Generalized anxiety disorder	0.20	0.02–0.36	Questionable	0.34	0.20 (0.16–0.24)
Posttraumatic stress disorder					
Dallas	0.63	0.48–0.75	Very good	0.50	0.46 (0.40–0.54)
Houston VA/Menninger	0.69	0.59–0.78	Very good	0.47	0.42 (0.37–0.46)
Pooled	0.67	0.59–0.75	Very good		
Complex somatic symptom disorder revised (Mayo)	0.61	0.40–0.77	Very good	0.10d[d]	0.08 (0.06–0.11)
Binge eating disorder (Penn)	0.56	0.32–0.77	Good	n/ac[c]	0.05 (0.03–0.07)
Alcohol use disorder (Houston VA/Menninger)	0.40	0.27–0.54	Good	0.26e[e]	0.29 (0.24–0.33)

Regier et al., Am J Psychiatry. 2013

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Challenges in Determining Number of Subjects

- N=90; Parallel-group; 2 arms: Study drug/Placebo
  - Study powered to detect effect size of 0.5
  - Capacity to estimate effect size on primary outcome limited by very few treatment studies carried out with MID fMRI
    - Roughly estimated effect size of 0.88
- We had to resist the tendency to power the study for clinical endpoints; it took several revisions before settled on smaller study with circuit outcome

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

General Limitations/Risks of "Fast-Fail" We Faced

- Can only study a limited set of targets
  - Requires developing means of establishing target engagement prior to proceeding into Phase Ib studies
- False-negative POC data (type 2 errors) could offset some or all of the cost savings generated by shifting attrition earlier
- Puts pressure on need for additional studies that form the basis for the early decision to have a relatively low uncertainty, which is not always possible.
- Cannot prevent Phase 3 failures due to relatively uncommon unanticipated adverse effects

Paul et al., Nature Reviews 2010

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Summary

- The solution to the current crisis is that early phase drug development has to become biomarker/RDoC-based, though methods not currently fully worked out
  - New biomarker-based/technology intensive studies have to be carried out
  - RDoC needs to be more fully developed
  - Trials need to be carried out to test the utility of this approach