

ISCTM Integrated Therapeutics Working Group

Integrated Therapeutics : Combining learning-based interventions with drug and neuromodulation devices. The challenges to trial design and regulatory approval.

Introduction

Drugs and devices are typically evaluated as solitary interventions in clinical trials but are often combined with other treatment modalities in clinical settings. Examples include patients taking an SSRI and receiving therapy to treat depression. The complexity of psychiatric disease often requires concomitant use of multiple treatments working through different mechanisms to achieve meaningful improvement.

Integrated therapeutics, defined as treatment combinations offering efficacy advantages or safety benefits, are attracting increasing attention as treatment strategies, especially for treatment-resistant conditions. Examples include MDMA combined with psychotherapy to treat PTSD or transcranial magnetic stimulation combined with symptom provocation to treat OCD.

This working group will focus on methodology issues related to designing and conducting trials of these interventions.

Topics to Address

- Defining types of Integrated Therapeutics
- How to evaluate efficacy: what type of studies to conduct (eg. 2x2 design)
- Outlining possible regulatory concerns

Working Group Goals

- Developing an Integrated Therapeutics Session for ISCTM Feb 2021 Meeting
- White Paper
 - Consensus on components of white paper
 - Identifying authors of white paper
 - Assign 2-3 authors for each section

Feb 2021 Session Proposal

Potential Speaker Topics

Speaker 1- Psilocybin +Psychotherapy for Depression

Speaker 2- MDMA + Psychotherapy for PTSD

Speaker 3- FDA: Regulatory discussion of psychedelic based treatments
-should include discussion of what FDA can and cannot regulate
-should discuss mechanism of REMs to regulate non-drug component
of treatment as it relates to safety and how safety is defined
(Potentially a separate REMs Speaker?)

Speaker 4- Transcranial Magnetic Stimulation (TMS) for treatment of OCD

Speaker 5- FDA: Regulatory approach to combined treatments involving devices

Speaker 6- Psychotherapy Research Speaker

Speaker 7- Oxytocin + Social Skills Training

Speaker 8- Speaker on Contrave (Bupropion + Naltrexone + Weight Loss Therapy)
as case study on how trials were designed and interpreted

Speaker 9- Placebo effect- Is it more problematic in studies of combined
interventions

White Paper Topics/Sections

Proposed Outline

- Definition of Terms
- Outlining Types of Integrated Therapeutics Involving a Learning-Based Intervention combined with a Drug/Device
- Trial Design
- Regulatory

Definition of Terms

- **Learning-based interventions (LBI)**: not necessarily in isolation, but when integrated with drug or device
 - Psychotherapy: An interactive approach or way of learning. In addition to learning, psychotherapy may provide other benefits during treatment (e.g., soothing/acute anxiolytic effects that can but need not result in learning-based change)
 - Other Examples: Social Skills Training; Exposure and Response Prevention Protocols
- **Neuromodulation (NM)**: interventions that directly change neuronal (or brain tissue, e.g., glia) function (e.g., inhibition or excitation of groups of cortical neurons by rTMS, decrease in presynaptic neuronal reuptake of serotonin by SRIs.) *This term is used in the broadest sense and includes drugs.*
 - This can include non-sensory peripheral nervous system stimulation to affect CNS targets (e.g., VNS device, photostimulation of SCN, etc.)

Describing Types of Integrated Therapeutic Designs: 4 Types of Designs

1. Uni-direction Enhancement

This type of treatment involves intervention A enhancing the effect of intervention B, where B may have none or only nominal activity in isolation, and requires A to activate or enhance the therapeutic effect of B to achieve a clinically meaningful effect. The nominal activity of B in isolation maybe defined in the context of time-

limited exposure or dose (eg. cognitive remediation has been shown to be effective when delivered over 12 weeks. However, it is unlikely to be effective when delivered over 1 week; but when d-cycloserine is added to 1 week of cognitive remediation, then it is effective)

e.g.

A: - d-cycloserine (NM),
B: - cognitive remediation (L)

A: - oxytocin (NM),
B:- social skills training (L)

Special Example of Uni-Directional Enhancement

#MDMA assisted psychotherapy (non-directed, patient centered psychotherapy)

A: MDMA (NM),
B: psychotherapy (L)

-according to their model, MDMA is accelerating/enabling a more meaningful psychotherapeutic experience that leads to clinical improvement. This situation is unique in that MDMA use results in a psychotherapeutic interaction that is distinctly different than in a non-drug state. There may be possible functional unblinding as the psychotherapy is likely modified by the MDMA. In the previous examples, the cognitive remediation and social skills training is likely not qualitatively different on-or-off the enhancing drug. The training may proceed faster if the training framework allows, but to the casual observer watching drug or non-drug training, there is likely no observable difference.

2. Bi-directional Interaction (alternative name and description- Contextual Combination)

This type of therapy involves two interventions, A and B, that may act bi-directionally to enhance each other's therapeutic effect. It maybe unclear without a 2x2 design where most of the clinical effect is arising from. A and B in isolation would each have a clinical effect.

e.g.

A:- varenicline (NM)
B: smoking cessation counseling (L)

3. Safety Context

This type of therapeutic combination involves two interventions, A and B, where A is the drug and B is the learning-based intervention. "A" induces a non-ordinary state in the patient that is highly conducive for confronting and processing experiences and memories that would normally be too distressing to confront and process. Some subjects maybe able to process under the influence of A by themselves, resulting in clinically meaningful improvement. However, the majority of subjects may need guidance and direction from a therapist while in this non-ordinary state in order to safely and productively process the experience/memories to achieve a therapeutic outcome. The risk or safety issue arises as an unguided/undirected non-ordinary state may result in an adverse experience or increased anxiety and distress.

e.g

A:- Psilocybin (NM)

B: - Psychotherapy (L)

4. Fully Integrated

This type of therapeutic combination involves two interventions, A and B, where either in isolation has no detectable clinical effect in the doses studied. Only when both are combined is there a clinical benefit.

e.g.,

A: deep TMS (NM)

B: - Provocation (extinction learning) (L)

Deep-TMS combined with simultaneous OCD symptom provocation for treatment of OCD. The proposed mechanism is that the provocation activates the circuit responsible for the OCD anxiety, and high frequency stimulation dTMS of that circuit results in improvement of symptoms.

Describing different approaches to integration

- Effect extension: e.g., adding therapy to drug to boost it to cross threshold of significance or in maintenance phase

- Effect hastening (acceleration): adding drug to therapy to be able to reach critical therapeutic interactions (e.g., corrective experiences) sooner
- Sequential treatment designs- Starting one intervention first and then the other (eg. provocation + dTMS is a good example of such a design)

		Independent efficacy	No independent efficacy	
		Independent efficacy for Learning-Based intervention (L)	No independent efficacy for Learning-Based intervention (L) in proposed dose/timeframe <ul style="list-style-type: none"> Efficacy of L hastened Efficacy of L extended <ul style="list-style-type: none"> Applies to intermittent Tx 	No independent efficacy for Learning-Based intervention (L) regardless of dose/timeframe
Independent efficacy	Independent efficacy for Neuromodulation (N)	<p>*Combination needed to achieve positive benefit-risk balance</p> <ul style="list-style-type: none"> N reduces risk of L alone L reduces risk of N alone L+N needed for benefit be clinically significant L represents assumed standard of care (e.g., Contrave)? <p>*L+N benefit > L benefit + N benefit (e.g., enhancement of therapeutic learning by esketamine treatment for TRD, potentially)</p>		Combination needed to achieve positive benefit-risk balance <ul style="list-style-type: none"> L represents assumed standard of care (e.g., perhaps standard RC drug trial) L reduces risk of N alone L+N needed for benefit be clinically significant
No independent efficacy	No independent efficacy for Neuromodulation in proposed dose/timeframe (N) <ul style="list-style-type: none"> Efficacy of N hastened Efficacy of N extended <ul style="list-style-type: none"> Applies to intermittent Tx 		Example: psychedelic psychotherapy?	
	No independent efficacy for Neuromodulation (N) regardless of dose/timeframe	<p>*Combination needed to achieve efficacy for N</p> <ul style="list-style-type: none"> E.g., (potentially Drug-enhanced therapy e.g., MDMA therapy, oxytocin enhanced social cognition training) <p>*N reduces risk of L alone (L reduces risk of N alone?)</p>		Combination needed to achieve efficacy <ul style="list-style-type: none"> L+N simultaneous (e.g., dTMS-exposure) L+N sequenced (e.g., prep therapy for psilocybin session, potentially)

Trial Design Issues

Delineating Trial Design based on Safety vs Efficacy objectives (Scientific Question vs Regulatory Question)

- Design of trials are going to be different depending on study objectives: Safety or Efficacy
- **Efficacy:** if you want to identify the active component or how much efficacy each component contributes to the overall treatment, a 2x2 design is required
- **Safety:** Just testing the combination treatment vs placebo is sufficient

Specifying when to conduct 2x2 studies vs just *Combination Treatment vs Placebo* Studies:

- Early phase: Potentially, a 2x2 trial is conducted in early phase of development to demonstrate a lack of efficacy of the individual treatments. Once this is established, then in later phases of development only *Combination vs Placebo* studies are needed.
- However, in situations where early phase 2x2 trials demonstrate efficacy of individual components alone, then in later phases the FDA may require a 2x2 design to demonstrate synergy in late phase
- If the therapy component is providing an essential safety element to the combination treatment then potentially a *combination treatment vs placebo* trial can be conducted without an earlier 2x2 design (eg. as is potentially being asserted in the psilocybin trials)
 - Additional considerations for a safety situation: What part of the therapy is essential for safety vs what is contributing to the efficacy? e.g. In the psilocybin studies should you “dismantle” therapy component and only include the safety portion: only include the drug session therapy element and remove the pre-drug and post-drug therapy sessions.
 - Could this be an approach to determine what therapy components REMS should require vs what is optional (i.e. what part of the therapy is the “practice of medicine” and cannot be regulated by the FDA or REMS)

Role of Discontinuation Design to Identify Mechanism of Action

Is there a role for discontinuation/randomized withdrawal studies to identify the mechanism of action responsible for clinical efficacy?

Regulatory Issues

Identifying FDA Mechanisms to Regulate Non-Drug/Non-Device Component

When is employment of REMS appropriate vs excessive?

- What is the threshold to qualify for REMS?
 - dTMS + Provocation, the risk from dTMS is likely not high enough to warrant REMS
 - Therapy component of Psilocybin-Therapy, may be essential for safety

Potential Methodology Questions

Fidelity to Learning-Based Intervention

- In trials, single sites typically adhere with high fidelity to psychosocial treatments.
- What happens in multi-site trials; importance to ensuring fidelity to treatment.
- Single site reduces internal variability but also generalizability
- Multi-site increases internal variability but also generalizability

Quantifying dose of Learning-Based Intervention

- How do you measure how engaged a patient is with Therapeutic component; what scales are used in psychotherapy world to quantify engagement? For neuromodulation/provocation, can you use fMRI to verify target engagement of provocation or quantify activation of that circuit (or can you use something like pupil dilation/tracking to quantify how activated the patient was during provocation)?

this is an important feature to define as psychotherapy/LBI can be dosed in terms of duration of exposure (e.g., how many sessions are delivered)

- Psychotherapy is typically thought of as ineffective if only given for 2 sessions, or at least the benefit is limited.
- This is an important distinction to specify the context when an intervention is ineffective; it is ineffective at that dose (i.e., 2 sessions of psychotherapy without drug would be ineffective)
 - Worth noting that psychotherapy research literature suggests that therapist experience is unrelated to therapist efficacy (mean effect achieved at end of treatment) but is related to 'potency' (number of session required to achieve effect)
- In psychedelic drug studies, how do you characterize how the drug changes the therapeutic component? Can that be a method to quantify the actual drug effect?