ISCTM
RAAD Working Group
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In this working group we discussed the development of a scale selection algorithm for rapid-acting antidepressants. It was theorized that the scales could be selected based on the known mechanism of action, onset of effect, and primary symptoms first impacted. This emerged based on feedback received following the publication of our previous working group findings and that, while the scale recommendations were useful, there is still concern around whether we are measuring the correct phenomena.

A brief presentation of the rationale for this proposed development was given and included a summary of the primary drug classes that are currently under investigation as RAADs, their purported mechanism of action, and the domains they impact. The topic of domains became important in making the distinction between improvement in domains of depression and improvements in the total construct (e.g., MADRS total scores).

Some of the domains under consideration during the working group discussion were: cognition, well-being, sleep, and appetite. We began with the following framework for discussion:

- Problem statement:
    - Select scales appropriate to the known characteristics of the compound and its impact on symptom severity expression.
- Elements:
    - Drug: onset anti-depressant action
    - What domains are being impacted?
    - Other scales or testing methods to supplement existing measures
- Develop matrix:
    - By indication and compound domain, scale type, onset of action

Attendees were asked to break out into discussion groups with those at their table. The discussion was intended to be focused on whether it would make sense to consider developing a scale selection algorithm for RAAD trials that takes into consideration the onset of antidepressant action, which domains are expected to be impacted and what other scales or testing methods should be used to supplement existing measures.

Each table had interesting discussion that went in a variety of directions. The most common theme was less about finding the right scale to assess the same symptoms that all the existing scales do and more about assessing different symptoms, taking a more qualitative approach, focusing more on the symptoms that are most relevant to the patient.

Specific suggestions included:

- Consider if we are looking at symptoms or the syndrome.
- Importance of scales like PGI to measure overall improvement which would theoretically focus more on symptoms of importance to the subject.
- Consider evaluating a more overall quality of life evaluation such as assessing "are you enjoying life?" or "if this is how you are for the rest of your life, how satisfied are you?"
- Evaluate how connection to emotions may change (in psychedelic space).
- Assess impact of symptoms on functioning more than we currently are – need to consider the impact of symptoms rather than the symptoms themselves.
- Capture more precisely the activities of daily life: social life, suicidal thoughts, cognition and sleep all need to improve.
- Measure domains that contribute to suicidality such as agitation and impulsivity.
- Examine how often it really makes sense to assess symptoms -- is it meaningful to examine symptom change across two hours?
- Have outcome focus on the most troublesome symptoms for the patient. Could they identify their most troublesome symptoms and assess change in those as a more meaningful metric of how effective a treatment is?
- Do you need to look at symptom improvement in the first day? With RAAD, how long are they going to work? We need to consider this and how long they will continue to have an impact. What is in scales like MADRS with objective markers like actigraphy as complement, sleep staging, etc.
- Inspiration from Seth Hopkins' talk – we need to be doing a lot more interrogation of item analysis. Trying to understand correlations and item changes, that makes sense in terms of circuitry and mechanisms.
- Integrate use of biomarkers such as vocal analytics and actigraphy as objective measures.
- Vocal analytics to assess affect changes, rapport, importance of dyadic relationship between patient and provider. Considerations about rapport.

- Considerations about cognitive impact of depression and how we need to be careful to ensure that scales are easy to complete in light of cognitive challenges.

Next steps:

Involve interested attendees in continued discussions about how we might be able to use this discussion as a jumping off point for additional RAAD assessment consideration, recommendations, and publication.