

Domain-Based Approaches to
Pathology in the Development of
Novel Psychiatric Therapies:
Enhancing Tractability in Discovery
and Trial Methodology

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Domain-Based Approaches

- Clinical Trials in CNS have traditionally included patients based upon criteria from the Diagnostic and Statistical Manual (DSM) and International Classification of Diseases (ICD).
- These diagnostic entities include heterogeneous populations that, most likely, do not share a common biology.
- Findings from various scientific disciplines – including genetics, neurobiology, neural circuitry, neuroanatomy, neuroscience, and neuropsychology have repeatedly demonstrated that the underlying pathology of major psychiatric disorders does not abide by the discrete entities of our classification systems.
- Instead, pathological neurobiology and behavior are more parsimoniously explained by symptom clusters that traverse diagnostic entities.

Domain-Based Approaches

- What is the relative value of a focus on domains of behavior and/or underlying biology as treatment targets as opposed to traditional DSM and ICD diagnoses in CNS clinical trials?
- In order to develop treatments that will more likely address the underlying neurobiology of psychiatric disorders, a more sensitive and efficient approach will be to design methods and outcomes that align with the structure of CNS pathology as it exists in the population.

The Sagrada Família is a large Roman Catholic church in Barcelona designed by Catalan architect Antoni Gaudí (1852–1926).

Construction commenced in 1882. At the time of his death in 1926, less than a quarter of the project was complete.

Construction passed the mid-point in 2010 with some of the project's greatest challenges remaining and an anticipated completion date of 2026—the centennial of Gaudí's death.

How can we expedite the development of biologically justified domain-based methods in CNS clinical trials ?



Domain-Based Approaches

- Q1: What are the domain-based approaches? Why do we believe this approach would enhance tractability in therapy development? What are the short and long-term implications on neuroscience R&D?
- Q2: What is the biological plausibility of the different symptom domains? What are the possible neural substrates underlying these domains? Are these substrates consistent across disease states and diagnoses? Do these substrates translate from animals to healthy individuals to patients?

Domain-Based Approaches

- Q3: What is the dimensional expression of the different symptom domains across clinical diagnoses? Are these domains measurable? What are the different psychometric properties needed to evaluate the severity of symptom domains in patients with different psychiatric or neurologic conditions?
- Q4: What are the pathways for drug development using the domain-based approach? How do they interact with current regulatory approaches? Will payers adopt their value models to integrate the domain-based approach?