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Inside the Pharmacodynamic Toolbox: How Questionnaires, Models and Tests of Cognition Can Accelerate the Development of CNS-Active Drugs

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ABSTRACT

Introduction: Despite the small sample sizes typically included in early phase clinical trials, strategic design and use of pharmacodynamic measures can greatly assist to characterize a new drug entity early in the clinical development stages. Assessing safety and potential efficacy early in development can identify what future studies may be needed to support drug approval. In certain cases, such study data can be instrumental in supporting waivers of dedicated studies.

Design: Evaluating a more in depth pharmacological profile of a drug can help uncover important benefits of safety and efficacy that can be further investigated in larger late stage trials and serve as important product differentiation features. Various validated models and measures can be included as early as in first-in human studies to provide meaningful data.

Objectives: This poster will review various models related to pain and other psychiatric conditions, including testing batteries of cognition, memory, attention, psychomotor function and pain/analgesia. A customized approach for each of the major therapeutic areas will be reviewed.

Conclusions: The selection of appropriate models requires an evaluation of a drug's targeted indication, mechanism of action and pharmacology. The use of models within a clinical trial requires consideration of staff/subject training, consistency of administration, controlled environment and frequency of administration.

INTRODUCTION

- Subjective and objective measures of drug effects can evaluate pharmacological activity, adverse events, and potential markers related to efficacy.
- Strategic design and use of pharmacodynamic (PD) measures (Table 1) can assist to:
  - Characterize new drug entities early in the clinical development stage
  - Identify studies that may be needed to support drug approval
  - In certain cases, PD data can be instrumental in supporting waivers of dedicated studies
- PD models can be used to assess psychiatric (eg, anxiety, depression, schizophrenia, and psychosis) and neurologic conditions (eg, pain, Alzheimer's disease, neurocognitive decline, and ADHD).

NEUROSCIENCE EXPERIMENTAL MODELS

- Neuroscience animal models are crucial for the examination of the neural circuits implicated in human brain disorders (eg, anxiety, depression, schizophrenia).
  - Mice engage in strong anxiety-like behaviors (eg, self-grooming, urination) when exposed to stressors (eg, novelty, bright light, social confrontation)
  - Fear conditioning in rats: measure fear response, anxiety, and memory
  - Forced swim test: assess depressive behavior in rodents

Limitations

- Cannot fully capture:
  - Feelings of sadness, guilt, or suicidal ideation
  - Cognitive-based symptoms of psychiatric conditions
- Behavioural responses can reflect changes in general activity.
- Low correlation between different behavioural responses taken in the same test, or the same responses measured in different tests.

Recommendation

- Consider a development program that includes animal models with translational value (direct or indirect) to human situations.

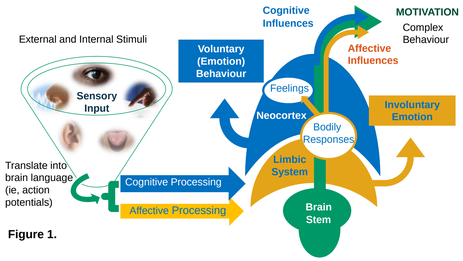

Figure 1.

PHARMACODYNAMIC MEASURES

Study Design

- **Key Considerations**
  - Reliability/replication
  - Dose-response
  - Accurate measurement
  - Subject enrichment
- Collecting accurate data on emotional responses, feelings, and cognitive abilities can provide valuable insights into the effectiveness of study drugs aimed to treat psychiatric or neurologic conditions.

- **Challenge**
  - Elucidating brain functions depends on the nuanced interpretation and understanding of complex behaviours.

- **Solution**
  - Clarify terminology to avoid interchangeable use of concepts that reflect different neurocognitive processes (eg, emotions *vs.* feelings).

Emotions

- Emotions physical and instinctive, prompt instant bodily reactions (eg, threats, rewards, etc.)
- Activated through brain-released neurotransmitters and hormones.
- Objective measures of physiologic (bodily) reactions
  - Pupil dilation (eye tracking)
  - Skin conductance (electrodermal activity [EDA] or [GSR])
  - Brain activity (EEG, fMRI)
  - Heart rate (ECG)
  - Facial expressions (fMRI)

Feelings

- Feelings the conscious experience of emotional reactions (ie, output of the brain perceiving and assigning a particular meaning to an emotion)
  - Originate in the neocortex and are shaped by personal experiences, beliefs, memories, and thoughts associated with a particular emotion.
- Can be measured using self-reporting tools
  - Interviews or surveys
  - Questionnaires (eg, anxiety inventory, depression inventory)
  - Self-rating scales (eg, visual analogue scales)

- **Bias potential**
  - Reliance on explicit subject responses
  - Reflect the cortical interpretation of sub-cortical processes

Cognition

- Generally interpreted as providing objective assessment of major cognitive domains
  - Language
  - Complex attention
  - Learning and memory
  - Executive function
  - Perceptual-motor function
  - Social cognition
- Cognitive variables (Figure 1)
  - Reaction times
  - Response accuracy (eg, correct words recalled)
  - Number of errors

Figure 1. Illustration of Cognitive Measures, Cambridge Cognition Software

- **Error potential**
  - Insufficient cognitive effort

PSYCHIATRIC AND NEUROLOGICAL CONDITIONS

CO_2 Model of Anxiety and Depression

- Validated cross-species models can help us better understand the etiology of neuropsychiatric disorders and assist in developing targeted treatment options.
- Cross-Species model requirements:
  - Same experimental stimulus
    - High levels of CO_2 promote a panic state in animal and human subjects (Figure 2)
  - Same outcome measurements
  - Quantitative data comparison shows corresponding effects across species

Figure 2. CO_2 Anxiety Model Illustration

Scopolamine Model of Cognitive Impairment

- Potent anticholinergic agent (antagonism) of acetylcholine at muscarinic (M1) receptors.
- Associated with memory, attention, information processing, and perceptual deficits similar to those present in schizophrenia and dementia.
- Induces transient schizophrenia-like symptoms ie, positive symptoms (eg, perceptual changes, delusions), negative symptoms (eg, blunted affect, emotional withdrawal), and cognitive deficits (eg, working memory).
  - Reversible cognitive and perceptual impairments in healthy volunteers.

Study Design

- Scopolamine: 0.4 mg, subcutaneous
- PD measures
  - Objective (cognitive): divided attention, choice reaction time, digit vigilance, and working memory
  - Subjective (behavioural): Visual Analogue Scale (VAS) for dry mouth, nausea, restlessness, confusion, drowsiness, and blurred vision.
- Timepoints: pre-dose and 0.5, 1.5, 3, 4, 6, 8/10 hours post-dose

Ketamine Model of Psychosis

- Phencyclidine derivative (antagonism of N-methyl-D-aspartate (NMDA) receptors resulting in glutamatergic dysfunction).
  - Associated with reversible perceptual and cognitive impairments in healthy volunteers.

Study Design

- Ketamine IV 0.3 mg/kg (dose equivalent to 60 mg IN) — 10 minutes infusion
- PD measures:
  - Objective (cognitive): spatial working memory — pre-dose and 1, 2, 4, 6, 8, 12, 24 hours post-dose
  - Subjective (behavioural): Bowdle VAS (psychedelic effects) — pre-dose and 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24 hours post-dose

Table 1. Examples of Pharmacodynamic Measures

Measure	Cognitive and Behavioral Domains
Simple and choice reaction time	Basic attention, psychomotor processing speed, selective attention
Divided attention	Divided attention, visual-motor coordination, processing speed
Digit vigilance	Sustained attention, reaction time
Digit symbol substitution test	Visual scanning, working memory, speed of information processing
Spatial working memory	Visual perception, working memory, strategy
Sternberg short-term memory	Learning, non-verbal memory, short-term storage capacity
Delayed word recognition	Verbal recognition and memory retrie,val speed
Hopkins verbal learning test, revised	Learning, semantic memory, immediate/delayed recall, recognition
Pupillometry	Pupil diameter (autonomic nervous system
Balance platform	Postural stability, body sway
Rating scales, questionnaires, VAS	Emotional states and desires, theory of mind

PAIN MODELS

Allodynia
Pain due to a stimulus that does not normally provoke pain

Hyperalgesia
An increased response to a noxious stimulus, caused by sensitization of peripheral nociceptors (primary hyperalgesia: the area of tissue injury) and/or by sensitization of central neurons (secondary hyperalgesia: outside the area of the original tissue injury)

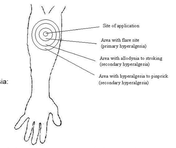

Figure. Illustration of hyperalgesia; manifested locally (primary hyperalgesia) and by central sensitization (secondary hyperalgesia), for example, after freeze injury or 30 minutes after application of capsaicin

Mechanical Stimulation

- Used to evaluate the effects of clonidine, oxycodone, morphine, mepivacain, bupivacain, gabapentin, carbamazepine, and amitriptyline.
- Activates both low threshold mechanoreceptors and nociceptors, non-specific
- Measures tactile sensitivity; surrogate marker of allodynia in states of peripheral and/or central sensitization
- Mechanical stimulation:
  - Touch, pin prick, balloon distention (Viscera), and pinch (eg, Von Frey hair, pin prick)

Cons: testing standardization and consistency

Thermal Stimulation

Heat

- Primary hyperalgesia on site of exposure and secondary allodynia, hyperalgesia in adjacent tissue
- Secondary hyperalgesia decreased by systemic opioids, gabapentin, ketamine, depending on route.
- Non-replicated efficacy in acetaminophen, adenosine (IV), glutamate receptor antagonist, and hyperbaric oxygen; lidocaine delayed response; steroids yielded conflicting results; NSAIDs (IV but not other routes)
- injury through application of heat (eg, thermodes, UVB)
  - Thermodes at ~47 °C applied for 5-7 minutes to a 9-16 cm^2 hairy skin contact area
  - Brief thermal stimuli increased temperature from 32-45 °C; hyperalgesia tested after 3 minutes at 45 °C
- Maximum effect at 75 minutes; duration 3 to 72 hours

Pros: good consistency, efficiency
Cons: high cost thermodes, skin injury mitigation steps

Cold (eg, cold pressor test, topical menthol, freeze injury)

- Cold pain mediated by nociceptors of cutaneous veins via activation of A-delta and C-fibres
- Can be used for diagnosing fibromyalgia or opioid-induced hyperalgesia
- Sensitive to imipramine, paroxetine, morphine, codeine, tramadol, and oxycodone
- Cold pressor test
  - Submersion of hand/forearm into cold water (1-5 °C, Figure 3)
  - Measures of pain thresholds and tolerance

Cons: requires standardization, responses affected by vascular reactions

Figure 3. Cold Pressor Task Illustration

Chemical Stimulation

Capsaicin

- Alkaloid found in pepper; induces intense burning sensations
- Agonist effect on transient receptor potential vanilloid-1 (TRPV1) ion channel receptors
- Surrogate model inducing secondary hyperalgesia responsive to some analgesic mechanisms of action
  - Gabapentinoids, SC/IV opioids, NMDA receptor antagonists (IV ketamine, ethanol), lidocaine-abated ID capsaicin hyperalgesia
  - Sodium channel blockers (lamotrigine, mexiletine had little/no effect)
  - Non-replicated studies showed positive results with hydrocortisone, adenosine, and clonidine
- Administration:
  - Topically (heat sensitization procedure, Figure 4)
  - Intra-dermal injection (central sensitization)

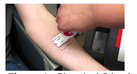

Figure 4. Chemical Stimulation Illustration

Electrical Stimulation

eg, electrical stimulation of skin, muscle viscera, etc.

- Excitation of nerve fiber populations dependent on stimulus intensity; C-fibers have higher activation threshold than A-delta
- Direct effect on fibers and therefore not specific to activation of nociceptors
- Used as supportive diagnostic tool for various neurological diseases
- Studies performed on opioids, tricyclic antidepressants, and NSAIDS
- Transcutaneous Electrical Nerve Stimulation (TENS)
- Electrical stimulators applied to either skin surface of intracutaneous tissue

Cons: higher variability; costly

CONCLUSIONS

- Models and PD tests can be useful for evaluating pharmacology, proof-of-concept, and safety early in drug development.
- Consider drug development programs that rely on validated translational models.
- Incorporating PD tests measuring different neuroscience domains (ie, physiologic, subjective, cognitive) can enhance the understanding of neuropsychiatric conditions and facilitate the development of curative treatments.
- Use clear terminology.
- Experienced sites are required to ensure consistency and reproducibility of testing conditions

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DISCLOSURES

Dr. Milovan, Ph.D. and Dr. Setnik, Ph.D. are employees of Altasciences

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