COGNITION: THE NEXT FRONTIER

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OPENING THOUGHTS

• “If we address the patient as a whole, they get better as a whole”
• “By questioning, we become aware and advance our thought process and views of the world”
• “The best preparation for tomorrow is to do today’s work superbly well” - Sir William Osler

LEARNING OBJECTIVES

• Appreciate the numerous receptors implicated in cognition and memory
• Understand the meaning and importance of cognition in psychiatry
• Apply a receptor knowledge to need for and selection of multi-modal pharmacological agents
• Reflect on the ethical and adherence issues surrounding these agents

OUR PREMISE AND PROMISE...

• To get the right drug to the right person at the right time for the right condition with a minimum of adverse effects, which requires balancing patient, psycho/social, transmitters, neurotransmitters of the medication AND patient. At the same time addressing ultimate risk-benefit for the patient, blending in lifestyle pre and post illness, all filtered through patient-driven objectives.

THERAPEUTIC THOUGHT PROCESS (TTP)

PHARMACY AUGMENTING MEDICINE
GENERAL APPROACHES TO DRUG THERAPY

WHAT MATTERS TO THEM?

- Severity of mental and/or physical pain
- Impact on awareness
- Drug allergies (intolerance vs. hypersensitivities vs. allergy)
- Other concurrent medications (Rx and Non Rx)
- Medical conditions
- Polymorphisms
- Compliance factors
- Cost
- TAIDCC

FIRST INGREDIENT...THE TTP

- T – therapeutics
- A – accuracy/allergies
- I – interactions
- D – duplication
- C – compliance/consent
- C – cost

NEUROANATOMY AND COGNITION

ROOT CAUSE ANALYSIS

BASIC ANATOMY

POSSIBLE STRUCTURAL MECHANISMS

- Specific neuronal pathways – unknown
- Reticular Formation and its connections (main sites of arousal and attention)
- Dorsal tegmental pathway projecting from mesencephalic reticular formation to the tectum and the thalamus
  - Metabolic (e.g., hepatic encephalopathy)
  - Structural (e.g., traumatic brain injury, stroke)
POSSIBLE STRUCTURAL MECHANISMS (2)

• Disrupted blood-brain barrier - Neurotoxic agents and inflammatory cytokines enter the brain (Contrast-enhanced MRI)

• Visual-perceptual deficits in delirium (hallucinations and delusions) – not due to cognitive impairment
  • Visual hallucinations (alcohol-withdrawal delirium) - polymorphisms of genes coding for dopamine transporter and catechol-O-methyltransferase (COMT)

THIS IS COGNITION…

COGNITION FOR TAXI DRIVERS…

NEUROTRANSMISSION AND COGNITION

ROOT CAUSE ANALYSIS

DOMAINS

WHAT IS COGNITION?

• Series of mental activities
• Ability and speed of processing information
  • Receive and transmission of signals
• Bio-psycho-social
  • Work
  • Home
  • Social
  • School
WHAT IS COGNITION? (2)

- Overall impacts on functionality
- Medication adherence
- Insight and awareness of body gestalt
- Care and self-care
  - Negative spiraling
  - Burden
    - Financial
    - Family
    - Self and Caregivers

HOW DO WE MEASURE COGNITION?

- Executive Performance Test: Functionality
- Verbal Fluency Test
- Clock Drawing Test
- Mini-Cognitive Assessment Instrument
- Mini-Mental State Examination (MMSE)
- Montreal Cognitive Assessments (MoCA)
- Confusion Assessment Test (CAM)
- Digit Span Tests (Auditory, Visual, Symbol)

MoCA

One-page
10 minutes to administer
Assesses delayed verbal memory, executive function, picture naming, orientation, construction, concentration and abstraction
www.mocatest.org

CAM

Acute Onset or Fluctuating
  No
  CAM -ve
  Inattention
    No
    CAM -ve
    Disorganized
      No
      Yes
      Altered LOC
      CAM +ve
    No
    Yes

WHAT DISEASE STATES NEGATIVELY IMPACT COGNITION?

- Disease States
  - Alzheimer’s
  - Dementia
  - Delirium
  - Psychosis and other psychiatric/affective
  - Insomnia
  - Psychiatric
  - Neuro auto-immune
  - ABI
  - Other medical (CA, HTN, DM, CVD)
  - Post-ictal
  - Encephalitis

METABOLIC DISORDERS

- Hepatic encephalopathy
- Wilsons disease
- Uremia
- Hypoxia (congestive heart failure, COPD, anemia)
DEFICIENCY DISEASES

- Wernicke-Korsakoff syndrome (thiamine)
- Megaloblastic anemia (vitamin B12, folate)
- Pellagra (niacin)

ENDOCRINE DISORDERS

- Thyroid disease (hypothyroidism, thyroid storm)
- Hypercalcemia (parathyroid)
- Cushing’s disease
- Pancreatic disease (diabetic ketoacidosis, hypoglycemia)

TOXINS (EXOGENOUS)

- Drugs of abuse: Amphetamines, Cocaine, Alcohol, LSD
- Prescription drugs: bromides, steroids, reserpine, methyltdopa, L-dopa, propranolol, scopolamine, atropine
- Industrial toxins: lead, mercury, manganese, carbon monoxide, organic solvents, heavy metals

CEREBRAL INFECTIONS

- Chronic meningitis (tuberculosis, cryptococcosis)
- Viral meningitis
- Syphilis (tertiary)
- Creutzfeldt-Jakob disease (slow virus)
- Acquired immunodeficiency syndrome

SYSTEMIC INFECTIONS

- Septicemia
- Bronchial pneumonia
- Urinary tract infection and Urosepsis
- Malaria
- Viremia

NEOPLASMS

- Any size
- Any type
- Metastases
- Non-Metastatic Phenomena
- Teratomas
- Space occupying lesions
MEDICATIONS AND COGNITION

ROOT CAUSE ANALYSIS

MEDICATIONS AND COGNITION

EXCITATORY AND INHIBITORY NEUROTRANSMITTERS

<table>
<thead>
<tr>
<th>Inhibitory</th>
<th>Excitatory</th>
</tr>
</thead>
<tbody>
<tr>
<td>GABA</td>
<td>Glutamate</td>
</tr>
<tr>
<td>Serotonin</td>
<td>Epinephrine</td>
</tr>
<tr>
<td>Glycine</td>
<td>Norepinephrine</td>
</tr>
<tr>
<td>Taurine*</td>
<td>PEA</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Histamine</td>
</tr>
<tr>
<td>Agmatine</td>
<td>Aspartic Acid</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Dopamine</td>
</tr>
<tr>
<td>Glycine</td>
<td>Glycine</td>
</tr>
</tbody>
</table>

*Neuromodulator

MAJOR NEUROTRANSMITTERS IN THE BODY

<table>
<thead>
<tr>
<th>Neurotransmitter</th>
<th>Role in the Body</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylcholine</td>
<td>A neurotransmitter used by the spinal cord to control muscle and by many neurons in the brain to regulate memory. It is excitatory.</td>
</tr>
<tr>
<td>Dopamine</td>
<td>The neurotransmitter that produces feelings of pleasure when released by the brain reward system. It usually inhibitory.</td>
</tr>
<tr>
<td>GABA (gamma-aminobutyric acid)</td>
<td>The major inhibitory neurotransmitter in the brain.</td>
</tr>
<tr>
<td>Glutamate</td>
<td>The major excitatory neurotransmitter in the brain.</td>
</tr>
<tr>
<td>Glycine</td>
<td>A neurotransmitter used mainly by neurons in the spinal cord. It probably mimics the effect of inhibitory neurotransmitter.</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>Norepinephrine acts as a neurotransmitter and a hormone. In the peripheral nervous system, it is part of the fight-or-flight response. In the brain, it acts as a neurotransmitter regulating normal brain processes.</td>
</tr>
<tr>
<td>Serotonin</td>
<td>A neurotransmitter involved in many functions including mood, appetite, and sensory perception. It is excitatory in some areas and inhibitory in others.</td>
</tr>
</tbody>
</table>

ACETYLCHOLINE

- Critical neurotransmitter
- Factors supporting this hypothesis:
  - Anticholinergic medications are a well-known cause of acute confusional states
  - Patients with impaired cholinergic transmission (Alzheimer disease) susceptible
  - Postoperative delirium – Serum anticholinergic activity is increased
DOPAMINE

- Brain – Reciprocal relationship between cholinergic and dopaminergic activities
- Factors in support:
  - Increased dopaminergic activity
  - Antipsychotics help in improving delirium

SEROTONIN

- Increased Serotonin:
  - Hepatic encephalopathy
  - Septic delirium
  - Hallucinogens (LSD) act as agonists at the site of serotonin receptors
  - Serotonergic agents can cause delirium

GAMMA-AMINOBUTYRIC ACID (GABA)

- ↑d inhibitory GABA levels – Hepatic encephalopathy
- ↑ Ammonia levels (hepatic encephalopathy) → ↑ in glutamate and glutamine (precursors to GABA)
- ↓ CNS GABA levels:
  - Benzodiazepine withdrawal
  - Alcohol withdrawal

CORTISOL AND BETA-ENDOPHINS

- Disruption of cortisol and beta-endorphin circadian rhythms
  - Possible hypothesis for delirium caused by exogenous glucocorticoids
  - Confluence with pain medications
  - Stress mechanisms
  - Diurnal changes in cognition
  - Diurnal changes in medications
  - Glucocorticoids are 3A4 inducers

INFLAMMATORY MECHANISMS

- Cytokines (Interleukin-1 and Interleukin-6)
- Interleukin-1 (endogenous pyrogen) released from cells:
  - Infection
  - Inflammation
  - Toxins
- Interleukin-1 & Interleukin-6:
  - Head trauma
  - Ischemia
  - Linkages to depression

WHAT RECEPTORS ARE IMPLICATED IN COGNITION?

- GABA
- 5-HT₆, 5-HT₇, 5-HT₉a
- 5-HT₁₂a, 5-HT₁₂c
- 5-HT₁₆a, 5-HT₁₆c
- H₁ receptors, H₃ receptors
WHAT RECEPTORS ARE IMPLICATED IN COGNITION? (2)

- Acetylcholine nicotinic receptors, Acetylcholine muscarinic receptors (muscarinic $M_1$)
- $D_1$, $D_2$, $D_3$
- NMDA receptors, Glycine site on the NMDA receptor
- Metabotropic glutamate receptors (mGluRs)
- mGluR2
- mGluR3

Adrenergic receptors
- $\alpha_1$ receptors

MEDICATIONS ASSOCIATED WITH COGNITIVE CHANGES

- Rule of thumb: Beers Criterion
- Antihistamines
- Antiarrhythmics (Digitalis)
- Antihypertensives
- Antidepressants
- Antimicrobials (Penicillin, Cephalosporins, Quinolones)
- Sympathomimetics
- $H_2$ blockers - Yes, ranitidine is implicated

MEDICATIONS ASSOCIATED WITH COGNITIVE CHANGES

- Opioids/ Narcotics - especially meperidine
- Psychoactive drugs - Lithium included
- Metoclopramide
- NSAIDs
- Cimetidine
- Gravol
- Sleeping medications (Nytol)
- Cough and cold remedies
- Herbal preparations

DRUGS WITH ANTICHOLINERGIC ACTIVITY

<table>
<thead>
<tr>
<th>AA &gt; 15 pmol/mL</th>
<th>AA 5 to 15 pmol/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>Chlorpromazine</td>
</tr>
<tr>
<td>Atropine</td>
<td>Diphenhydramine</td>
</tr>
<tr>
<td>Clozapine</td>
<td>Nortriptyline</td>
</tr>
<tr>
<td>Dicyclomamine</td>
<td>Olanzapine</td>
</tr>
<tr>
<td>L-hyoscyamine</td>
<td>Oxxybutynin</td>
</tr>
<tr>
<td>Thoridazine</td>
<td>Paroxetine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AA &lt; 5 pmol/mL</th>
<th>AA only at highest concentrations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>Amoxicillin, Levofoxacin, Cephalaxin</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>Citalopram</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Doxepin</td>
</tr>
<tr>
<td>Lithium</td>
<td>Diphenoxylate</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>Donepezil</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Duloxetine</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>Fentanyl, Hydrocodone</td>
</tr>
<tr>
<td>Temazepam</td>
<td>Furosemide</td>
</tr>
<tr>
<td></td>
<td>Lansoprazole, Metformin</td>
</tr>
<tr>
<td></td>
<td>Phenytoin, Topiramate</td>
</tr>
<tr>
<td></td>
<td>Phosphoramide</td>
</tr>
</tbody>
</table>

WHAT COGNITIVE ENHANCERS ARE CURRENTLY AVAILABLE?

- One of the most common forms of dementia is Alzheimer’s Disease (AD)
- In the early stages, patients often present with small difficulties in recalling new information
- As the disease progresses, patients will experience a gradual deterioration of memory and spatial orientation
- Changes in personality, mood, and behavior will also develop, as well as a decreased ability to function on a daily basis
- In general, a decade after initial diagnosis, patients often have lost many of their basic functions (e.g., motor control)
WHAT COGNITIVE ENHANCERS ARE AVAILABLE? (2)

- NMDA receptor antagonist
  - Memantine
- Cholinesterase inhibitors (ChEIs)
  - Donepezil
  - Galantamine
  - Rivastigmine
  - Tacrine (USA)

- Of note, proposed pathophysiology of alzheimers is the amyloid and tau hypotheses in which protein aggregates form in the brain a patient with AD

CHOLINESTERASE INHIBITORS

Dual Mechanism of Action

WHAT COGNITIVE ENHANCERS ARE AVAILABLE? (3)

- Of note, proposed pathophysiology of alzheimers is the amyloid-b proteins and tau hypotheses in which protein aggregates form in the brain a patient with AD
- Regional neurodegeneration
- Subsequent cognitive decline
- Neuropsychiatric disturbances
- These proposed disease pathways are still being investigated, as well as a number of drugs with mechanisms connected to two pathways

WHAT COGNITIVE ENHANCERS ARE AVAILABLE? (BUT WE HADN’T THOUGHT ABOUT THEM!)

- Back to receptor basics
- Why do antipsychotics work?
- Are all atypicals alike?
- Version 2.0-3.0
- Which one work best for cognition
- Why?
- NMDA antagonists
- Impact of Glycine
- The Serotonin Story

ATYPICAL ANTIPSYCHOTICS AND AFFINITIES

| Drug | DL | Dr | D1 | D2 | D3 | D4 | H1 | H2 | H3 | 5HT1A | 5HT1B | 5HT2A | 5HT2B | 5HT3 | 5HT4 | 5HT6 | Serotonin | Dopamine | GABA | NMDA |
|------|----|----|----|----|----|----|----|----|----|-------|-------|-------|-------|-------|-------|-------|________|________|______|_______|
| Aripiprazole | ++ | ++ | ++ | ++ | ++ | ++ | +  | ++ | +  | ++   | ++   | ++   | ++   | ++   | ++   | ++   | ++     | ++     | ++   | ++     |
| Olanzapine | ++ | ++ | ++ | ++ | ++ | ++ | +  | ++ | +  | ++   | ++   | ++   | ++   | ++   | ++   | ++   | ++     | ++     | ++   | ++     |
| Quetiapine | ++ | ++ | ++ | ++ | ++ | ++ | +  | ++ | +  | ++   | ++   | ++   | ++   | ++   | ++   | ++   | ++     | ++     | ++   | ++     |
| Ziprasidone | ++ | ++ | ++ | ++ | ++ | ++ | +  | ++ | +  | ++   | ++   | ++   | ++   | ++   | ++   | ++   | ++     | ++     | ++   | ++     |
| Paliperidone | ++ | ++ | ++ | ++ | ++ | ++ | +  | ++ | +  | ++   | ++   | ++   | ++   | ++   | ++   | ++   | ++     | ++     | ++   | ++     |
| Ziprasidone canola | ++ | ++ | ++ | ++ | ++ | ++ | +  | ++ | +  | ++   | ++   | ++   | ++   | ++   | ++   | ++   | ++     | ++     | ++   | ++     |
| Ziprasidone | ++ | ++ | ++ | ++ | ++ | ++ | +  | ++ | +  | ++   | ++   | ++   | ++   | ++   | ++   | ++   | ++     | ++     | ++   | ++     |

*Table 3: Common Cognition Receptors and Common Atypical Antipsychotic Affinities (Ki)*

**Note:** Higher affinity indicates a lower binding affinity.

### ATYPICAL ANTIPSYCHOTICS AND AFFINITIES (2)

**Table 3: Common Cognition Receptors and Atypical Antipsychotic Affinities (Ki)**

| Drug | DL | Dr | D1 | D2 | D3 | D4 | H1 | H2 | H3 | 5HT1A | 5HT1B | 5HT2A | 5HT2B | 5HT3 | 5HT4 | 5HT6 | Serotonin | Dopamine | GABA | NMDA |
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ATYPICAL ANTIPSYCHOTICS AND AFFINITIES (3)

Symbols refer to binding affinity (Ki):
Over 1000nM: Minimal or no receptor affinity: -0
100-1000nM: ++
1.0nM: ++++
<0.1nM: High receptor affinity: ++++

Legend: * Also acts as an H2 antagonist
PA: Partial Agonist
%: No labial affinity
LA: Long Acting Injectable Formulation (USA and/or Canada)

COGNITION: THE ANTIPSYCHOTIC AND LAI STORY

• Agents of choice?
  - Selection based on receptor affinity
  - Adverse effects based on receptor affinity (Better correlation)

• LAI usage and cognition

• Impact on adherence?

• Cost of non-adherence?

WHAT AGENTS MAY BE EMERGING AS COGNITIVE ENHANCERS?

• Other drugs under development and investigation are targeting pathways involved in:
  - Neuroinflammation,
  - Mitochondrial dysfunction, and
  - Neuroprotection
  - Receptor specificity

WHAT IS THE COST OF NON-ADHERENCE IN COGNITION?

• Poor compliance is often defined as adhering to <70% of the medications prescribed over the last week
• Baseline cognitive abilities significantly impact medication adherence
  - Accessing medications
  - Understanding prescribed directions
  - Scheduling and adjusting
  - Continuous access to medications via refills
  - Ability to determine what to do when a dose is missed

WHAT IS THE COST OF NON-ADHERENCE IN COGNITION? (2)

• Suspicion and entrenchment
• Treatment resistance
  - MIC Concept of receptor resistance
  - Up- or down-regulation
• Neurobiological changes
  - Hippocampal atrophy
• Discontinuation Syndrome
• FINISH

ETHICAL CHALLENGES SURROUNDING ENHANCING COGNITION

• Moral Concerns
  - “Smart Pills”
  - “Brain Boosters”
• Definition of Enhancement vs Treatment
• Advancing one’s abilities
  - Cognitive pharmacological enhancement
  - “Oxandrolone for the nerds”
• Does pharmacological enhancement remove or create obstacles to fair and equal opportunity?
QUESTIONS