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…

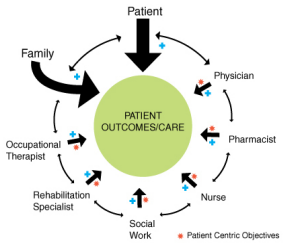
- To get the right drug to the right person at the right time for the right condition with a minimum of adverse effects, which requires balancing patient, psycho/ social, transmitters, neurotransmitters of the medication AND patient. At the same time addressing ultimate risk-benefit for the patient,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

THERAPEUTIC THOUGHT PROCESS (TTP)

PHARMACY AUGMENTING MEDICINE

CPCCM MODEL

FIGURE 1
Conceptulization of the Collaborative Patient/Person - Centric Care Model



Lamoure, J. et al. EPub March 2011. Canadian *Healthcare Network*.

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**

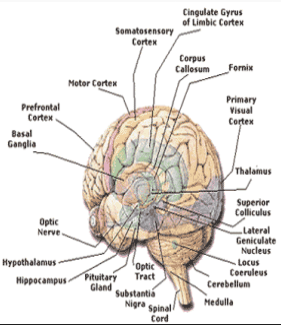
FIRST INGREDIENT…THE TTP

- 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

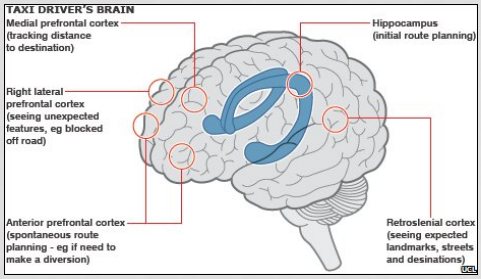
- Specific neuronal pathways – unknown
- Reticular Formation and its connections (main sites of arousal and attention)
- Dorsal tegmental pathway projecting from mesencephalic reticular formation to the tectum and the thalamus
  - Metabolic (eg, hepatic encephalopathy)
  - Structural (eg, traumatic brain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

POSSIBLE STRUCTURAL MECHANISMS (2)

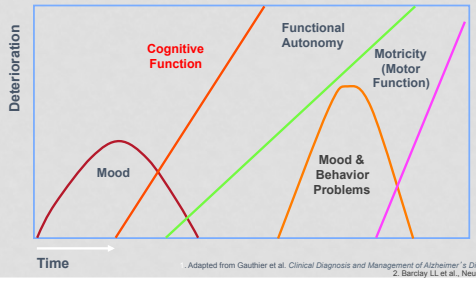
- Disrupted blood-brain barrier - Neurotoxic agents and inflammatory cytokines enter the brain (Contrast-enhanced MRI)
- Visual-perceptual deficits in delirium (hallucinations and delusions) – not due to cognitive impairment
  - Visual hallucinations (alcohol-withdrawal delirium) - polymorphisms of genes coding for dopamine transporter and catechol-O-methyltransferase (COMT)

THIS IS COGNITION…

COGNITION FOR TAXI DRIVERS…



DOMAINS



NEUROTRANSMISSION AND COGNITION

ROOT CAUSE ANALYSIS

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)

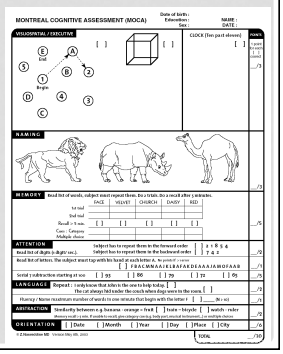
- Overall impacts on functionality
- Medication adherence
- Insight and awareness of body gestalt
- Care and self-care
  - Negative spiraling
  - Burden
    - Financial
    - Family
    - Self and Caregivers

HOW DO WE MEASURE COGNITION?

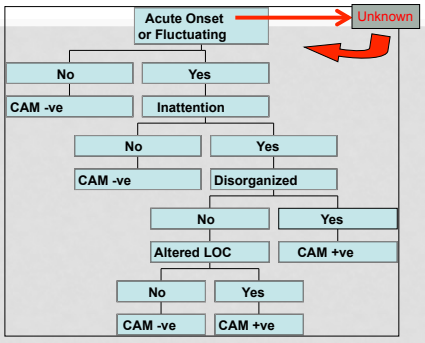
- Executive Performance Test: Functionality
- Verbal Fluency Test
- Clock Drawing Test
- Mini-Cognitive Assessment Instrument
- Mini-Mental State Examination (MMSE)
- Montreal Cognitive Assessments (MoCA)
- Confusion Assessment Test (CAM)
- Digit Span Tests (Auditory, Visual, Symbol)

MoCA

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



CAM



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, methyldopa, 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

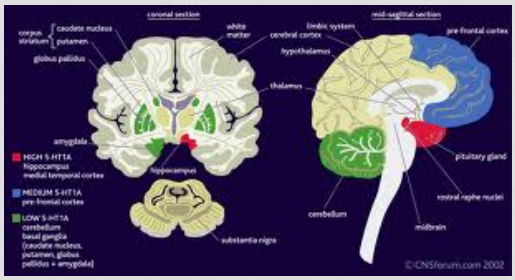
NEOPLASMS

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

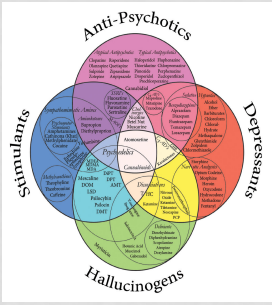
MEDICATIONS AND COGNITION

ROOT CAUSE ANALYSIS

MEDICATIONS AND COGNITION



MEDICATIONS AND COGNITION (2)



EXCITATORY AND INHIBITORY NEUROTRANSMITTERS

Inhibitory	Excitatory
GABA	Glutamate
Serotonin	Epinephrine
Glycine	Norepinephrine
Taurine*	PEA
Dopamine	Histamine
Agmatine	Aspartic Acid
	Dopamine
	Glycine

*Neuromodulator

MAJOR NEUROTRANSMITTERS IN THE BODY

Neurotransmitter	Role in the Body
Acetylcholine	A neurotransmitter used by the spinal cord neurons to control muscles and by many neurons in the brain to regulate memory. In most instances, acetylcholine is excitatory.
Dopamine	The neurotransmitter that produces feelings of pleasure when released by the brain reward system. Dopamine has multiple functions depending on where in the brain it acts. It is usually inhibitory.
GABA (gamma-aminobutyric acid)	The major inhibitory neurotransmitter in the brain.
Glutamate	The most common excitatory neurotransmitter in the brain.
Glycine	A neurotransmitter used mainly by neurons in the spinal cord. It probably always acts as an inhibitory neurotransmitter.
Norepinephrine	Norepinephrine acts as a neurotransmitter and a hormone. In the peripheral nervous system, it is part of the flight-or-flight response. In the brain, it acts as a neurotransmitter regulating normal brain processes. Norepinephrine is usually excitatory, but is inhibitory in a few brain areas.
Serotonin	A neurotransmitter involved in many functions including mood, appetite, and sensory perception. In the spinal cord, serotonin is inhibitory in pain pathways.

NIH Publication No. 00-4877

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
- Serotoninergic 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-ENDORPHINS

- 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-HT_6 , 5-HT_7 , 5-HT_{7A}
- 5-HT_{2A} , 5-HT_{2C}
- 5-HT_{1A} , 5-HT_{1C}
- H_1 receptors , H_3 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

- α_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

AA > 15 pmol/mL

- Amitriptyline
- Atropine
- Clozapine
- Dicyclomamitriptyliine
- Doxepin
- L-hyoscyamine
- Thioridazine
- Tolterodine

AA 5 to 15 pmol/mL

- Chlorpromazine
- Diphenhydramine
- Nortriptyline
- Olanzapine
- Oxybutynin
- Paroxetine

DRUGS WITH ANTICHOLINERGIC ACTIVITY (2)

AA < 5 pmol/mL

- Citalopram
- Escitalopram
- Fluoxetine
- Lithium
- Mirtazapine
- Quetiapine
- Ranitidine
- Temazepam

AA only at highest concentrations

- Amoxicillin, Levofloxacin, Cephalexin
- Celecoxib
- Diazepam
- Digoxin
- Diphenoxylate
- Donepezil
- Duloxetine
- Fentanyl, Hydrocodone
- Furosemide
- Lansoprazole, Metformin
- Phenytoin, Topiramate
- Propoxyphene

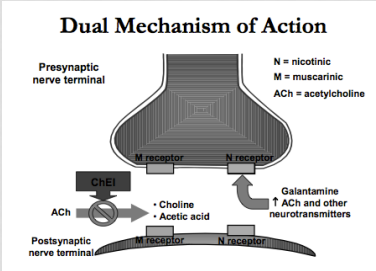
WHAT COGNITIVE ENHANCERS ARE CURRENTLY AVAILABLE?

- 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



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	D2 Antag.	D2 PA	D3	5HT1A PA	5HT2A Antag	5HT2C	5HT7	α1	α2	NRI	SRI
Aripiprazole		+++	+++	+++	+++	++	+++				
Asenapine	+++		+++	++	++++	++++	++++	+++	+++		
Clozapine	++		+	+	++	++	++	++	++		
Iloperidone	++		++	++	++++	++	+	++++	++		
Lurasidone	+++		?	+++	+++		++++	++			
Olanzapine	++		++		+++	++	+	++			
Paliperidone	+++		+++	+	++++	++	+++	+++	++		
Quetiapine	++		+	+	+	+*	+	+++	+	++*	
Risperidone	+++		+++	+	++++	++	+++	+++	++		
Ziprasidone	+++		++	++	++++	++++	+++	+++		++	+

Binding affinities based on data from the National Institutes of Mental Health Psychoactive Drug Screening Program online Ki database. +Ki≥100nM; ++Ki≥10nM; +++ Ki≥1nM; ++++ Ki <1nM. Note that a higher Ki is indicative of a lower binding affinity.

ATYPICAL ANTIPSYCHOTICS AND AFFINITIES (2)

Table 3: Common Cognition Receptors and Atypical Antipsychotic Affinities (K_i) [12,35-43]

Drug/Receptor	D2	D3	5HT2a	5HT2c	5HT7	Alpha1	Alpha2c	H1	M1
Clozapine	+	+	+++	++	++	+++	++	+++	+++
Olanzapine/LAI	++	++	+++	++	+	++	+	+++	+++
Paliperidone/LAI	+++	+++	++++	++	+++	+++	++	++	-
Quetiapine	+	+	+	+	+	+++	+	+++	+
Risperidone/LAI	+++	+++	++++	++	+++	+++	++	++	-
Ziprasidone	+++	+++	++++	++++	+++	+++	+	+	-
Lurasidone	+++	?	+++	0	++++	++	0	-/0	-
Asenapine	+++	++++	++++	++++	++++	+++	+++	+++*	-
Aripiprazole/LAI	+++PA	+++	+++	++	+++	++	++	++	-

Lamoure J. Optimizing Cognitive Functionality in Severe Mental Illness. An Evidence-Informed Medicine Clinician Primer. CMI:Psy 2013: In review

ATYPICAL ANTIPSYCHOTICS AND AFFINITIES (3)

Symbols refer to binding affinity (Ki):

Over 1000nM: Minimal or no receptor affinity: -/0
100-1000nM: +
10-100 nM: ++
1-10nM: +++
<1nM: High receptor affinity: ++++

Legend: * Also acts as an H2 antagonist
PA: Partial Agonist
0: No listed affinity
?: Unknown
LAI: Long Acting Injectable Formulation (USA and/or Canada)

Lamoure J. Optimizing Cognitive Functionality in Severe Mental Illness. An Evidence-Informed Medicine Clinician Primer . CMI:Psy 2013: In review

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