Neuropharmacology in Rehabilitation and Beyond
A Practical Review By Dr Robin Sekerak
Conceptualization of Neuropharmacology in Brain Injury
"There are things we know that we know. There are known unknowns. That is to say there are things that we now know we don't know. But there are also unknown unknowns. There are things we do not know we don't know”.

Who said it?
Donald Rumsfeld

Who said it first?
Who said it best?
“We see what we are looking for, we look for what we know, and what we don’t know we never see.”

- Goethe

"You ain't gonna learn what you don't want to know"

- Jerry Garcia, The Grateful Dead
The Brain is the most complex system in the Universe – Koch and Laurant
Disorders of the Brain are complex and defy nosological classification.
Disorders of neurobiological impairment

• **Down’s Syndrome** (trisomy 21) – reduced brain volume: smaller volumes in frontal and temporal areas and cerebellum. Reduced dendritic spines and synapses. K Gardiner, 2010

• **Schizophrenia** – Hypodopaminergic activity in the mesocortical system - negative symptoms. Hyperdopaminergic activity in the mesolimibic system – positive symptoms. Frankenburg
  - Loss of brain volume appears to result from reduced density of axons, dendrites, and synapses that mediate associative functions of the brain.
  - Cognitive deficits — poor memory, inability to maintain attention and poor problem solving

• **Autism** – Disorders of ?: Cerebellum – animals with cerebellar disorders show perseverative behaviors and fail to attend to appropriate distractors. Bobee
  Corticocerebellar Diaschisis.
  Limbic Forebrain and medial temporal lobe – abnormalities found. Huaser

• **Depression** – Dysregulation of the Hippocampus and HPA axis. Severe stress causes changes neurons, including a reduction in dendritic arborizations. Antidepressants produce the opposite effects: they increase dendritic arborization.

• Psychiatry has focused on establishing diagnostic categories based on clinical symptoms. There is a disconnection between current psychiatric disease classifications and... biological findings, which emphasizes the need to look for neurobiological characteristics shared across diagnoses..

• The diagnostic groups included were schizophrenia, bipolar disorder, depression, addiction, obsessive-compulsive disorder and anxiety.

• Brain gray matter loss converged across diagnoses in three regions: the dorsal anterior cingulate (dACC), right insula and left insula... the common gray matter loss regions were an interconnected network during tasks and at rest and that lower gray matter in this network was associated with poor executive functioning.
Centrally acting medications with complex and varied actions are classified by the nosologic category of the symptoms they treat:

• Antidepressants treat depression
• Antipsychotics treat psychosis
• Mood stabilizers treat emotional reactivity
• Neurostimulants.....well, they stimulate the neuro.
“If you’ve seen one brain injury, you’ve seen one brain injury.”
– The problem with neuropharmacology in brain injury

“Unlike other neurologic disorders, traumatic brain injury is the most heterogeneous” – Dr Joseph Giacino
Evidenced based medicine helps us see the forest for the trees. But sometimes we can’t see the tree in the forest.
There is not a single FDA-approved drug for the treatment of cognition or behavior in acquired brain injury.
Persons with TBI are often very sensitive to the effects of a medication and to the side effects. Even though they may require average or high doses. Idiosyncratic and “paradoxical” reactions are not uncommon.
“Neuropsychiatric problems are more prevalent and longer-lasting in TBI patients than in the general population. About 40% of TBI victims suffer from two or more psychiatric disorders, and a similar percentage experience at least one unmet need for cognitive, emotional, or job assistance 1 year after injury”.

- Vaishnavi, 2009
### Common Psychiatric Symptoms in TBI

**Neurobehavioral or neurocognitive symptom**

<table>
<thead>
<tr>
<th>Psychiatric Symptom</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aggression</td>
<td>30%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>10-70%</td>
</tr>
<tr>
<td>Apathy</td>
<td>10%</td>
</tr>
<tr>
<td>Cognitive Impairment</td>
<td>25-70%</td>
</tr>
<tr>
<td>Depression</td>
<td>25-50%</td>
</tr>
<tr>
<td>Mania</td>
<td>1-10%</td>
</tr>
<tr>
<td>Psychosis</td>
<td>3-8%</td>
</tr>
</tbody>
</table>

Vaishnavi, S 2009
Neuropharmacology in Brain Injury - fuzzy logic

• Centrally acting medications act on complex functional systems, not on anatomic areas or unitary psychiatric disorders.
• They do not act directly on higher cortical functions or affective disorders but on neurotransmitters, receptors and transporters in these functional systems, through synaptic and nonsynaptic transmission.
• Medications have primary and secondary effects: 1 – affect levels of monoamines. 2 – through modification of receptor dynamics, protein synthesis, gene expression, collateral sprouting; normalize neurobiological functions and improve the brain’s adaptive capacity.
• In efforts to restore or normalize brain function. Changes in synaptic strength are believed to be the basis for learning and memory.
The Neurotransmitter Basis for Neuropharmacology.

- Glutamate is an amino acid used at fast excitatory synapses in the brain. It is also used at most synapses that are "modifiable", i.e. capable of increasing or decreasing in strength. Modifiable synapses are thought to be the main memory-storage elements in the brain. Excessive glutamate release can overstimulate the brain and lead to excitotoxicity causing cell death.

- GABA is a monoamine used at the great majority of fast inhibitory synapses in virtually every part of the brain. Many sedative/tranquilizing drugs act by enhancing the effects of GABA.

- Acetylcholine operates in many regions of the brain, using nicotinic and muscarinic receptors. It is involved in arousal (wakefulness and attention), emotion, learning, motor system function, short-term memory, reward perception (minor role), and Long term depression (LTD).

- Dopamine is a monamine transmitter in the brain: cognitive control and working memory (co-regulated by norepinephrine), mood, motivation, motor system function, reward perception (primary mediator).

- Serotonin is a monoamine neurotransmitter. It functions to regulate appetite, sleep, memory and learning, temperature, mood, behaviour, muscle contraction, and function of the cardiovascular system and endocrine system. It is speculated to have a role in depression.

- Norepinephrine is a monoamine neurotransmitter. It is involved in anxiety, arousal (wakefulness and attention), circadian rhythm, cognitive control and working memory (co-regulated by dopamine), hunger, medullary control of respiration, negative emotional memory, reward perception.

- Neurotransmitters, Wikipedia
Basic Tenets of Neuropharmacology in TBI

- Know what you are treating (best educated guess).
- Think of the causes and other potential treatments.
- **MAKE SURE YOU ARE NOT TREATING ANOTHER MEDICATION.**
- Requires an interdisciplinary approach to the correct diagnosis and the correct treatment. And, at the correct time.
- Enhance adaptive neuroplasticity, avoid maladaptive neuroplasticity. Timing may be important.
- Patient and family centered.
- Be part of the rehab team and the conversation. Hear what they are saying and what the family is saying.
- Talk to your colleagues.
- Review case studies. **DO CASE STUDIES. APPLY METRICS BEFORE AND AFTER INTERVENTION** when able.
- Multi-modal approach. An adjunct to other treatments.
- Think about secondary benefits – Can I hit more than one bird with this stone - as well as potential side effects.
- Start low go slow.
- Polypharmacy may be a good thing – lower dose has fewer side effects, multiple receptors/pathways.
- ECG at baseline, and....
The “SYMPTOMS” we want to address

- Hypoarousal
- Hyperarousal
- Cognitive Dysfunction: Impaired attention, Impaired processing speed, Impaired memory, Executive Function
- Fatigue
- Mood disorders: Depression/anxiety
- Mania
- “Agitation”
- Aggression
But we also have

- Apathy/Abulia
- Disorders of sleep
- Nausea
- Headaches/pain
- Urinary problems – incontinence and retention
- Anorexia/hyperphagia
- Constipation
The Medications

• What they are supposed to do
• What else do they do
• What you may not want them to do
• Side effects
• Drug-drug interactions
• What not to use
Placebo-Controlled Trial of Amantadine for Severe Traumatic Brain Injury

Joseph T. Giacino, Ph.D., John Whyte, M.D., Ph.D., Emilia Bagiella, Ph.D., Kathleen Kalmar, Ph.D., Nancy Childs, M.D., Allen Khademi, M.D., Bernd Eifert, M.D., David Long, M.D., Douglas I. Katz, M.D., Sooja Cho, M.D., Stuart A. Yablon, M.D., Marianne Luther, M.D., Flora M. Hammond, M.D., Annette Nordenbo, M.D., Paul Novak, O.T.R., Walt Mercer, Ph.D., Petra Maurer-Karattup, Dr.Rer.Nat., and Mark Sherer, Ph.D.

CONCLUSIONS

Amantadine accelerated the pace of functional recovery during active treatment in patients with post-traumatic disorders of consciousness.
Review Articles of Pharmacologic Treatment in TBI for behavior and cognition.


- Pharmacological management of neurobehavioral disorders following traumatic brain injury – A state of the art review. JRRD, vol 46, 6, 2009 Chew & Zafonte


The (never say never) NEVER use medications

- Haloperidol (strong anti-dopaminergic)
- TCAs and Anticholinergics (won’t you be surprised!).
- Benzodiazepines (Gaba-ergics/gaba-mimetics)
- Meperidine
<table>
<thead>
<tr>
<th>Classic and commonly used terms</th>
<th>Proposed new terms (WPA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuroleptics (conventional antipsychotics, typical antipsychotics)</td>
<td>First generation antipsychotics</td>
</tr>
<tr>
<td>Atypical antipsychotics (serotonin-dopamine antagonists)</td>
<td>Second generation antipsychotics</td>
</tr>
<tr>
<td>Dopamine partial agonists (Aripiprazole)</td>
<td>Third generation antipsychotics</td>
</tr>
</tbody>
</table>

Mailman RB, Murthy V. *Third generation antipsychotic drugs: partial agonism or receptor functional selectivity?* Current pharmaceutical design 2010;16:488-501
The Antipsychotics
- apples and oranges

• First generation (typicals)
  Haloperidol
  Chlorpromazine
  Thioridazine
The Antipsychotics - apples and oranges

• Second Generation (Atypicals): – Stahl
  Higher HT2A activity. More specific for mesolimbic than striatal dopamine system.

• Clozapine, Olanzapine, Quetiapine
• Risperidone, Ziprasidone
• 3\textsuperscript{rd} generation: Aripiprazole,
• Others: Sulpride, Amisulpride, Sertindole, Perospirone
First Generation Antipsychotics

• D2 Antagonism

Second Generation Antipsychotics

• 5HT2A/D2 antagonism
First Generation Antipsychotics

• Higher risk of neurological side effects

Second Generation Antipsychotics

• Higher risk of metabolic side effects
Atypical Antipsychotics

D₂-Receptor Occupancy

- **Haloperidol**: 65%
- **Risperidone**: 65%
- **Olanzapine**: 80%
- **Quetiapine** (∆100):

Atypical Antipsychotics In Vivo Binding Affinities

Haloperidol

Clozapine

Risperidone

Olanzapine

Quetiapine

Ziprasidone

Casey 1994
The CATIE TRIAL
Olanzapine in other disorders – Borderline Personality Disorder

• Olanzapine has shown superiority over placebo for symptoms such as:
  – Anxiety
  – Depression
  – Anger and hostility
  – Impulsive aggression
  – Interpersonal sensitivity

• There is not convincing information suggesting that any antipsychotic agent changes the underlying character structure of patients with BPD

Tasman, A; Lieberman, J; Key, J; Maj, M. Psychiatry. 3rd ed. John Wiley & Sons, 2008
Examples of potential Anticholinergic Burden placed on our patients

<table>
<thead>
<tr>
<th>High</th>
<th>Medium</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline, atropine, benztropine,</td>
<td>Baclofen, cetirizine, desipramine,</td>
<td>Captopril, carbidopa-levodopa, clonazepam,</td>
</tr>
<tr>
<td>chlorpheniramine, chlorpromazine, cyclizine,</td>
<td>loperamide, loratadine, nortriptyline,</td>
<td>codeine, dexamethasone, diazepam, digoxin,</td>
</tr>
<tr>
<td>hyoscine (all formulations), imipramine,</td>
<td>olanzapine, prochlorperazine</td>
<td>diltiazem, dipyridamole, fentanyl, furosemide,</td>
</tr>
<tr>
<td>oxybutynin, promethazine, thioridazine</td>
<td></td>
<td>haloperidol, Isosorbide, mononitrate,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>lorazepam, methylprednisolone, metoclopramide, morphine,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>oxazepam, oxycodone, paroxetine, prednisone, pramipexole, quetiapine, ranitidine, risperidone, seligiline, temazepam, tramadol, warfarin</td>
</tr>
</tbody>
</table>
## Anticholinergic Burden

**Table 3**
Commonly Prescribed Drugs with High Anticholinergic Activity

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-arrhythmics</td>
<td>Dextroamphetamine, Diphenhydramine (present in Tylenol)</td>
</tr>
<tr>
<td>Disopyramide</td>
<td>PM and other over-the-counter formulations</td>
</tr>
<tr>
<td>Anticholinergic Antiparkinsonian Agents</td>
<td>Hydroxyzine</td>
</tr>
<tr>
<td>Benztrpine</td>
<td>Promethazine</td>
</tr>
<tr>
<td>Biperiden</td>
<td>Trihexyphenidyl</td>
</tr>
<tr>
<td>Orphenadrine</td>
<td>Gastrointestinal Antispasmodics</td>
</tr>
<tr>
<td>Trihexyphenidyl</td>
<td>Belladonna alkaloids (sennosides and others)</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>Clinidium (present in Librax, which also has chlordiazepoxide)</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>Dicyclomine</td>
</tr>
<tr>
<td>Mesoridazine</td>
<td>Diphenoxylate</td>
</tr>
<tr>
<td>Thoridazine</td>
<td>Hyoscymine</td>
</tr>
<tr>
<td>Antitussives</td>
<td>Propantheline</td>
</tr>
<tr>
<td>Detromethorphan (present in Mucufen DM)</td>
<td>Mydriatics</td>
</tr>
<tr>
<td>Antivertigo Medications and Medications for Motion Sickness</td>
<td>Atropine</td>
</tr>
<tr>
<td>Dimenhydrinate</td>
<td>Homatropine</td>
</tr>
<tr>
<td>Meclizine</td>
<td>Tropicamid</td>
</tr>
<tr>
<td>Scopolamine patch</td>
<td>Opioid Analgesics</td>
</tr>
<tr>
<td>Drug Combinations</td>
<td>Meperidine</td>
</tr>
<tr>
<td>Donnatal (atropine, hyocyamine, scopolamine, phenobarbital)</td>
<td>Tertiary-Amine Tricyclic Antidepressants</td>
</tr>
<tr>
<td>Librax (clinidium and chlordiazepoxide)</td>
<td>Amitriptyline</td>
</tr>
<tr>
<td>Limbitrol (chlordiazepoxide and amitriptyline)</td>
<td>Clomipramine</td>
</tr>
<tr>
<td>Triavil (perphenazine and amitriptyline)</td>
<td>Doxepine</td>
</tr>
<tr>
<td>First-Generation H₁ Antihistaminics</td>
<td>Imipramine</td>
</tr>
<tr>
<td>Brompheniramine</td>
<td>Trimepramine</td>
</tr>
<tr>
<td>Chlorpheniramine</td>
<td>Cytroheptadine</td>
</tr>
</tbody>
</table>

*These medications should be used with extreme caution in the elderly and avoided in frail elderly and elderly with cognitive impairment.

Cognitive Effects of Anticholinergics

• Strongest Evidence Yet' Links Anticholinergic Drugs, Dementia  Sue Hughes, Medscape, January 27, 2015

• Just 2 Months' Exposure to Anticholinergics Affects Cognition  Pauline Anderson, Medscape May 22, 2013

• Pain Patients at Cognitive Risk From Anticholinergic Burden?  Pauline Anderson, Medscape, April 15, 2013

• A younger population may manifest CNS events..cognitive changes, dizziness, somnulence, sedation.  Staskin 2007

• M1- cognitive impairment, memory loss. (M2 – increase heart rate, prolonged QT, M3 – constipation, blurred vision, dry mouth).
Other Anticholinergic side effects

- Acute confusional state
- Delerium
- Memory Problems
- Decreased sweating
- Hyperthermia
- Decreased salivation/dry mouth
- Urinary retention
- Constipation
- Sinus tachycardia/QT prolongation/arrhythmias
- Blurred vision
- Narrow angle glaucoma
- Worsening of reactive airway disease
Antiemetics and the injured brain

**Highly anticholinergic:**
Cyclizine, Dimenhydrinate, Meclizine, Promethazine, Trimethobenzamide

**Antidopaminergic:**

**Metoclopramide** - 2009, the Food and Drug Administration (FDA) required a Black Box warning regarding the increased risk of tardive dyskinesia when metoclopramide is used at high doses or over long periods of time. Over 1000 lawsuits for Tardive Dyskinesia.

- may occasionally cause bradyarrhythmias progressing to cardiac arrest, paroxysmal SVT, hypotension, circulatory collapse, QT prolongation, Torsade de Pointes, heart block, and hypotension in patients without evidence of underlying functional or structural cardiac abnormalities

**Prochlorperazine**

**Preferred:**
Ondansetron
Granisetron
Dolasetron
The Antidepressants
TCAs


• **Nortriptyline** – less side effects than amitriptyline, most studies do not support a difference in action

• **Trazadone** - efficacious for sleep maintenance difficulties, its associated cognitive and motor impairments. It produced small but significant impairments of short-term memory, verbal learning, equilibrium and arm muscle endurance across time-points in normal subjects, mean age 44, dose 50mg. Roth et al.
The Antidepressants: SSRIs

SSRI’s

**Fluoxetine** – long half life, activating, least selective serotonin reuptake inhibitor - norepinephrine reuptake, dopamine reuptake, serotonin-2C receptors. Associated with highest rate of anxiety and agitation. Least associated with weight gain. Drug-drug interactions cytochrome P450 2D6, cytochrome P450 3A4

**Sertraline** – supported in TBI literature. The second most potent inhibitor of serotonin reuptake and the second most selective blocker of serotonin over noradrenaline uptake, dopamine reuptake (more potent dopamine uptake inhibitor than other SSRIs), norepinephrine reuptake, minimally increases sleep efficiency and reduces nocturnal wakefulness time, which may benefit patients with sleep disturbances.

**Paroxetine** – Short half life. Discontinuation syndrome. *most potent blocker of muscarinic receptors among the SSRIs* - higher rate of anticholinergic effects, such as dry mouth, constipation, and cognitive disruption. Highest rate of sexual dysfunction. Highest associated weight gain.

**Citalopram** – few drug-drug interactions. Prolonged QT at higher doses. most selective serotonin reuptake inhibitor - may be less effective than others. Associated with low rates of insomnia, anxiety, and other activating side effects.

**Escitalopram** – more rapid onset of action than Citalopram. most selective serotonin reuptake inhibitor - may be less effective than others. Associated with low rates of insomnia, anxiety, and other activating side effects.
The Antidepressants: SNRIs and others

• **Venlafaxine** – NE/5HT inhibitor. More NE inhibition at higher doses > 150mg. Weakly blocks Dopamine reuptake. Better side effect profile than TCAs. Improves neuropsychological deficits in attention, memory, psychomotor speed, processing speed, and executive function in depression. 2\textsuperscript{nd} line therapy in Migraine (excellent combo with Metoprolol) and tension-like HAs, adjunctive pain medication in pain disorders. Used as 2\textsuperscript{nd} line tx in ADHD.

• Risks: Can induce mania if bipolar not previously recognized. Serotonin syndrome. Serotonin withdrawal symptoms – treat with fluoxetine or B blocker.

• **Duloxetine** – NE/5HT inhibitor. More balanced NE/5HT. Weakly blocks dopamine reuptake. May be better for pain. Risks similar.
SSRI, SNRI potential side effects

- Apathy
- Agitation
- Anergia
- Akasthias
- GI upset, nausea, anorexia
- Sexual dysfunction
- Weight gain
- Serotonin (5-HT) Syndrome – with MAOI or short interval between tx. Increased risk with carbamazapine, dextromethorphan, TCAs, sumatriptan, pentazocine
Risks associated with commonly used medications in TBI treatment

Table 4

Clinical Presentation of Serotonin Syndrome and Differential Diagnosis

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Serotonin Syndrome</th>
<th>NMS</th>
<th>Anticholinergic Delirium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tachycardia</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hypertension</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Muscle rigidity</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Hyperthermia &gt;41.1°C</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Hyperreflexia</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Myoclonus</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Shivering</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Acute onset</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Restlessness, confusion, agitation</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Bowel sound</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

NMS: neuroleptic malignant syndrome; +: present; −: not present.
Source: Reference 2.