Central Nervous System PRN Focus Session—Management of the Patient with Traumatic Brain Injury
Activity No. 0217-0000-11-102-L01-P (Knowledge-Based Activity)

Tuesday, October 18
3:30 p.m.–5:30 p.m.
Convention Center: Rooms 317 & 318

Moderator: Michele Y. Splinter, Pharm.D., BCPS
Clinical Associate Professor, University of Oklahoma College of Pharmacy, Oklahoma City, Oklahoma

Agenda

3:30 p.m.	Emerging Treatment—Bench to Bedside *Sunita Dergalust, Pharm.D., BCPS* Clinical Pharmacist, Neurology/Neurosurgery, West Los Angeles VA Healthcare Center, Los Angeles, California
4:20 p.m.	Treatment of the Neurobehavioral Sequelae of TBI *Stacia R. Wilhelm, Pharm.D., BCPS* Clinical Coordinator, Craig Hospital, Englewood, Colorado
5:10 p.m.	Panel Discussion *Sunita Dergalust, Pharm.D., BCPS* *Stacia R. Wilhelm, Pharm.D., BCPS*

Faculty Conflict of Interest Disclosures

Sunita Dergalust: no conflicts to disclose.
Stacia R. Wilhelm: no conflicts to disclose.

Learning Objectives

1. Review current standards and practices on the clinical management of TBI in the acute setting.
2. Evaluate promising intervention strategies for treatment of TBI.
3. Interpret results of recent pharmacological trials.
4. Recognize cognitive deficits associated with TBI and assess pharmacotherapy to treat these deficits.
5. Recognize behavior disturbances associated with TBI and formulate an appropriate treatment plan.

Self-Assessment Questions

Self-assessment questions are available online at *www.accp.com/am*

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Pharmacologic Treatment of Neurobehavioral Effects of Traumatic Brain Injury

Stacia Wilhelm, Pharm.D., BCPS

The presenter has no actual or potential conflict of interest in relation to this program.

Objectives

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- Recognize cognitive deficits associated with TBI and assess pharmacotherapy to treat these deficits
- Recognize behavior disturbances associated with TBI and formulate an appropriate treatment plan

Craig Hospital

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- Specialty rehabilitation of TBI and SCI patients
- Ranked in the Top 10 rehabilitation hospitals by *U.S. News & World Report* for over 20 years
- Federally designated as a Model Systems Center for both TBI and SCI research
- TBI National Statistical Database

TBI Model Systems

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- Funded by National Institute on Disability and Rehabilitation Research (NIDRR)
- Partner with VA, DOD, and NIH
- Currently 16 TBIMS centers
- Systematically collect data for research analysis
- Stimulate more rigorous research

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Guidelines for the Pharmacologic Treatment of Neurobehavioral Sequelae of Traumatic Brain Injury

Warden DL, Gordon B, McAllister TW, et al. Guidelines for the pharmacologic treatment of neurobehavioral sequelae of traumatic brain injury. *J Neurotrauma*. 2006;23:1468-1501

Evidence Based Practice

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Standards	Guidelines	Options
Based on at least 1, well-designed class I study with adequate sample OR overwhelming class II evidence	Based on well-designed class II studies	Based on class II or class III studies with additional grounds to support a recommendation

Obstacles to Developing Standards of Care

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- Heterogeneity of patient population
  - Individual injury
    - Neuroanatomy
    - Neurophysiology
    - Neurochemistry
  - Variability of brain function
    - Pre-morbid brain function
    - Post-traumatic sequelae

Obstacles to Developing Standard of Care

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- Variable responses to medications
  - Some patients benefit
  - Some patients get worse
  - Some patients more sensitive
  - Some patients resistant or need extreme doses
- Compliance issues
  - Memory
  - Adverse effects and interactions

Obstacles to Developing Standards of Care

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- Measuring cognition and behavior
  - Patient may test well, but function poorly
  - Patient may test poorly, but function well
- Variations in biochemistry balance
  - Serotonin
  - Dopamine
  - Acetylcholine
  - Norepinephrine

* Lack of evidence ≠ lack of efficacy *

Neurotransmitters

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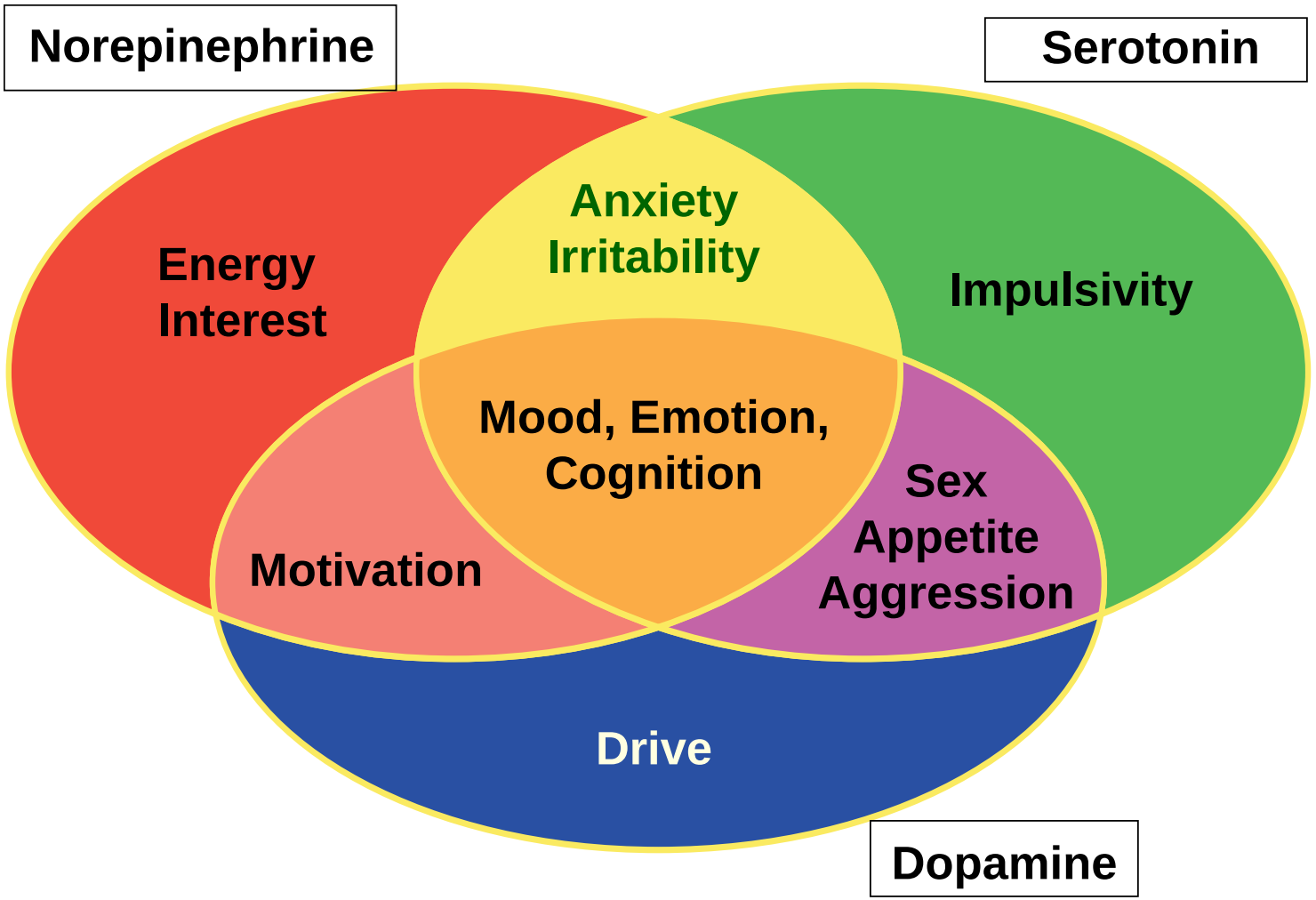
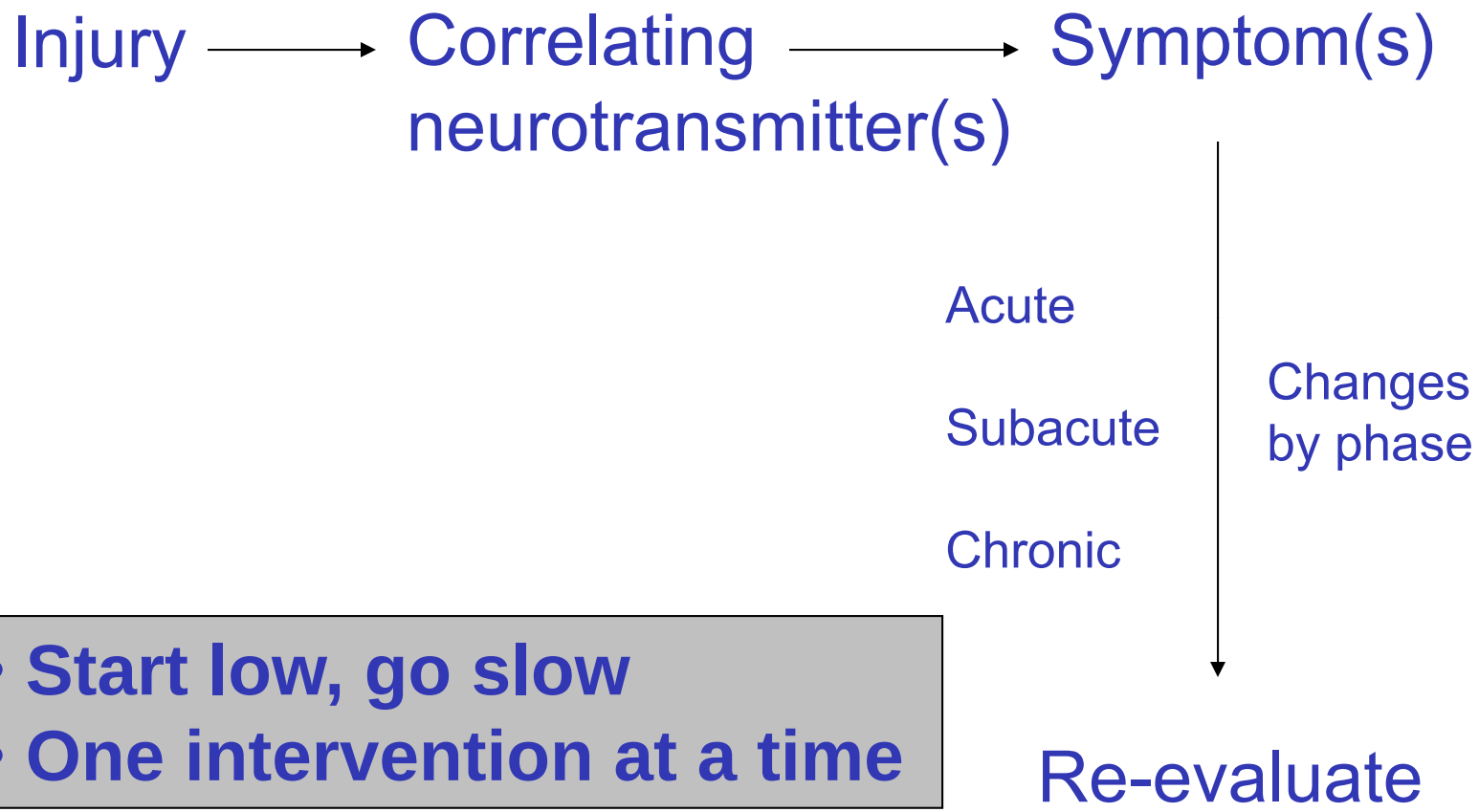
- Serotonin
  - Memory
  - Emotion
  - Sleep/wake
- Dopamine
  - Voluntary movement
  - Motivation
- Acetylcholine
  - Memory
  - Parasympathetic nervous system
- Norepinephrine
  - Wakefulness
  - Arousal

Neurotransmitters

- Glutamate
  - NMDA receptor
  - Cognition
  - Overstimulation → cell death
- GABA
  - Inhibitory neurotransmitter


Norepinephrine
Serotonin
Energy
Interest
Anxiety
Irritability
Impulsivity
Mood, Emotion,
Cognition
Motivation
Sex
Appetite
Aggression
Drive
Dopamine

Treatment Plan



- **Start low, go slow**
- **One intervention at a time**

Brain Injury Sequelae

- Cognitive deficiencies
  - Attention/concentration and speed of processing
  - Memory
  - Executive functions
- Behavioral
- Emotional
- Other
  - Fatigue
  - Insomnia
  - Aphasia
  - Pseudobulbar affect (PBA)

Treatment of Cognitive Deficiencies

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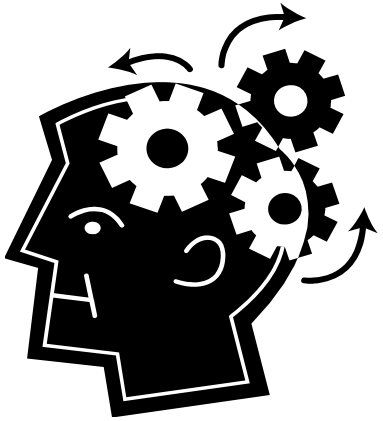
- Dopamine, acetylcholine, serotonin, norepinephrine
- No “standards”, just guidelines and options
- Dopamine enhancers
  - Bromocriptine (Parlodel®)
    - Guideline-level recommendation
    - Executive functioning
      - Divided attention
      - Initiation
      - Mental flexibility

Treatment of Cognitive Deficiencies

- Dopamine enhancers
  - Amantadine (Symmetrel®)
    - NMDA antagonist
    - General cognitive functions
    - Attention/concentration and speed of processing
    - Apathy/poor initiation
    - Motivation
    - Perseveration

Treatment of Cognitive Deficiencies

- Dopamine enhancers
  - Carbidopa/levodopa (Sinemet®), pramipexole (Mirapex®), selegiline (Eldepryl®)
    - Initiation
    - Alertness
    - Wakefulness



Treatment of Cognitive Deficiencies

- Stimulants
  - Methylphenidate (Ritalin®)
    - Dopamine and norepinephrine
    - Guideline- and option-level recommendations
    - Memory
    - Attention/concentration and speed of processing
    - Mental processing
    - Learning
    - Arousal
    - Apathy/poor initiation
    - General cognitive functions

Treatment of Cognitive Deficiencies

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- Stimulants
  - Dextroamphetamine (Dexedrine®)
    - Dopamine and norepinephrine
    - Attention
    - Working memory
  - Modafinil (Provigil®)
    - Dopamine, histamine, alpha-1 agonist, inhibits GABA
    - Attention
    - Apathy/poor initiation
    - Memory
    - Speed of processing

Treatment of Cognitive Deficiencies

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- Acetylcholinesterase inhibitors
  - Donepezil (Aricept®)
    - Guideline-level recommendation
    - Better general functioning
    - Attention/concentration and speed of processing
    - Learning
    - Memory
    - Apathy/poor initiation

Treatment of Cognitive Deficiencies

- Acetylcholinesterase inhibitors
  - Other acetylcholinesterase inhibitors
    - Galantamine (Razadyne®)
    - Rivastigmine (Exelon®)
    - Physostigmine

Treatment of Cognitive Deficiencies

- Other options
  - Memantine (Namenda®)
    - NMDA receptor antagonist
    - Cognitive function
    - Memory
  - Bupropion (Wellbutrin®)
    - Dopamine and norepinephrine reuptake inhibitor
    - Cognitive function

Treatment of Cognitive Deficiencies

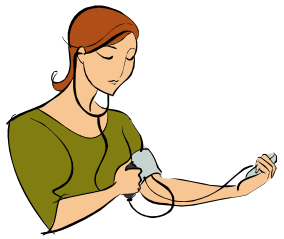
- Other options
  - Atomoxetine (Strattera®)
    - Selective norepinephrine reuptake inhibitor
    - Attention (lower doses)
    - Memory
    - Arousal (higher doses)
    - Apathy/poor initiation
    - Speed of processing

Self-Assessment Question

- A 51 y/o female involved in a MVA resulting in diffuse axonal injury is experiencing deficits in wakefulness, arousal, purpose, and initiation. An appropriate neurotransmitter target for pharmacotherapy includes:
  - A. Glutamate agonist
  - B. GABA agonist
  - C. Dopamine agonist
  - D. Dopamine antagonist

Treatment of Aggression

- Disruption to dopamine, norepinephrine, acetylcholine, serotonin
- No standards
- Guideline-level recommendations
  - Propranolol (Inderal®)
  - Pindolol



Treatment of Aggression

- Options
  - Antihypertensives
    - Metoprolol (Lopressor®)
    - Clonidine (Catapres®)

- Options
  - Mood stabilizers
    - Carbamazepine (Tegretol®)
    - Valproic acid (Depakote®)
    - Lithium (Lithobid®)

Treatment of Aggression

- Options
  - Antidepressants
    - Sertraline (Zoloft®)
    - Paroxetine (Paxil®)
    - Fluoxetine (Prozac®)
    - Citalopram (Celexa®)

- Options
  - Antidepressants
    - Trazodone (Desyrel®)
    - Amitriptyline (Elavil®)
    - Desipramine (Norpramin®)
    - Protriptyline (Vivactil®)

Treatment of Aggression

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- Options
  - Atypical antipsychotics
    - Risperidone (Risperdal®)
    - Clozapine (Clozaril®)
    - Olanzapine (Zyprexa®)
    - Quetiapine (Seroquel®)
    - Ziprasidone (Geodon®)
  - Stimulants
    - Methylphenidate (Ritalin®)
    - Dextroamphetamine (Dexedrine®)
- Options
  - Hormones
    - Estrogens
    - Medroxy-progesterone (DepoProvera®)
  - Others
    - Amantadine (Symmetrel®)
    - Buspirone (Buspar®)

Self-Assessment Question

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- A patient's brain CT scan shows bilateral frontal and diffuse axonal injury. He is impulsive and agitated. The best option for pharmacologic treatment of his agitation is:
  - A. Haloperidol
  - B. Diazepam
  - C. Diphenhydramine
  - D. Propranolol

Treatment of Psychiatric Disorders

- Serotonin, norepinephrine, dopamine
- Depression/emotional deficits
  - Antidepressants (TCA and selective serotonin reuptake inhibitors)
    - Nortriptyline (Pamelor®)
    - Amitriptyline (Elavil®)
    - Desipramine (Norpramin®)
    - Citalopram (Celexa®)
    - Escitalopram (Lexapro®)
    - Paroxetine (Paxil®)
    - Sertraline (Zoloft®)

Treatment of Psychiatric Disorders

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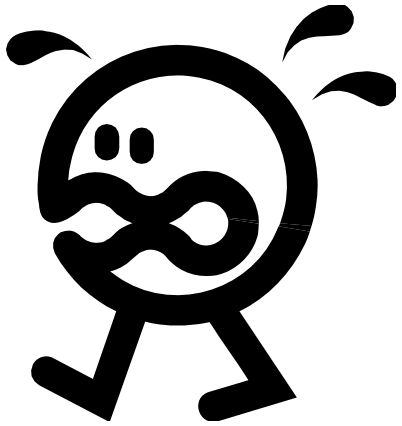
- Depression/emotional deficits
  - Venlafaxine (Effexor®), serotonin/norepinephrine
  - Atomoxetine (Strattera®), norepinephrine
  - Modafinil (Provigil®), ↓ GABA
- Bipolar disorder
  - Valproic acid (Depakote®)
  - Carbamazepine (Tegretol®)
  - Lithium
- Psychosis
  - Olanzapine (Zyprexa®)
  - Clozapine (Clozaril®)

Treatment of Psychiatric Disorders

- Anxiety
  - Tricyclic antidepressants (TCA)
  - Selective serotonin reuptake inhibitors (SSRI)
  - Benzodiazepines
    - Lorazepam (Ativan®)
    - Clonazepam (Klonopin®)
    - May interfere with cognition



Self-Assessment Question

- An obstacle to treating a TBI patient with depression includes:
  - A. The patient may be more sensitive or less responsive to medication
  - B. The patient's previous history does not contribute to current symptoms
  - C. Depression in TBI patients is not affected by neurotransmitters
  - D. Two medications should be started simultaneously

Medications for Fatigue

- Acetylcholinesterase inhibitors
- Methylphenidate (Ritalin®)
- Modafinil (Provigil®)
- Atomoxetine (Strattera®)

Medications for Insomnia

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- Trazodone (Desyrel®)
- Imipramine (Tofranil®)
- Nortriptyline (Pamelor®)
- Mirtazapine (Remeron®)
- Ramelteon (Rozerem®)

Medications for Aphasia

- Tricyclic antidepressants
  - Nortriptyline (Pamelor®)
  - Desipramine (Norpramin®)
- Increase serotonin and norepinephrine

Pseudobulbar Affect

- Uncontrollable, inappropriate affect
- Some success
  - Antidepressants (TCA, SSRI)
  - Dopaminergic agents

Pseudobulbar Affect

- Dextromethorphan/quinidine (Nuedexta®)
  - Discovered while studying different use for ALS
  - Dextromethorphan
    - Cough suppressant
    - NMDA antagonist
  - Quinidine
    - Antiarrhythmic agent
    - Slow metabolism of dextromethorphan

Side Effects

- Are sometimes “therapeutic”
- Vary among medications in each class
- Guide medication selection
- Make some medications inappropriate for brain injury patients

Medications to Use with Caution in TBI

- Benzodiazepines
  - Exacerbate confusion ("benzodiazepine psychosis")
  - Impairs memory
  - Common for insomnia and agitation
  - Stopping the medication may be the "therapeutic event"

Medications to Use with Caution in TBI

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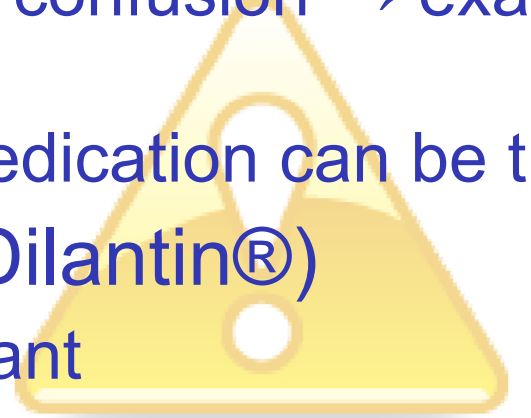
- First generation antipsychotics (Haldol®)
  - Block dopamine → interferes with recovery
  - Sedation → confusion → exacerbate aggression
  - Stopping medication can be therapeutic
- Phenytoin (Dilantin®)
  - Anticonvulsant
  - Impairs cognitive function recovery initially
  - Better alternatives for seizure prophylaxis



Self-Assessment Question

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- A TBI patient recently transferred from the ICU has been receiving haloperidol for aggressive behavior. He continues to be assaultive toward caregivers, especially at night. The best intervention would be:
  - A. Adding lorazepam PRN
  - B. Adding amantadine PRN
  - C. Increasing the haloperidol dose
  - D. Stopping the haloperidol

Self-Assessment Question

- A TBI patient with a pre-morbid history of seizure disorder is currently receiving levetiracetam and phenytoin. An intervention to facilitate cognitive recovery would be:
  - A. Stop levetiracetam and increase phenytoin dose
  - B. Stop phenytoin and add lacosamide
  - C. Add phenobarbital
  - D. Avoid making any changes to current regimen

Summary

- Obstacles to good evidence
  - Heterogeneity of patient population
  - Variable responses to medications
  - Compliance issues
  - Measuring cognition and behavior
  - Variations in biochemistry balance

Summary

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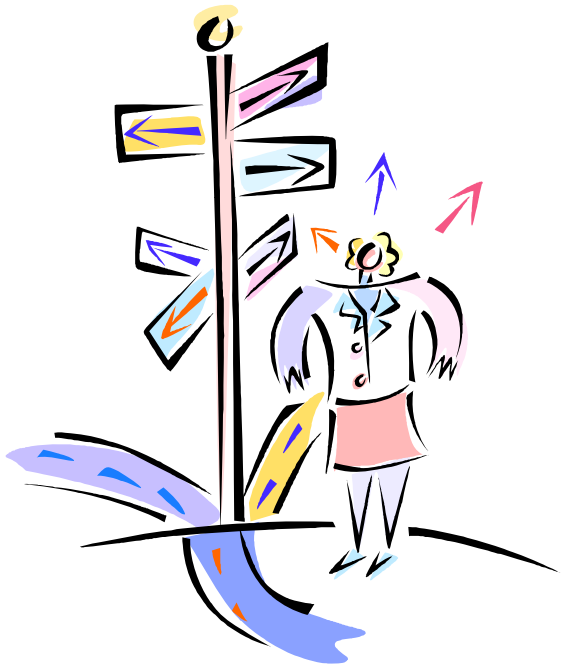
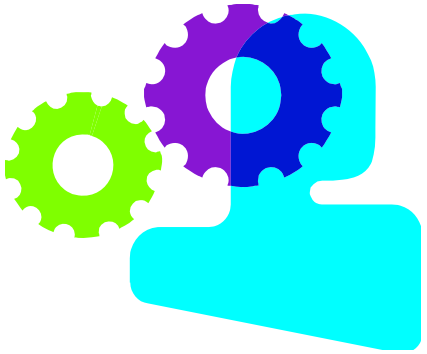
- Limited evidence
  - Few standards
  - Few guidelines
  - Lots of options

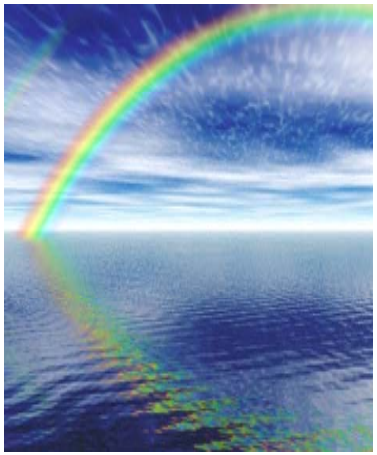


Summary

- Treatment of cognitive deficiencies
  - Dopamine enhancers
  - Stimulants
  - Acetylcholinesterase inhibitors
  - Norepinephrine reuptake inhibitor
  - NMDA antagonist



Summary



- Treatment of aggression
  - Beta blockers
  - Alpha adrenergic agonist
  - Mood stabilizers
  - Antidepressants
  - Atypical antipsychotics
  - Stimulants
  - Dopamine enhancers

Summary

- Psychiatric disorders
  - Depression
  - Bipolar disorder
  - Psychosis
  - Anxiety

- Treatment
  - TCA, SSRI
  - Mood stabilizers
  - Atypical antipsychotics
  - TCA, SSRI
- Try to Avoid
  - First generation antipsychotics
  - Benzodiazepines

Summary

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- Treatment of fatigue
  - Acetylcholinesterase inhibitors
  - Methylphenidate (Ritalin®)
  - Modafinil (Provigil®)
  - Atomoxetine (Strattera®)

Summary

- Treatment of sleep disorders
  - Trazodone (Desyrel®)
  - Imipramine (Tofranil®)
  - Nortriptyline (Pamelor®)
  - Mirtazapine (Remeron®)
  - Ramelteon (Rozerem®)

Summary

- Treatment of aphasia
  - Nortriptyline (Pamelor®)
  - Desipramine (Norpramin®)
- Treatment of pseudobulbar affect
  - Dextromethorphan/quinidine (Nuedexta®)
  - Antidepressants (TCA, SSRI)
  - Dopaminergic agents

Summary

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- Side effects to monitor
  - Sexual side effects
  - Headache, GI
  - Dizziness
  - Insomnia
  - Sedation
  - Weight gain
  - Extrapyramidal symptoms

Summary

- Medications to try to avoid
  - Benzodiazepines
  - First generation antipsychotics
  - Phenytoin (Dilantin®)

Thank you for your attention.

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Selected References

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