Implications of Stimulants on Traumatic Brain Injury

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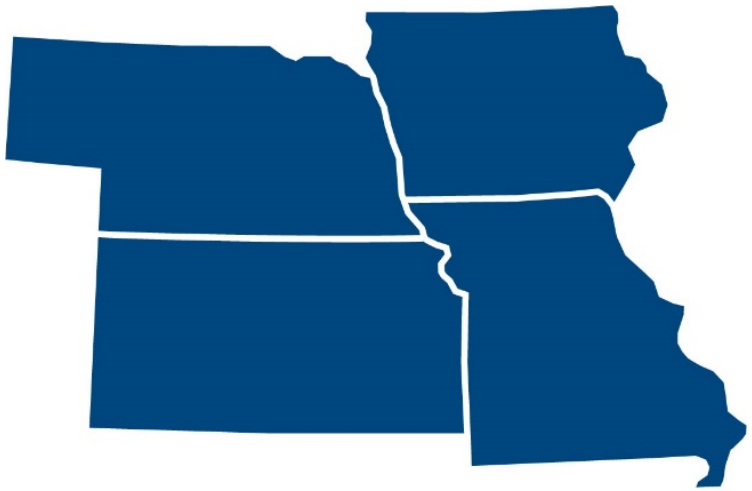

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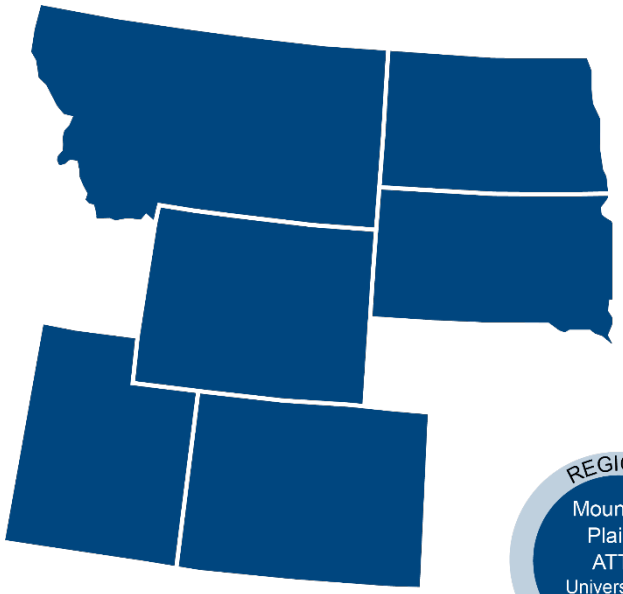

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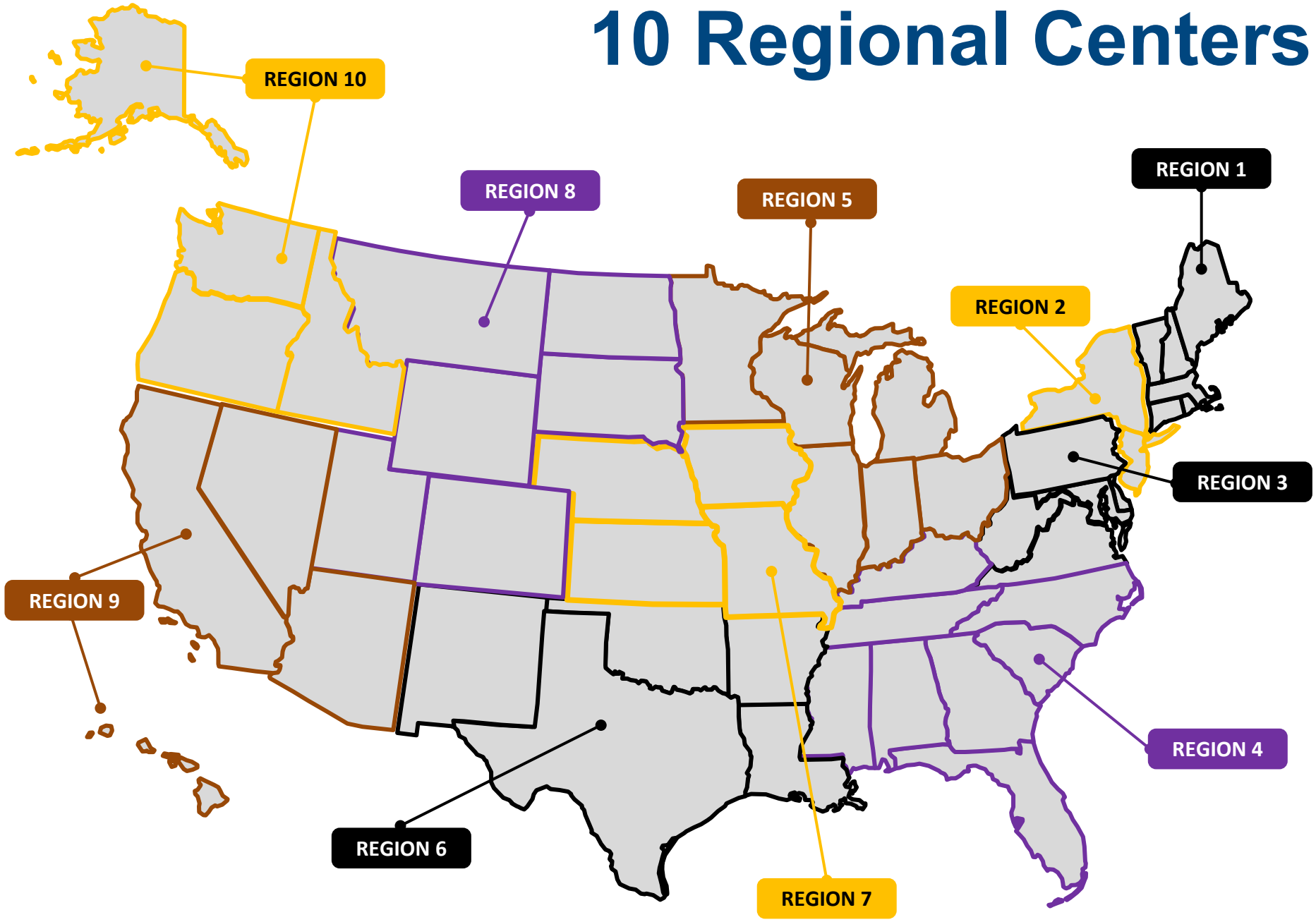
HHS Regions

10 Regional Centers



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- Iowa Board of Certification
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- NASW
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Housekeeping Items

- All attendees are muted and attendees cannot share video during this session.
- Remember to ask questions using the Q&A feature
- How to access training materials

Dr. Frank R. Sparadeo

- Practiced as a neuropsychologist for over 34 years
- Experience evaluating and treating people with people experiencing brain disorders or chronic pain, and/or addiction.
- Most recently involved in the formation of a special program in the combined problem of chronic pain and addiction
- Experience in switching patients from pain meds to suboxone
- Closely involved in the treatment of chronic pain utilizing a new theoretical approach that relies on information theory to reduce pain responses. The neuromatrix theory of pain is the basis of this treatment.

Neurobiology

Neurobiology 101

- The nerve cell
- 100 billion neurons
- Numerous types of nerve cells but most function in a similar way
- Proper functioning of the CNS depends on communication between neurons
- Cell body, dendrites, axon and terminal buttons
- Dendrites receive and conduct information to the cell body

Neurobiology: Complexity at Every Level

- Within the neuron
- A number of tiny structures responsible for moment-to-moment operation and survival of the cell.
- Each neuron receives oxygen, glucose and a host of other molecules from capillaries that like adjacent to the cell.
- Some of the more important molecules delivered to the neurons via the blood stream are amino acids, which serve as the building blocks of proteins.

Neurobiology: Cell Function

Each cell must manufacture a multitude of proteins, which are then used for many different purposes including the production of receptors, enzymes that regulate intracellur biochemical processes, growth factors and structural elements of the cell.

Each cell produces its own messenger molecules (neurotransmitters), which are secreted by the cell which then impact the next cell

Brain Organization

Brain Stem

Limbic System

Diencephalon

Basal Ganglia

Prefrontal cortex

Cortex

Hypothalamus

- The size of a pea and lies at the base of the brain
- Complex structure responsible for regulating a host of biologic functions including circadian rhythm, sleep cycles, appetite, sex drive and regulation of both the autonomic NS and most of the endocrine glands
- Serotonin, NE and DA are thought to be crucial in regulating certain aspects of hypothalamic functioning

Hypothalamus/Limbic System

Intimately connected to the structures of the limbic system and to the pituitary gland

The structures of the limbic system include:

- Amygdala, septum, cingulate and hippocampus—and this is common to all mammals
- Three primary functions of the Limbic System
- Appraisal of emotional stimuli
- Initiation of emotional responses (Fight or Flight response)
- Shutting down reactivity after external stressors have subsided (restoring to homeostasis)

Cerebral Cortex, Amygdala, Neuroendocrine System

- Incoming information is appraised by way of two main processing centers: The cerebral cortex and amygdala and the neuroendocrine system
- Cerebral cortex is highly evolved. Capable of complex information and critical thinking
- The amygdala is subcortical (below both temporal lobes) and has the capacity to register, perceive and analyze sensory data.

Information Processing

The processing of environmental stressors in the amygdala is crude

Engages in gross pattern recognition and if such patterns resemble objects or events previously associated with danger, neuronal impulses exiting the amygdala elicit a fight-or-flight response (independent of the cerebral cortex).

Room for misperception (e.g., rope = snake).

This primitive fear-appraisal system is believed to be adaptive and aids in the facilitation of survival.

Traumatic Brain Injury

When an individual experiences a TBI the initial acute medical process if focused on saving the individuals life and in less severe injuries advising the patient and family of methods of responding to the injury that will enhance recovery.

The patient is referred from the acute care hospital to a rehabilitation program. The level of care is determined by an evaluation process that addresses physical and cognitive impairments.

Patients are categorized based upon level of impairment which can be severe, moderate or mild. Often references to level of impairment are primarily focused on cognitive and functional decline from pre-injury levels.

The patient is then accepted into some type of rehabilitation program where improvement is monitored closely, and restorative therapies are administered

TBI Recovery

Regardless of the level of cognitive impairment the rehabilitation professional is focused on assisting the patient in improving cognitive status

Improving cognitive status requires knowledge of the patient's pre-injury history. Factors such as academic history, work history, emotional history and social history are important in setting goals and also keeping risk factors in mind.

TBI survivors with a substance use history are likely to return to substance use

TBI survivors with a history of LD or ADHD will be more difficult to assist than survivors without that history

Family history and current level of family functioning influences the TBI recovery process

Typical TBI Related Cognitive Impairment

In almost all TBI cases some damage or disruption occurs to the frontal lobes.

Frontal lobe damage can be manifested in numerous cognitive impairments from impulse control impairment to metacognitive impairment

It is usually the residual frontal lobe impairments that are a barrier to satisfactory long-term recovery. Frontal lobe disruption interferes with vocational rehabilitation, social skills and interpersonal relationships, goal setting, stress management, empathy, reflection and other issues.

In mild to moderate TBI it is common to see a set of cognitive weaknesses/impairments that are similar to those demonstrated by people diagnosed with ADHD.

Functions of the PFC

Regulation of Top-down Attention

Concentrate and sustain attention especially when bored

Focus on info that is important but not salient by inhibiting processing of irrelevant stimuli and enhancing relevant stimuli

Inhibits internal and external distractions

Divides and shift attention in multi-tasking

Responsible for attention regulation through its effet on the sensory cortices

Prefrontal Cortex

Prefrontal cortex is responsible for inhibition of inappropriate behavior

Can guide behavioral output by projections to the motor and the premotor cortices along with the basal ganglia and cerebellum

PFC and Behavior

The PFC is involved in the regulation of emotions

The ventromedial prefrontal cortex has projections to amygdala, hypothalamus and nucleus accumbens and weakens reactions to disinhibited aggressive impulses and emotional dysregulation

Abnormalities in the VMPFC from TBI can result in the individual engaging in antisocial behavior

Executive Network

The executive control network coordinates a set of cognitive skills that are responsible for the planning, initiation, sequencing and monitoring of complex goal-directed behavior

Following TBI this network may become underactive because of reduced functional connectivity

TBI and Attention Case Example

- The lasting effects of TBI can look amazingly similar to ADHD, leading some to wonder about a possible relationship between ADHD and TBI.

- John was a 24-year-old student evaluated for cognitive impairments after his injury. He sustained a moderate to severe TBI from a motorcycle accident. Wearing a helmet probably saved his life, but it didn't protect his brain from injury in the accident. Before his motorcycle crash, he had no major cognitive or interpersonal problems. Afterward though, he was constantly distracted, impulsive, unable to plan or organize, terrible at multitasking, and his friendships and romantic relationships became unstable or ended badly.

- Sounds like adult ADHD, right? But because of the drastic changes after his accident, we know that John's problems came from his TBI. He had no early history to suggest ADHD.

TBI/ADHD Comparisons

	Brain Injury	ADHD
IQ	Not an indicator of future performance; often a decline in selected IQ subtests related to areas of damage; changes over lifetime	Typically, average to above average; IQ stable & predictor of future performance
Cognitive Problems	Attention, memory, language comprehension, concept formation, integrating, organizing, generalizing information, problem solving, judgment, mental inflexibility	Typically, not associated with this condition; difficulties may emerge due to cumulative impact of impulsivity and inattention
Memory	Recent memory disorder with poor carryover for new learning	Inattention and poor concentration may look like memory issues
Academic Skill Levels	Some old skills remain; peaks and valleys of performance; gaps in learning	On target, but poor attention and concentration affect skills

Comparisons

	Brain Injury	ADHD
Behavior	Brain damage and memory loss decrease successful use of behavior modification strategies	Low incidence of aggression, considered secondary symptom with hyperactivity; positive response to behavior modification strategies
Social	Loss of peers; poor adaptive behaviors; egocentric; hyper/hypo sexual; basic social skills affected	Poor attention/impulsivity causes difficulty with peers; immature; lacks basic social skills
Emotions	Emotionally labile and unpredictable; often emotions do not match situations	Difficulty dealing with and expressing feelings; exhibit more depressive symptoms than typical peers
Recognition of Deficits	Recalls pre-injury status; may deny deficits; inability to recognize/accept post injury deficits or compensatory strategies	May be unaware unless pointed out; may notice change when medication is effective
Self-esteem	Lowered	Intact, lowered as failure sets in
Status Changes	Based on recovery, may be irregular but generally improving	Varied depending upon medications and appropriate accommodations
Self-Regulation	Inconsistent may require some external support	Poor unless medication is used

ADHD Treatment

- Behavioral and cognitive enhancement techniques
- Social Skills Training
- Medications
- Stimulants
- Nonstimulants – Alpha-2 Adrenergic Agonists
- Certain Anti-depressants

Medications for ADHD

- Approximately 70% response rate for stimulants
- Although stimulants are similar, there are differences. Thus, of a trial with one stimulant (e.g., methylphenidate) is less optimal, then it is advisable to conduct a trial on another stimulant (e.g., dextroamphetamine)
- If systematic trials are conducted on each of the three classes of stimulants, good outcomes are seen in about 90% of patients treated.

Cognitive Recovery Enhancement in TBI

- Enhancing cognitive recovery beyond natural recovery is the goal of every rehabilitation professional.
- It is the goal of recovery from TBI to assist the patient to maximize recovery such that the level of functioning is as close to the pre-TBI level as possible.
- In addition to formal therapies such as physical therapy, occupational therapy, recreational therapy, psychotherapy the rehabilitation team is concerned about the patient retaining the gains made in formal rehabilitation once the patient is discharged.
- In some cases, medications can be used to enhance recovery and also maintain gains made.
- In recent years Stimulant medications have been used to enhance recovery, maintain gains, assist in vocational rehabilitation, assist in mood regulation, impulse control and executive functioning.

Stimulants and Cognitive Recovery

- Although there is some substantive research suggesting that certain classes of medication may accelerate cognitive recovery or improve cognitive functioning in individuals with TBI, the data is inconsistent.
- Anecdotal reports and single case studies continue to serve as a primary foundation upon which care providers make decisions today to use these medications.
- A framework for making decisions about the use of these medications still remains to be developed, including the choice of medication versus localization of injury, time since injury, types of problems, and environmental variables.

Recent Interest in Stimulant Medications

- Methylphenidate and Amphetamine salts, marketed under the trade name Ritalin and Adderall, are used to treat millions of children with Attention Deficit Hyperactivity Disorder (ADHD).
- Though stimulants certainly can produce side effects their benefits usually outweigh liabilities.
- Stimulants increase frontal lobe activity in individuals who have difficulty developing self-regulation and self-control. Though problems in the frontal lobe, particularly the right pre-frontal cortex of people with ADHD may differ from the frontal lobe dysfunction that occurs post TBI, it is likely there is sufficient similarity between these two sets of problems to expect that stimulants would be of benefit in treating these symptoms.
- Ritalin enhances cognitive performance, including working memory and executive function.
- Psychostimulants appear to be a reasonable choice for treating certain types of mood, behavioral and cognitive symptoms following TBI. Particular problems related to faulty or inefficient self-control appear to respond best. An increasing number of studies with children and adults suffering from TBI utilizing stimulants have demonstrated their therapeutic value. Still, however, some studies do not find clinically significant results.

Drugs and Dopamine

- Drugs that impact the dopamine system in the brain, including Amantadine, Bromocriptine and Sinemet, may improve some aspects of cognitive functioning but at the expense of others.
- Medications such as the anti-hypertensives, Tenex and Clonidine, have also been reported to have mixed results in the treatment of attentional problems. Problems related to apathy and difficulty with initiation may respond to these preparations as well as to serotonin based anti-depressants such as Prozac and Zoloft.
- Anti-Parkinson medications such as Sinemet has been found to improve emotional and behavioral deficits in individuals with moderate to severe TBI.

Need for Medication Research

- An increasing body of research suggests that many medications can alleviate cognitive dysfunction following TBI and may in fact enhance recovery.
- Large scale, multi-site studies examining the use of these medications in populations of individuals with TBI has yet to be undertaken. Therefore, it is difficult to know whether using these medications today should represent the standard of care for TBI patients.
- Many children and adults with TBI whom I have evaluated and followed have benefited from these medications.
- Although there is no precise science to adjusting these medications, I have observed a number of individuals across all age ranges respond exceptionally well, particularly to Amphetamine Salts and Methylphenidate following TBI. For some the medicine is used acutely. For others, however, the medicine becomes a long-term treatment compensating for loss of and enhancing self-regulation.

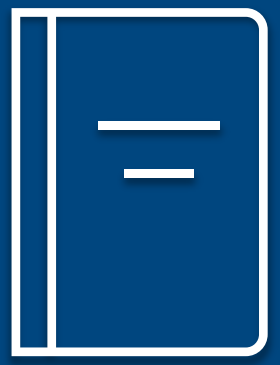
TBI: Importance of Understanding Levels of Severity

- When discussing TBI it is important to understand levels of severity as well as cognitive profiles
- Severity levels are typically stated as mild, moderate and severe as related to the cognitive and physical sequelae of the TBI.
- Cognitive profiles vary regarding areas of weakness and impairment and areas of preservation
- Such issues as fatigue, sleep disturbance, appetite disturbance, impaired initiation, impaired motivation, impaired judgment and impulsivity must all be understood before considering medications.
- The use of stimulant medications are commonly prescribed in patients with hypersomnolence or excessive fatigue following TBI and also narcolepsy.

Understanding ADHD and Medications

- It is helpful to look at the many years of experience using medications for ADHD as a way of understanding how these medications help.
- The signs and symptoms of ADHD have many similarities to the cognitive symptoms often seen in mild TBI
- Poor inhibitory control is a cardinal deficit in the developmental form of attention-deficit hyperactivity disorder (ADHD) (but it has also been reported in children who have sustained traumatic brain injury (TBI) in childhood). ADHD is a common consequence of TBI in children and has recently come to be referred to as secondary ADHD or S-ADHD

Response Inhibition

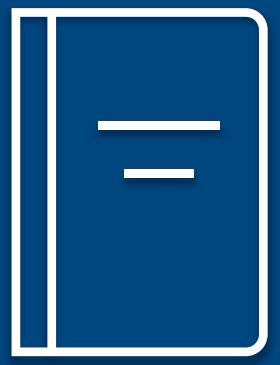


- The neurobiology of response inhibition involves frontal-striatal pathways. However, the origin of poor circuitry is different in the two groups. In children with ADHD, developmental processes have generated atypical brain structure and function in regions concerned with inhibitory control

- In children with TBI, a period of typical brain development has been interrupted by physical trauma that often includes frontal contusions. Similarity in inhibitory control in children with TBI, S-ADHD, and ADHD would implicate impaired frontostriatal systems. Conversely, perhaps TBI and/or inhibitory control performance shapes the expression of ADHD, leading to an etiologically distinct form of ADHD.

- Better understanding of the commonalities as well as the differences with regard to inhibitory (and other) processes will lead to an appreciation of the pathophysiological mechanisms with possible implications for differing (or similar) treatment approaches.

Recent Findings: Response Inhibitions



An inhibitory control deficit is demonstrated in ADHD, TBI and S-ADHD. Similar patterns of inhibitory control in childhood ADHD and TBI may be related to structural brain changes and neurochemical alterations that involve networks that affect, among other areas, the frontal lobes.

Poor voluntary response suppression in childhood may be related to perturbed neurodevelopment of, or to damage to functional connectivity in frontal subcortical circuits.

Alternatively, it may be the case that more widespread substrates subserve executive control while frontal regions continue to develop into the teenage years. Nevertheless, how frontal-striatal circuits are similar and different in ADHD and TBI is important, but not fully understood.

Response Inhibition in TBI

Recent research found that children with TBI had poor inhibitory performance irrespective of injury severity. It may be the case that the presence of cognitive impairment is perhaps a function of lesion location rather than severity per se.

Published studies suggest that injury severity involving cerebral pathology among frontal and extra-frontal brain areas contributes to problems with executive control processes, including response inhibition.

Stimulant Medications Most Used for ADHD

Stimulant medications can help manage symptoms, such as:

- Short attention span
- Impulsive behavior
- Hyperactivity
- Response Inhibition

Stimulants Ease ADHD Symptoms

- These drugs ease ADHD symptoms in about 70% of adults and 70% to 80% of children.
- They tend to cut down on hyperactivity, interrupting, and fidgeting.
- They can also help a person finish tasks and improve relationships

Issues to Consider about Stimulants

- Low risk of abuse
- Best to administer medication each day without days off
- Start treatment with immediate-release formulations and then switch to extended-release preparations, if tolerated and effective
- Stimulants work only for a short period of time, and the positive effects wear off in the late afternoon or evening.
- Co-administration of certain antidepressants may be an option for targeting symptoms later in the day.
- Most people with ADHD successfully treated with stimulants will require ongoing medication treatment will into adolescence and possibly adulthood.

How Do Stimulant Drugs Work?

- For someone with ADHD these medications boost the levels of certain brain chemicals, like dopamine and norepinephrine.

- They assist with intraneuronal communication (helps neurons in your brain talk to one another).

- If you take Stimulants for ADHD, you'll get slow and steady doses, just like your brain would create increases in dopamine and norepinephrine. That helps boost your energy, helps you pay better attention, and keeps you alert. These medications are effective in improving response inhibition.

Most Common Side Effects of Stimulants

- Initial Insomnia (if taken later in the day)
- Solution: Earlier dosing; clonidine or trazodone given at bedtime
- Anorexia: generally, affects the patient only when the drug is active (i.e., usually only interferes with appetite at lunchtime). Has not been associated with significant problems obtaining adequate nutrition. Focalin seems to have less of this effect
- Stomachache
- Solution: give with food
- Mild dysphoria
- Solution: switch classes of stimulants; add an antidepressant such as bupropion
- Lethargy, sedation, or impaired concentration; usually indicates the dose is too high

Short-acting, Intermediate-acting, and Long-acting Stimulants for ADHD

- The short-acting forms are usually taken two or three times a day, and the long-acting ones just once a day. The benefit of short-acting is that you have more control over when you have medication in your system. The downside is you have to remember to take them often.

- A positive of the long-acting type is that you don't have to remember to take them as often, usually just first thing in the morning. They may also cut down on some side effects. But it may be harder to wind down at night until you get your medication dose and timing right.

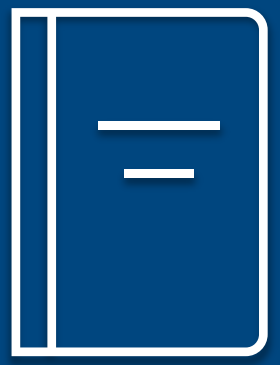
Other “Stimulants” Used to Treat Core Symptoms

- Alpha-2 Adrenergic Agonists
- Clonidine (Catapres, Kapvay) and guanfacine (Tenex, Intuniv) may be used to treat core ADHD symptoms, however they are most effective in reducing irritability, aggression and impulsivity and in promoting sedation (to treat initial insomnia)
- Alpha-2 Adrenergic Agonists combined with Stimulants is a common practice (both for treatment of ADHD and for comorbid ADHD and tics).

Alpha-2 Adrenergic Agonists

Generic	Brand Name	Typical doses
Clonidine	Catapres, Kapvay	0.15 - 0.4 mg tid or qid
Guanfacine	Tenex, Intuniv	0.25 -1.0 mg bid or tid

Amantadine



- Amantadine is a dopaminergic and NMDA-antagonist (approved by the FDA for influenza prevention and Parkinson's Disease).
- Amantadine is relatively benign side effects (assuming adequate renal function) compared to other agents
- Recent research suggests some cognitive benefit from amantadine. Notably, there is strong evidence amantadine improves rate of recovery acutely in those with prolonged disorder of consciousness. Additionally, Amantadine seems to improve executive function but not attention and memory
- Reddy et al. (2013) found 100 mg of Amantadine bid had significant improvement in verbal memory and reaction time but not for visual memory and visual motor processing speed

Antidepressants for Attention Impairment

- 20% of ADHD children and 50% of adults with TBI develop symptoms of depression.
- Certain classes of antidepressants have been shown to have positive effects on attentional impairments. Not all antidepressants treat ADHD or attentional difficulty, only those that increase the availability of dopamine or norepinephrine are useful.
- Treatment outcomes with antidepressants are not as robust as those seen with stimulants but they afford several advantages:
- Once-a-day dosing
- No need for triplicate prescription
- No addiction potential
- Clinical effects last 24 hours a day
- Can treat comorbid depression

Antidepressant Used for Attention Deficits

Generic	Brand Name	Typical doses
Bupropion	Wellbutrin SR/LA	150 – 300 mg
Atomoxetine	Strattera	1.2 – 1.8 mg/kg

Atypical Stimulant Medications

- Provigil (Modafinil) and Nuvigil (armodafinil) are oral prescription drugs to improve wakefulness in adults with excessive sleepiness associated with narcolepsy, obstructive sleep apnea and shift work disorder.

- Because these drugs increase alertness, healthy people have used them as “smart drugs” to increase mental performance and wakefulness. Working adults have also used them to work longer hours without sleeping. This type of use is not approved by the FDA and is therefore considered “off-label” use.

- The military has used these drugs to keep soldiers and pilots alert while deployed.

- There is little evidence to support the use of Provigil to improve learning and memory.

Provigil and Nuvigil

- Although Provigil and Nuvigil work in the safe way, they come in different dosages and have different chemical makeups and side effects

- The advantage of Nuvigil is the flexibility of strengths available. It allows people to start at lower doses and go to higher doses over time if needed.

- In a study comparing Nuvigil and Provigil it was found that Nuvigil blood concentrations were higher than Provigil later in the day. It was concluded that Nuvigil improved wakefulness throughout the day.

Mechanisms of Action Poorly Understood

- Provigil/Nuvigil does not involve catecholamine release or reuptake.
- There is a decrease in GABA and an increase in serotonin and glutamate levels
- Provigil/Nuvigil has a direct effect on the levels of synaptic NE and DA transporters, which have a direct impact on arousal and behavioral activity
- Provigil/Nuvigil seems to indirectly affect the extracellular levels of serotonin, glutamate, histamine, orexin and GABA
- Provigil/Nuvigil seems to be more selective for cortical than for subcortical effects
- Amphetamines tend to activate the striatum and large regions of the cerebral cortex (which are dopamine rich) while Provigil mostly activates the hippocampus, amygdala and anterior hypothalamus. This conclusion has more support in the literature.

Provigil vs. Adderall

- Although Provigil and Nuvigil have wakefulness effects similar to the stimulants (amphetamine and methylphenidate), the FDA approved the drugs for different uses.
- Stimulants such as Adderall and Ritalin are used to treat ADHD in patients as young as 6 years old. Provigil and Nuvigil are approved only for adults with certain sleep disorders
- Studies have found Modafinil has fewer side effects than amphetamine. For example, Provigil is less habit-forming, has not reports of withdrawal symptoms and has milder side effects than Adderall
- Adderall is a Schedule II substance, not a Schedule IV substance like Provigil. This means there is a greater risk for abuse with Adderall. Adderall can also cause sexual side effects.

Neurobiology: Provigil / Nuvigil

- Provigil/Nuvigil enhance dopamine signaling (meaning they make your body more sensitive to dopamine, however, the exact mechanism for this is still unknown
- These medications do not appear to change the amount of dopamine or epinephrine released which is the way typical stimulants work. Instead, Provigil/Nuvigil may have a stimulant effect by suppressing how well another type of neurotransmitter (GABA) works.
- Nuvigil has a longer half-life, and the once-a-day dosing makes it a good first-line choice, starting at 150 mg.

Side Effects: Provigil / Nuvigil

- Use cautiously with people with histories of arrhythmias or heart disease
- Chest pain, high blood pressure, and palpitations are much less common with these drugs than with stimulants like amphetamines
- Neither Provigil or Nuvigil cases high blood pressure
- The most common side effect of both is headache, occurring in 15-20% of the time.
- Other less common side effects are nausea, dry mouth, anorexia and diarrhea

Case Example: 48-year-old Female

- 45 yr. old female with a recent history of moderate to severe concussion at the time of a MVA in which she was a passenger in a car that was hit head on and then spun around jerking her head initially back and forth then side to side and she struck her head against the passenger window. She experienced a very brief LOC (a few seconds) followed by disorientation and confusion. She was taken to the hospital for evaluation and released to home and medical follow-up.
- Patient is a psychiatric nurse and was working full time at the time of the injury
- 3 months following the injury this patient was struggling and unable to return to work and came to my office for a comprehensive neuropsychological evaluation
- Neuropsychological findings were subtle. She demonstrated some mildly slowed processing speed, mildly impaired working memory and distractibility. Additionally, she experienced excessive fatigue and sleepiness and also dizziness.

Case Example: 48-year-old Female (continued)

- Following the neuropsychological evaluation, it was recommended that Ritalin (20 mg bid) be considered. She was also scheduled for psychotherapy to help her with emotional issues (fear, disappointment, low mood).
- Ritalin worked quite well at first and she reported not only improved energy but also improved mood. The improved energy allowed her to become more active socially. She continued to have difficulty with distractibility. After about a month she asked to discontinue the Ritalin due to side effects that included some agitation and moodiness and sleep difficulty.
- Her daytime sleepiness and low energy levels returned so she was prescribed Nuvigil.
- Nuvigil improved her energy level, and she did not experience any side effects. She continued in psychotherapy and went back to work. The cognitive difficulty she demonstrated on testing did not seem to be problematic once the daytime sleepiness and overall fatigue was eliminated.

Consequences of Misdiagnosis when Using Stimulants

Diagnosis	Consequences
Anxiety Disorder	Increased Anxiety
Agitated Depression	Increased Agitation
Preschizophrenic	Psychosis
Bipolar Disorder	Increased manic symptoms—may cause cycle acceleration
Situational Stress	Failure to address psychological issues

Who Should Not Take a Stimulant Drug?

You should not take stimulants if you have:

- Underlying heart problems
- Glaucoma (buildup of pressure in eyes)
- Severe anxiety, tension, agitation, or nervousness
- Tics (body movements you can't control that happen over and over)
- Tourette's Syndrome, or someone in family has it
- A history of psychosis or are psychotic
- Taken a monoamine oxidase inhibitor (MAO) within 14 days of when starting stimulant medication.
  - Examples of this type of medication include phenelzine (Nardil) and tranylcypromine (Parnate).

What Are the Side Effects of Stimulants?

- Headache
- Upset stomach
- Higher blood pressure
- These often go away after a few weeks of taking these medicines. That's because one's body can adjust to the medication. But if they don't get better, let doctor know.
- Less of an appetite
- Weight loss (Sometimes taking medication after meals can help avoid this. Or add high-calorie snacks or shakes)
- Nervousness
- Insomnia (difficult time sleeping)
- Tics

How Stimulants Work: Part 1

Dopamine and norepinephrine play a key role in the areas of the brain responsible for regulating attention and executive function. Stimulant medication reduces ADHD symptoms by increasing the dopamine levels in your brain. It does this by slowing down how much dopamine is reabsorbed back into the neural network.[1]

As a result, more neurotransmitter is held in the synapse between neurons long enough for it to properly bind to the receptor, helping messages within the brain be more effectively transmitted and received. This improves activity and communication in those parts of the brain which operate on dopamine and norepinephrine and signal for specific tasks.

How Stimulants Work: Part 2

Brain imaging studies have demonstrated that when you're on stimulant medication, there's increased metabolic activity in the prefrontal cortex, specific subcortical regions, and the cerebellum—all important centers for executive function. These areas of the brain appear more active when neurotransmitter levels are elevated.

The differences in the way stimulants work may explain why some people with ADHD respond to one type of stimulant medication_better than another.

Methylphenidate

Research suggests that methylphenidate increases levels of dopamine by blocking the reuptake of dopamine and norepinephrine in your brain. That is, it reduces how much of the neurotransmitter is reabsorbed into the neuron so that more is left in the synapse. It also promotes dopamine release from within the neuron, which sends more out into the synapse.

Common methylphenidate-based stimulants include:

- Concerta (methylphenidate extended-release tablets)
- Focalin (dexmethylphenidate)
- Metadate (methylphenidate hydrochloride)
- Ritalin (methylphenidate)

Methylphenidate with TBI

Research has indicated that Methylphenidate used at usual doses (20 mg bid or tid) is safe and improves mental fatigue

The effect of treatment was dose-dependent

The most prominent effect (improved fatigue) with Methylphenidate was found at a normal dose three times/day

A significant improvement in fatigue was also noted with a low dose as compared to a placebo

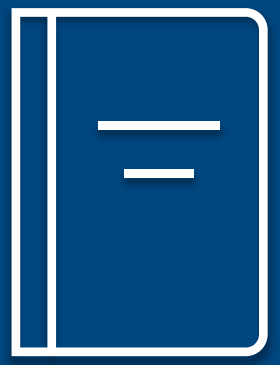
Methylphenidate and Cognitive Improvement

While it is clear from multiple investigations that Methylphenidate improves excessive fatigue in TBI patients it is not clear that this drug improves cognitive functioning. The literature demonstrates studies that show no positive cognitive impact and other studies demonstrate positive impact.

Those that demonstrate positive impact seem to suggest that usual doses of Methylphenidate (20 mg tid) improves processing speed, attention and working memory

More complex self-regulatory attention did not seem to improve

Common Amphetamine-based Stimulants



Amphetamines (another type of stimulant medication) mostly increase the release of dopamine and norepinephrine from their storage sites into the synapse. A less significant mechanism of amphetamines is slowing the reuptake of the neurotransmitters.

Common amphetamine-based stimulants include:

- Adderall (amphetamine dextroamphetamine)
- Vyvanse (lisdexamfetamine dimesylate)

Focalin

- Dexmethylphenidate
- As an isomer of methylphenidate, the active ingredient also in Ritalin, Concerta, Metadate and Daytrana it is supposed to have a more potent effect than drugs containing methylphenidate
- Focalin is available as an immediate-release tablet and is quickly absorbed after administration and reaches maximum concentrations in the blood after 1 to 1.5 hours. Half-life is 4 hours per dose
- Focalin works as effectively as all other Stimulants for symptoms of ADHD.
- Research has suggested that Focalin is more effective with children whereas Adderall is more effective with adults.

When Should a Stimulant be Recommended?

The issue of whether the use of Stimulants and atypical stimulants as well as non-stimulants can be helpful seems clear from the literature that with respect to excessive fatigue (a common symptom of TBI) all of these medications have a positive effect. Stimulants seem to have the most robust impact and the impact appears to be dose-dependent.

As to whether any of these medications are helpful in expediting recovery or improving cognitive functioning is an unresolved issue. The literature is not consistent on the impact of these medications following TBI in relation to cognitive recovery.

One area of improvement that seems most promising is processing speed. Several studies have indicated improvements in processing speed.

The Problem of Complexity

- Processing speed impairment can occur for various reasons which present a complexity in determining whether a particular stimulant medication will be helpful.
- Sometimes as fatigue levels improve processing speed improves automatically.
- Premorbid factors are a complexity. The prevalence of premorbid ADHD in people with TBI is higher than the average population. People who have ADHD are often risk takers.
- What is the role of reward-deficiency syndrome. These people have lower levels of dopamine due to genetic polymorphisms. Will they recover from TBI the same way as a person without reward deficiency syndrome? Will stimulants work and if so on which symptoms?
- It is necessary to determine the hypothesized area of the brain that is most involved in the symptom complaints and neuropsychological results. Then it is important to hypothesize about the likely neurotransmitter systems that are involved. Finally, it is important to understand the neuropharmacology of the medication to aid in choosing the one that will most likely result in a benefit to the patient.

Frontal Lobe and Medications

- Concept of “Frontal Tone”
- Generalized hyper-responsivity
- Easily Agitated
- Pressured Speech (without manic features)
  - Beta Blockers are frequently used for these symptoms
- Orbital-Frontal Syndromes
- Aggressive, hyperactive, impulsive, euphoric, sexually disinhibited, poor judgment
- Clinically may present as manic which is often related to frontotemporal injuries (with temporal lobe involvement)
- Medications effective for this syndrome: Stimulants, Tenex, Seroquel, Mood stabilizers

Frontal Lobe Syndrome

- Superior Frontal Syndromes (Mesial Frontal)
- Apathy, paucity of responding
- Poor initiation
- Flat affect, aprosodic speech

Medications that seem effective with superior frontal syndrome are stimulants

Temporal Lobe Syndrome

Temporal Lobe and Affect

Limbic system damage can generate both aggression, hypersexuality, uncontrollable anger, uncontrollable depression symptoms, “manic” features, general emotional lability

Medications that have demonstrated efficacy

Mood stabilizing medications including Depakote, Lamictal and Trileptal

Antipsychotics including Abilify, Seroquel, Zyprexa, Thorazine (usually only when agitation is present)

Be Cautious about using antidepressants as serotonergic medications can exacerbate lability and agitation.

Temporal Lobe and memory

Amnestic Syndrome

Deficit in Learning and Memory (primary and secondary)

Medications

Stimulants and non-stimulant

Ritalin, Focalin, Adderall, Vyvance, Strattera

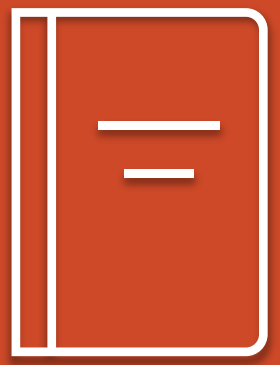
Non-stimulant drugs (Cognitive Enhancing Drugs)

Amantadine

Complex Case Study

- 60-year-old male high level financial executive with an MBA
- Began developing cognitive difficulty that included a lack of focus, difficulty sustaining attention, easily fatigued, slow processing speed, increased forgetfulness and interpersonal difficulty (personality change)
- He also developed severe pain on the left side of his body
- MRI demonstrated a vascular lesion in his Thalamus. Neurosurgery was held off because of danger of the procedure. After waiting several years with ongoing cognitive difficulty that was worsening, he decided to have brain surgery.
- Following brain surgery, he was left with the same cognitive deficits with the added problem of executive function impairment, and he now has Central Pain (thalamic pain) and also hypersomnolence
- Now has a left dorsolateral frontal vascular malformation. Surgery is not indicated yet

Case Study: Neuropsychological Deficits



Neuropsychological deficits include:

- Working memory impairment
- Excessive vulnerability to distraction
- Poor decision making (Iowa Gambling Test)
- Slow Processing Speed
- Severe Fatigue and daytime sleepiness

Recommendations

- Cognitive Rehabilitation
- SNRI medication
- Oxycodone
- Medical Marijuana (low THC and high CBD)
- Stimulant medication
- Tried methylphenidate but he had side effects
- Focalin—excellent result