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EXECUTIVE FUNCTION DEFICIT
Pharmacotherapy for Executive Function Syndromes

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Roles & Conflicts

- Medical Director, Tri-County Mental Health Services
- The Psychiatrist for Central Maine Health Care (by contract)
- Medical Director, Family Psychiatry of Maine (private practice)
- President, MAPP
- Secretary, MCCAP
- No financial conflicts
- Personal: this talk is an exposure therapy exercise
Learning objectives

1. Learn to recognize 3 categories of executive function syndromes commonly seen in adults, and differentiate them from “bipolarism,” “borderline” and “manipulators.”

2. Learn to use algorithms for safe and effective prescribing of stimulant medications

3. Learn to use other-than-stimulant medications to improve executive functioning
Gratitudes

- To my patients, whose patience has been my guide
- To my wife and children for their perseverance
Questions

- What is an executive function syndrome?
- How do I get one?
- What do they look like in adulthood?
- How can they be shrunk?
Some Important Executive Functions

- Self-monitoring
- Inhibition (vs impulsivity)
- Emotional regulation
- Initiation (vs inertia or apathy)
- Planning (vs stimulus-bound)
- Cognitive flexibility (vs perseveration)
- Organizing
- Working memory
- Sensory gating (e.g. misophonia, hallucinations)
- Dampened reward response
- Behavioral learning (versus lack thereof)
Behavior Rating Inventory of Executive Function (BRIEF)

- Rating scales validated for children and adolescents
- Parent Informant
- Teacher Informant
- Adolescent Informant
- Metacognition: initiate/plan/working memory/organize/monitor
- Behavior regulation Index: inhibit/shift/emotional control
- This instrument captures many core aspects of executive function, as observed.
Delis-Kaplan Executive Function System

- This instrument captures many important aspects of executive function by testing them directly.
- It is normed for both children and adults.
- Requires a trained test administrator.
- Trails-making/Tower of London/Sequencing/working memory, etc.
- Produces a fine-grained picture of the patient’s executive function capabilities in a calm, quiet, 1:1 setting.
Vanderbilt ADHD rating scales

- Free, fairly quick, repeatable
- Captures many areas of executive function
- Also items for anxiety, depression, antisocial behaviors
- But items are definitely kid-oriented.
Adult ADHD Self-Report Scale

- Free, repeatable
- Self-report
- 15 Adult-oriented items
- Captures most classic ADHD symptoms
- No version for other reporters
- No items for mood, anxiety
- No items for more wide-ranging executive functions

http://naceonline.com/AdultADHDtoolkit/assessmenttools/assessmenttools_section-1.pdf
Diagnostic Entities associated with EF impairment

- ADHD (inattentive, hyperactive/impulsive, combined)
- Schizophrenia
- Autistic Spectrum Disorder
- Cluster B personality disorders
- Childhood Lead Toxicity
- Prenatal Exposure Syndromes (alcohol, valproate, etc etc)
- A host of other neurodevelopmental disorders
- Major Neurocognitive Disorders (Dementias)
- Traumatic brain Injury
- Post-stroke syndromes
- ADDICTIONS, both chemical and behavioral
About Prenatal Alcohol Exposure

- 40% of American pregnancies are alcohol exposed
- 5% of Americans are affected (some sub-populations higher)
- Impairments in behavioral learning
- Impaired sense of continuous time
- Impulsive
- Easily led astray, but also manipulative
- Will lie persistently in face of overwhelming evidence
- Excess emotionality/dysregulation
- Facial features
- Cardiac abnormalities, horseshoe kidneys, rapid hepatic metabolism

https://pediatrics.aappublications.org/content/138/2/e20154256.long
The facial features

FETAL ALCOHOL SYNDROME

- low nasal bridge
- epicanthal folds
- minor ear abnormalities
- short palpebral fissures
- indistinct philtrum
- flat midface and short nose
- micrognathia
- thin upper lip

Sequelae of ND-PAE

- School disruption (61%)
- Trouble with the Law (60%)
- Confinement experience (50%)
- Inappropriate sexual behaviors (49%)
- Drug/alcohol problems (35%)
- Mental Health diagnoses affecting adaptive function (94%)
DSM diagnoses attributable to ND-PAE

- Anti-social personality disorder
- Borderline Personality Disorder
- Narcissistic Personality Disorder
- Mood/Bipolar Disorder NOS
- Intermittent Explosive Disorder
- Disinhibited Social Engagement Disorder (indiscriminant type RAD)
- Many cases of ADHD
- Many cases of ASD
- Schizophrenia & schizoaffective in combination with developmental delays
Ameliorations

- DBT
- OT/PT
- Psychopharm
  - Stimulants
  - Alpha agonists
  - Atomoxetine
  - Bupropion
  - Amantadine
  - Antipsychotics
  - Anti-epileptic drugs
DBT

- Well Known therapy/skills training for emotional regulation & interpersonal effectiveness
- ADHD = “DBT Deficit Disorder.”
Games and exercises
Skills
Tricks and aids
NOT computer-based cognitive training
NOT biofeedback
Stimulants

- There are exactly TWO to choose from
- Methylphenidate
- Amphetamine
- They are nearly identical
- They have nearly identical effects and side effects
- There are numerous delivery systems/branded products
Methylphenidate

- Metabolism by carboxylesterase CES1A1 to ritalinic acid
- D - enantiomer half-life 3-4 hours
- L – enantiomer half-life 1-2 hours
- Norepinephrine and dopamine reuptake inhibitor
- Numerous delivery systems and extended release products
- Patch, solutions and suspensions, chewables, OROS, delayed-release
amphetamine

- Amphetamine sulfate salts
- Levo- and Dextro-amphetamine
- Lysine-dextro-amphetamine
- Increases monoamine release into synapse
- Also weak MAOI activity
- weak dopamine reuptake inhibitor,
- moderate noradrenaline reuptake inhibitor
- very weak serotonin reuptake inhibitor
- CYP 2D6 substrate
- Half-life 9-14 hours
- p-hydroxyamphetamine, an hallucinogen
Slight preference for MPH, personally

- Slightly fewer adverse behavioral reactions
- Half the risk of inducing psychosis at therapeutic doses
- Cheaper
- But, more allergic rashes
Common adverse effects

- Stomach ache (mitigate with food)
- Decreased appetite (mitigate with high-fat, high-protein diet and meals delivered when stimulant not in effect) (mitigate with med change, cyproheptadine or AAP if otherwise indicated)
- Headaches (mitigate with med/dose change)
- Tics (mitigate with med change or alpha agonist, SSRI, AAP, et al)
- Picking (scabs, nail beds, etc) (reduce dose or add alpha agonist or SSRI)
- Zombie Effect (emotional constriction) (reduce dose)
- Agitation: STOP
Less Common Adverse Effects

- Psychosis (mitigate with discontinuation, AAP, CYP450 testing/interaction check)
- Agitated reaction (mitigate with discontinuation, CYP450 testing/interaction check, assess for additional neuro/psychopathology)
- Palpitations/tachycardia (assess if subjective or objective, on/off stimulant)
- Hypertension (assess for on/off stimulant effect)
- Allergic rash (discontinue, assess potential for other factors)
- Rebound (as dose wears off, symptoms get worse than baseline briefly) (switch to lisdexamphetamine or Quillivant)
- Sudden cardiac death
Target symptoms to monitor

- Impulsivity
- Emotional regulation
- Sensory gating
- Distractibility
- Hyper-motoric behavior
- Frustration tolerance
- Focus on un-engaging material/tasks
- Transition tolerance & adaptability
- Insomnia
Dose-finding trial

- Start with a guestimation of
  - Degree of symptoms
  - Volume of distribution (weight)
  - Anything you have learned about the individual’s drug metabolism
- Choose a target dose
Dose-finding trial

- I always start with plain, immediate release MPH or MAS
- Start one step lower than target dose
- Move up in 5 mg increments
- Try each step 2-3 times only
- It’s properly adjusted when
  - Target symptoms improve markedly
  - It works in about 30 minutes
  - It lasts 4+ hours
2nd visit (2 weeks)

- Assess for following dose-titration instructions
- Assess for response:
  - Most effective measure is change in mental status exam
  - Change in report of others
- Assess for adverse reactions
- If target dose achieved and few ADR’s, then consider long-acting and/or adjust dose timing.
Adaptation to dose

- Is inevitable
  - Receptor adaption
  - CYP450/glucuronidation adaptation
  - Gut transporter adaptation
  - Increasing volume of distribution
- Happens faster for pre-pubertal patients
- Is not a sign of addiction, but maybe diversion
- Requires periodic dose increases
- Eventually requires switching to the other stimulant
Monitoring for diversion

- PMP and/or Mainecare Portal: every visit
- Lack of change in mental status (observed or reported)
- Urine test is negative
- Vague reports of effects
- Third party reports

- These are all indicators of need for a conversation about other ways to treat the symptoms
Methylphenidate options

- Methylphenidate (Ritalin)
- Dexmethylphenidate (Focalin)
- Dexmethylphenidate (Focalin XR)
- Methylphenidate (Ritalin SR, Metadate ER, Methylin ER)
- Methylphenidate ER (Concerta, Daytrana patch, Jornay PM, Metadate CD, Quillivant XR suspension, Quillichew ER, Ritalin LA)
Amphetamine options

- Amphetamine/dextroamphetamine (Adderall)
- Dextroamphetamine (Dexedrine, ProCentra, Zenzedi)
- Amphetamine sulfate (Evekeo)
- Amphetamine (Adzenys XR-ODT, Dyanavel XR)
- Dextroamphetamine ER (Adderall XR)
- Lisdexamfetamine (Vyvanse)
- Mixed salts of a single-entity amphetamine product (Mydayis)
Alpha Agonists: clonidine and guanfacine

- Great for comorbid anxiety, especially in kids under 10
- Great for tics
- Clonidine comes in
  - IR (6 hours)
  - ER (about 12 hours)
  - Patch (weekly)
- Guanfacine comes in
  - IR (8-10 hours)
  - ER (24 hours)
Adverse Effects of Alpha Agonists

- Sedation
- Hypotension
- Clumsiness
- Stomach ache (guanfacine IR)
- Accommodation
- Worsening inattention
Atomoxetine

- Norepinephrine reuptake inhibitor
- Also increases extracellular dopamine in frontal lobe
- Once a day, builds to a therapeutic level
- Takes at least two weeks and often 4-6 weeks to develop efficacy
- Works well about 2/3 of the time, in my experience
- Some get intolerable headaches, insomnia, GI upset, or agitation
- Some get no effect even at high doses
- I start two steps below target dose. Titrate at 5-7 day intervals.
Wellbutrin is a mild stimulant
- Norepinephrine and dopamine reuptake inhibitor
- It’s a good antidepressant.
- It helps stabilize the reward circuitry – helpful for cravings
- It’s good for mild to moderate cases of ADHD
- Carries increased risk for seizures, so caution in the TBI & stroke population
- Can cause agitated response in some FASD individuals
  - (these individuals also likely to have similar response with atomoxetine)
Amantadine

- Helps shorten duration of flu by one day on average
- Helps with bradykinesia in Parkinson disease
- Can help with parkinsonism caused by antipsychotics
- Good literature supporting use in TBI
  - Apathy
  - Fatigue
  - Irritability
  - Impulsivity
Amantadine

- Helpful in ADHD, TBI (acute and chronic applications)
- Helpful in FASD even when agitated reactions to stimulants, atomoxetine and Wellbutrin have occurred
- Dose BID.
  - Morning dose higher
  - Second dose in mid-afternoon
  - Later dosing will cause insomnia
  - Child: start 100/50
  - Adult: start 200/100
Amantadine Pharmacology

- Primarily excreted unchanged in the urine – levels very sensitive to GFR
- Increased dopamine release
- Decreased dopamine reuptake
- Increases population of post-synaptic dopamine receptors
- Mild NMDA antagonist
- Mild Anticholinergic
Amantadine Adverse Effects

- Per labelling: anticholinergic effects
- Central nervous system effects: insomnia, anxiety, aggressive behavior, hypertonia, hyperkinesia, tremor, confusion, disorientation, depersonalization, fear, delirium, hallucination, psychotic reactions, lethargy, somnolence and coma.
- Per experience (case series 80+ patients):
  - Hypotension – dose reduction
  - Bradycardia – dose reduction
  - Rare agitation, delirium – STOP IT
Tougher cases of TBI and/or FASD

- When all the above failed due insufficient or adverse effects
- Reach for the toxic stuff when behavioral risks are high
- Antipsychotics
  - In the sense of "Major Tranquilizers"
- Select anti-epileptic drugs
  - Oxcarbazepine
  - Carbamezpine
  - Depakote
Antipsychotics

- Serious sedatives & major tranquilizers
- Anxiolytic
- Dopamine blockade improves some executive functions somewhat
  - Slows thought process enough for a “second thought”
  - Reduces anxiety
  - Dulls aggressive impulses
Aripiprazole and brexipiprazole

- Partial dopamine agonism is a stimulant-like effect
- Has slight SSRI activity that is anxiolytic
- Is a serious sedative and terrific tranquilizer
Oxcarbezapine

- Not very effective for bipolar disorder
- Helps quite a lot with TBI and FAS people
- Mild risk for blood dyskprasias and hyponatremia
- Occasional paranoid and psychotic reactions
  - Entirely reversible with discontinuation.
Valproic Acid

- More toxic, but highly effective
- For TBI and FASD
- Not for use in persons of gestational potential, IMHO
  - Fetal valproate syndrome just as bad as FASD
- Pancreatitis, blood dyscrasias, liver toxicity, hypothyroidism, etc
- Just because Depakote works, doesn’t mean it’s bipolar
Looking to the future…

- Neurostimulation of the trigeminal nerve
- Saffron
Unproven & disproven

- Computer-based brain training
- Neuro-feedback
Nutritional and complimentary treatments

- Fish Oil
- Avoiding artificial red food coloring (and maybe yellow)
- Iron supplementation (only if low iron)