Managing ADHD and ADHD-like conditions with complex comorbidities: A Case-based Discussion

Dr. Mark Katz
Medical Director of the Rapid Assessment for Psychopharmacologic Treatment (RAPT) Clinic and the Consult Liaison Service
Southlake Regional Health Centre
Assistant Professor, University of Toronto
Faculty/Presenter Disclosure

• Faculty: Dr. Mark Katz
• Relationships with commercial interests:
  – Grants/Research Support:
  – Speakers Bureau/Honoraria: Janssen Shire Lundbeck Pfizer Allergan Sunovion BMS Otsuka
  – Consulting Fees:
  – Other:
Disclosure of Financial Support

• This program has received financial support from Janssen in the form of an unrestricted educational grant

• **Potential for conflict(s) of interest:**
  – Dr. Mark Katz has received financial support from the abovementioned grant from Janssen Inc., makers of Concerta (oros-methylphenidate)
Mitigating Potential Bias

Dr. Katz is solely responsible for the creation of this talk and its content.
The term long acting psychostimulant is used rather than specific product names except where data is presented on generic vs. brand name differences.
Attention Deficit–Hyperactivity Disorder (ADHD)

• ADHD is a persistent, psychiatric, neurobiological disorder diagnosed using three core symptom domains: inattention, hyperactivity, and impulsivity

• ADHD affects 3% to 9% of school-age children

• ADHD affects 2% to 12% of post-secondary students

• > 50% of individuals continue to have significant, impairing symptoms in adult life

• Adults with ADHD suffer higher rates of job loss, divorce, and accidents compared to their non-ADHD counterparts

Causes of ADHD

Genetics

- Scientists agree that ADHD is a medical neurobiological disorder:
  - Family, twin, and adoption studies have found that the disorder is often inherited
  - Some dopamine genes have been shown to be associated with ADHD
  - Parents with ADHD have a > 50% chance of having a child with ADHD
  - If a child has ADHD, the likelihood that another family member will also have the disorder is five times greater

Environmental / central nervous system (CNS) factors

- ADHD symptoms may occasionally be caused by:
  - Injury to the brain
  - Prenatal exposure to toxins or high blood lead levels

Heritability Co-efficient of ADHD

Height

Schizophrenia

Asthma

Breast cancer

Average genetic contribution based on twin studies

Hudziak, 2000
Nadder, 1998
Levy, 1997
Sherman, 1997
Silberg, 1996
Gjone, 1996
Thapar, 1995
Schmitz, 1995
Edelbrock, 1992
Gillis, 1992
Goodman, 1989
Willerman, 1973

Regions of the Brain Involved in Executive Functioning


Cingulate Gyrus$^{1,2}$
- Sustaining & shifting attention
- Flow of thoughts
- Collaborate/adapt

Prefrontal Cortex$^{6,7}$
- Judgment, analysis
- Problem solving
- Critical and forward thinking

Caudate Nucleus$^5$
- Emotions

Cerebellum$^{3,4}$
- Cognitive dysfunction
- Reading difficulties
- Poor concentration
- Flow/sequence of activity
Anterior Cingulate Cognitive Division Is Not Activated in ADHD

Activation
- Organizing
- Prioritizing
- Initiating
- Time Management
- Analysis
- Synthesis

Focus
- Focus
- Concentration
- Changing tasks
- Flexibility

Action
- Self-control
- Inhibition
- Emotions
- Motivation
- Impulses
- Objectivity

Memory
- Working memory
- Information recall

Emotion
- Frustration
- Management
- Introspection
- Control of emotions

Effort
- Alertness
- Sustaining effort and interest
- Speed of execution

ADHD Presentation Can Differ in Adults Compared to Children

- In DSM-5, subtypes have been replaced by specifiers of current presentation (placing emphasis on current symptom profile rather than longitudinally stable subtypes)
- ADHD presentation specifiers:
  - Predominantly inattentive presentation
  - Predominantly hyperactive-impulsive presentation
  - Combined presentation (exhibits both inattentive and hyperactive/impulsive symptoms)
- As patients with pediatric ADHD mature, some attenuation of ADHD severity is common

Adult ADHD: DSM-5 Criteria

• 5/9 symptoms from inattention and/or hyperactivity and impulsivity criteria present for 6 months
• In addition, the following conditions must be met:
  – Several symptoms present before age 12 years
  – Several symptoms present in 2 or more setting, (e.g., at home, school or work; with friends or relatives; in other activities)
  – Symptoms interfere with or reduce the quality of, social, school, or work functioning
  – Symptoms must not be better explained by schizophrenia/psychotic disorder or another mental disorder

A person with ADHD can now have mild, moderate or severe ADHD

Care Beyond Childhood - DSM-5 makes a special effort to address adults affected by ADHD to ensure that they are able to get care when needed

www.dms5.org
PEDIATRIC TO ADULT SYMPTOM EVOLUTION: INATTENTION

- Difficulty sustaining attention
- Loses important items
- Appears not to listen
- Difficult organizing
- Lacks follow-through

- Difficulty sustaining attention to reading or paperwork
- Misplaces things
- Easily distracted/forgetful
- Poor time management
- Difficulty finishing tasks
- Poor concentration

Pediatric to Adult Symptom Evolution: HYPERACTIVITY

- Squirms and fidgets
- Runs or climbs at inappropriate times
- Cannot play or work quietly
- “On the go,” driven by a motor
- Talks excessively

- Inefficiencies at work
- Inner restlessness
- Overwhelmed
- Self-selects active jobs
- Talks excessively

Goodman DW, Thase ME, Postgrad Med 2009;121:5;20-30
Pediatric to Adult Symptom Evolution: IMPULSIVITY

- Blurs out answers
- Cannot wait his or her turn
- Intrudes on or interrupts others

- Impulsive job changes
- Drives too fast
- Easily frustrated

Goodman DW, Thase ME, Postgrad Med 2009;121:5;20-30
Patients With ADHD Are at Increased Risk

**PHYSIOPATHOLOGY**
85% of adults with ADHD meet criteria for a comorbid condition.

**DRIVING**
2–4x more motor vehicle crashes than non-ADHD population.

**EDUCATION**
~32–38% of adolescents never complete high school education.

**RELATIONSHIPS**
↑ long-standing interpersonal problems and strained marital relations.

**OCCUPATION**
13 missed days of work per year, on average.

Potential Consequences of Impairments in Executive Functioning

STD = sexually transmitted diseases

STD = sexually transmitted diseases
Note: These data are primarily from longitudinal, naturalistic follow-up studies, and outcomes were not assessed according to treatment status.

Red Flags for Adult ADHD

Discussion – When to screen?

- Childhood history or first degree relative
- Multiple failed drug trials in MDD with residual symptoms
  - E.g. was there a history of focus or attention issues before the depression
- Low self-esteem; feelings of worthlessness
  - E.g. feeling of being a failure, sense of I should have been able to do better, I was smarter than I performed
- Substance Abuse - especially alcohol, marijuana, caffeine
  - E.g. use of really large amounts of caffeine “need the stimulation”

Red Flags for Adult ADHD

Discussion – When to screen?

- Difficulty sustaining attention
  - *E.g.* mixing up/forget instructions for medication, forget critical information until later in the visit, terrible historians, answers are off topic/convoluted/provides way too much information

- History of disruptive or impulsive behaviour
  - *E.g.* bankruptcy, dating the bad boys and girls, affairs, gambling,

- Interpersonal relationship difficulties
  - *E.g.* frequent partner changes, multiple failed relationships, antisocial, divorce, sibling fights

- Talkative, loud, interrupts frequently or inappropriately
  - *E.g.* rude to your staff, impatient in your office

Red Flags for Adult ADHD

Discussion – When to screen?

- Organizational skill deficits
  - *E.g. missed appointments, frequently late, unfinished projects, procrastination, issues noted by family/boss*
  - *Depressed people complain about messing up a lot, but others don’t see it as that bad, in ADHD, its the opposite, whatever they think they are doing wrong, the family and bosses think it’s even worse*

- Consistent inconsistency
  - *E.g. Relationships, jobs, goals*

- Erratic work history
  - *E.g. multiple job changes, several jobs in the last few years*

- Poor driving record
  - *E.g. frequent driving/parking tickets, high number of accidents, have difficulty staying focused when others are in the car, difficulty maintaining a steady speed*

Comorbidities in ADHD: this is where it gets complicated

- Other psychiatric conditions can
- Mimic ADHD
- Overlie and Obscure ADHD
- Complicate ADHD
- A number of medical disorders can present with symptoms that look very much like ADHD and require similar treatment (secondary ADHD)
- The clinician needs to be able to diagnose other relevant conditions with ADHD
- Recognize when ADHD is hidden beneath the surface
- Determine which condition to treat first
- (for an excellent review see Katzman, Bilkey et al, BMC Psychiatry: 2017; 17:302. Adult ADHD and Comorbid Disorders)
Considering Comorbidities

- 50% to 90% of children and 85% of adults with ADHD have at least one comorbid condition

- In most cases, ADHD does not exist in isolation. Evaluation requires screening for possible comorbid disorders and consideration of biological, social, and psychological factors

What percentage of your adult ADHD patients have a comorbid disorder?

Rates of ADHD among patients with other comorbid disorders within the previous 12 months

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>ADHD Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Depression</td>
<td>9.4%</td>
</tr>
<tr>
<td>Bipolar Disorder</td>
<td>21.2%</td>
</tr>
<tr>
<td>Chronic Dysthymia</td>
<td>22.6%</td>
</tr>
<tr>
<td>Any Anxiety Disorder</td>
<td>9.5%</td>
</tr>
</tbody>
</table>

NATIONAL COMORBIDITY SURVEY

Case 1: Richard

- 26 year old single male working FT in IT
- Presents with an 8-10 year history of severe social anxiety and chronic MDD diagnosed and managed by two previous psychiatrists
- Has already failed several SSRI, 2 SNRI and a tricyclic antidepressant; tends to feel flat, numb, less able to think clearly and more socially anxious with most treatments
- Trial of Parnate the MAOI ineffective
- CBT focusing on social anxiety “not helpful”
- Cautious trial of bupropion did not worsen anxiety; actually felt a little less depressed with modest improvement in functionality
- Retaking of the history: long history of inattentiveness which led to embarrassing social episodes and a shattering of self confidence in adolescence; did average in school despite high intellect, did reasonably well in college but seemed to work twice as hard as other students
Case 1: Richard (continued)

• PHQ-9 14; GAD-7 18 and ASRS v1.1 4/6 positive
• On mental status presents as sad, scattered, shy, lacking confidence, poor eye contact, not suicidal.
• What are the most relevant diagnoses here? What else would you like to know?
• What would you focus on in treatment? He is currently on 300 mg of Wellbutrin XL
Comorbidity of Adult ADHD and Other Disorders is Bidirectional

Patients with adult ADHD often present with several comorbid psychiatric disorders

Mood Disorders

Based on 12-month prevalence results of the National Comorbidity Survey (n = 3,199 adults, age 18-44).

Adults with ADHD may look like they have a mood disorder when they do not

- Patients with ADHD often deal with failure and may become demoralized, depressed or dysthymic
- Lack of motivation may mimic anhedonia
- Chronic sleep problems and restlessness may mimic insomnia secondary to depression

# Presentation of ADHD vs. Depression

<table>
<thead>
<tr>
<th>ADHD</th>
<th>Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Childhood onset</td>
<td>• Episodic</td>
</tr>
<tr>
<td>• Affective instability (with rapid recovery)</td>
<td>• Anhedonia, consistent low mood (for at least 2 weeks)</td>
</tr>
<tr>
<td>• Baseline is hyperactive (in boys)</td>
<td>• Low energy</td>
</tr>
<tr>
<td>• Enthusiasm for select activities</td>
<td>• Melancholia/anhedonia</td>
</tr>
<tr>
<td>• Demoralized during life transitions</td>
<td>• Worthlessness</td>
</tr>
<tr>
<td>• Talkativeness</td>
<td>• Little spontaneity</td>
</tr>
<tr>
<td>• Concentration (poor vs. selective)</td>
<td>• Weight loss/gain</td>
</tr>
<tr>
<td>• Difficulty getting to bed, initial insomnia</td>
<td>• Suicidality</td>
</tr>
<tr>
<td><strong>Onset during childhood</strong></td>
<td><strong>Usually occurs in late 20s</strong></td>
</tr>
</tbody>
</table>

CADDRA Practice Guidelines, 3rd Ed. [https://caddra.ca/pdfs/caddraGuidelines2011.pdf](https://caddra.ca/pdfs/caddraGuidelines2011.pdf);
Mao AR, Findling RL. *Postgrad Med* 2014; 126: 42-51. (adapted)
Step 4 – Unique vs. overlapping signs and symptoms

ADHD\(^1-4\)
- Distractibility
- Impulsivity
- Poor time management
- Family history of ADHD

Overlapping\(^1-4\)
- Irritability
- Restlessness
- Psychomotor agitation
- Psychosocial stressors
- Low self-esteem
- Alcohol use

Mild depression\(^1-4\)
- Anhedonia
- Lack of interest/motivation
- Low energy

2. CADDRA Practice Guidelines, 3rd Ed. [https://caddra.ca/pdfs/caddraGuidelines2011.pdf](https://caddra.ca/pdfs/caddraGuidelines2011.pdf);
3. Mao AR, Findling RL. *Postgrad Med* 2014; 126: 42-51;
Medical treatment of ADHD and comorbid depression

• Determine whether the patient is depressed secondary to ADHD or vice versa
• Treat the “primary” (i.e. more severe, disabling and pervasive) condition first
  – Usually moderate or severe depression is treated first
  – If mild or persistent depression with ADHD, treat ADHD first as this may ameliorate dysphoria
  – Once stabilized, treat the other condition
• Assess for suicide risk at each follow-up visit

Medications in patients with comorbid ADHD and depression

- SSRIs will often produce only a partial response in depression when ADHD is present\(^1\)
  - \(\frac{1}{3}\) of patients referred for resistant depression may have ADHD\(^2\)
- Stimulants may be less effective for treatment of ADHD in patients with comorbid depression\(^1\)
  - Stimulants may also produce a dysphoric look in 30\% of patients even in absence of depression
  - Dose adjustment may improve dysphoria
  - If dysphoria persists, try switching ADHD medication

2. Sternat T et al. World Congress ADHD 2016 (Poster P-07).
Canadian recommendations for treatment of ADHD in adults with comorbid stable MDD

<table>
<thead>
<tr>
<th>Line</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First Line</strong></td>
<td>Bupropion*, antidepressant* + long-acting stimulant, antidepressant* + CBT</td>
</tr>
<tr>
<td><strong>Second Line</strong></td>
<td>Desipramine*, nortriptyline*, venlafaxine*</td>
</tr>
<tr>
<td><strong>Third Line</strong></td>
<td>Antidepressant* + short-acting stimulant, antidepressant* + atomoxetine, antidepressant* + lisdexamfetamine</td>
</tr>
</tbody>
</table>

* These treatments are not indicated for the treatment of ADHD; as such, they should be considered off-label use. Order of agents listed within a line of treatment is not based on any differences in efficacy.

ADHD: attention-deficit/hyperactivity disorder;  
CBT: cognitive-behavioural therapy.  

### Presentation of ADHD vs. Anxiety

<table>
<thead>
<tr>
<th>ADHD</th>
<th>Anxiety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Childhood onset</td>
<td>Childhood onset</td>
</tr>
<tr>
<td>Specific worries e.g. being late, forgetting, losing things</td>
<td>Excessive general worry causing physical symptoms</td>
</tr>
<tr>
<td>Restless</td>
<td>Fear of being judged</td>
</tr>
<tr>
<td>Irritable</td>
<td>Panic attacks with fear of recurrence</td>
</tr>
<tr>
<td>Perseveration</td>
<td>Repetitive, intrusive thoughts</td>
</tr>
<tr>
<td>Feeling overwhelmed</td>
<td>Compulsive behaviours to relieve anxiety</td>
</tr>
<tr>
<td>Novelty seeking</td>
<td>History of trauma with flashbacks, hyperarousal and avoidance</td>
</tr>
<tr>
<td></td>
<td>Avoids new/unknown situations</td>
</tr>
</tbody>
</table>

Comorbidity of Adult ADHD and Other Disorders is Bidirectional

Patients with other psychiatric disorders often present with adult ADHD as a comorbid diagnosis.

Anxiety Disorders

Based on 12-month prevalence results of the National Comorbidity Survey (n = 3,199 adults, age 18–44).

Prevalence and burden of ADHD and anxiety

- Up to 50% of adults with ADHD have a history of anxiety disorders¹

- Anxiety symptoms are more severe and have an earlier onset in individuals with ADHD²

- ADHD is often diagnosed later in patients with anxiety³

  – Presence of anxiety may inhibit impulsivity

- Substance abuse disorders are common²

Course of ADHD and anxiety

- Anxiety may be a natural extension of ADHD as symptoms tend to be internalized over time
- Inattentive ADHD has a stronger link to anxiety than other types, especially in females who are highly sensitive
- Anxiety may arise as a compensation to repeated and negative external stimuli
- Once anxiety develops, attention can be further compromised leading to low self-esteem

Is it ADHD or anxiety?

• Problems concentrating and restlessness may be caused by a primary anxiety disorder and not by ADHD
  – Check for other signs of anxiety and family history of anxiety

• Evaluate for ADHD symptoms not typical of anxiety
  – E.g. stimulus-seeking behaviour, disinhibition, difficultly with organization and time management

• Determine if symptoms developed *de novo* as a result of new onset anxiety or a particular stressor

Case 2: Meagan

- 27 yr old single woman seen in UCC
- Recent visit to ED after an OD following a relationship breakup and episode of binge-drinking with friends
- History of intense chaotic relationships, destabilization with break ups, problems with managing anger, intermittent suicidality
- Difficulty finding and keeping work
- Mood swings some of which were untriggered and unrelated to life events, highs lasting days and low periods up to a few months
Case 2: Meagan con’t

• Longstanding low self esteem, early adopter of alcohol and substances in the context of academic difficulties and behavioral problems as a child; pregnant at 17, 2 children by age 22

• Hx of learning disability and severe problems with inattention; frequently called to office for behaviour including fighting

• No childhood trauma; sexual assaults x2 as a teen

• Family history of substance abuse, criminality and Bipolar Disorder
Meagan con’t

• What are the diagnostic possibilities?
• How would you manage Meagan from a pharmacologic and non pharmacologic point of view?
Presentation of ADHD vs. Bipolar Mood Disorder

**ADHD**
- Constant
- Childhood onset
- Reactive mood
- Initial insomnia
- Scattered thoughts
- Low self-esteem
- Impulsivity (chronic)
- Family history of ADHD

**Bipolar Disorder**
- Cyclic
- Early or late onset
- Non-reactive mood
- Increased energy, decreased need for sleep
- Racing thoughts
- Grandiosity (Type I)
- Impulsivity (transient)
- Family history of bipolar affective disorder

Dodson WW, ADDvance Magazine, 2000; (adapted)
Step 4 – Unique vs. overlapping signs and symptoms

ADHD\textsuperscript{1,2,3}
- Forgetful, Inattentive,
- Poor follow-through
- Early smoking & drug use
- Anger outbursts

Overlapping\textsuperscript{1,2,3}
- Talkative, rapid thoughts, rapid/excited speech
- Restless, high energy level
- Irritable
- Trouble falling asleep
- Lack of focus, many ideas
- Financial problems
- Distractible
- Impulsivity

Bipolar disorder\textsuperscript{1,2,3}
- Decreased need for sleep,
- Spending & sexual indiscretions,
- Grandiosity,
- Flight of ideas,
- Phasic substance abuse

Patients with comorbid bipolar disorder and ADHD have poorer outcomes

Analysis of the first 1000 patients enrolled in STEP-BD: overall prevalence of ADHD was 9.5%. ADHD: attention deficit/hyperactivity disorder; BD: bipolar disorder.

ADHD and Borderline Personality Disorder

• Overlapping features:
  • both are chronic and enduring
  • Impulsivity and risk taking behaviours
  • problems with anger control/affective dysregulation
  • Low self esteem
  • Difficulties with future planning

• Differentiating features
  • Interpersonal sensitivity
  • Abandonment anxiety
  • Intolerance of aloneness in Borderline PD
  • Identity disturbance
  • Idealization/devaluation
  • Suicidality
  • Feelings of emptiness
  • Micropsychotic episodes

• Centrality of inattentiveness in ADHD

(Phillipson et al, 2006; Asherson et al, 2014)
Medical treatment of comorbid bipolar disorder and ADHD

• Treat bipolar disorder first
  – Use 1st-line treatments for acute mania and maintenance of stability
  – CANMAT guidelines: lithium valproate, atypical antipsychotics

• Treatment of ADHD can be offered when BD is stabilized
  – Preferably with a long-acting stimulant

Tips for using ADHD medications in patients with comorbid bipolar disorder

• “Start low, go slow” until a therapeutic dose is reached
• Weekly contact during titration phase
• Schedule follow-up visits every 2-3 weeks during titration period to check response, side effects, functioning

• If patient switches from euthymia to mania/hypomania on stimulant medication:
  • Withdraw the stimulant
  • Treat the bipolar symptoms
  • Once mood stabilizes, cautiously restart the stimulant

What about treating ADHD and Borderline PD?

- Treat ADHD first because of ease, rapidity and effectiveness; impulsivity and capacity for problem solving under stress may improve.
- No clear cut medication that works in BPD.
- Dialectical Behavior Therapy is the treatment of choice; medication play a secondary role.
Developmental Relationship Between ADHD and Substance Abuse

**Gestation**
- Family-genetic factors link ADHD and SUD risk
- Alcohol and nicotine *in utero* exposure increase

**Child**
- Comorbid ADHD linked to early-onset cigarette smoking and SUD

**Adolescent**
- ADHD treatment may protect against cigarette and SUD
- Exposure to parental SUD increases SUD in ADHD

**Adult**
- ADHD linked to more cigarette smoking and SUD
- ADHD linked to more severe/chronic SUD
- ADHD linked to less remission from cigarette smoking and SUD
- ADHD treatment does not increase SUD

SUD = substance use disorders

Adapted from Wilens TE, Morrison NR. *Curr Opin Psychiatry* 2011;24:280
Comorbidity of ADHD and SUD

Patients with adult ADHD have a greater incidence of comorbid SUD

Substance disorder prevalence (%)

- Alcohol abuse
- Alcohol dependence
- Drug use
- Drug dependence
- Any substance disorder

In patients with ADHD
Prevalence of SUD: Prospective 4-Year Follow-up Study

Overall Rate of SUD: $p < 0.001$ across groups

- Unmedicated ADHD (n = 19)
- Medicated ADHD (n = 56)
- Non-ADHD control (n = 137)

ADHD and Substance Abuse

- Legal products
  - Tobacco:
    - 1.7 times higher risk of smoking
    - Start smoking at early age
  - Coffee and colas
  - Alcohol
- Drugs
  - More frequent cannabis use
  - Cocaine, stimulants
  - Hallucinogens

Treatment with psychostimulants does not increase risk of drug dependence. In fact, treating ADHD could reduce risk of substance abuse.

Impact on Practice

- Treating ADHD may help protect against the onset of cigarette smoking, SUD, and SUD-related criminality in adolescent and young adulthood.
- Substance abusing individuals with ADHD may require treatment of both the SUD and the ADHD.
- Because stimulants can be misused, extended-release stimulants in high-risk individuals may be preferred.

(Crunelle et al, 2018)
Case 3: Sheila

• 53 yr old married woman with history of Hodgkin’s lymphoma which relapsed after standard R-CHOP chemotherapy. She was treated with an autologous stem cell transplant and high dose chemotherapy.
• Referred to Psychosocial Oncology several months after transplant, in complete remission but with moderate symptoms of depression, some recurrence anxieties and prominent cognitive complaints out of keeping with the level of depression
• No psychiatric history including depression or ADHD as a child
• Trouble with memory, forgetfulness, distractibility, difficulty making decisions
• She kept losing her keys, forgetting what she was doing next, mixing up appointments, unable to plan a dinner party like before her transplant or organize her closet
• ?What’s wrong with Sheila? What can we do about it?
Secondary ADHD

- Head injury (repeated concussions, motor vehicle accidents)
- Neurological disorders (brain tumours, stroke, multiple sclerosis, HIV encephalopathy)
- Cancer-related brain fog
- Palliative care: depression in advanced cancer and hypoactive delirium (target symptoms may be fatigue, somnolence, lowered alertness)
- The residual cognitive and executive dysfunction seen in TRD (CANMAT puts stimulants as level 3 augmentation strategy)
- Evidence base for using stimulants is very weak, but there is a long clinical tradition supplemented by case reports, uncontrolled trials and a limited number of controlled trials, some with mixed results in the above mentioned conditions
  
  (Sinita et al, 2014; Chan et al, 2015; Roy et al 2016; Ebede et al, 2017; McIntyre et al, 2017)
Residual Cognitive Symptoms in MDD

Patients with partial or full remission after 3 months of treatment:
Patients (%) reporting cognitive and physical impairment

- Cognitive impairment ranged from 30% to 50% of patients
- Symptoms may have been residual, adverse events or a combination

Midlife ADHD in Women: Is Menopause A Window of Vulnerability?

- There are gender differences in the predominant subtype of ADHD\(^1\)
  - Females $\rightarrow$ Inattentive
  - Males $\rightarrow$ Hyperactive/impulsive

- Although ADHD is diagnosed in twice as many boys as girls, in midlife, more women than men self-report a diagnosis of ADHD\(^2\)

- Some women report cognitive difficulties emerging in midlife that strongly resemble cognitive impairments in adults with ADHD\(^3\)

- Could menopause (or the related estrogen changes) have any effect or interaction with ADHD symptomatology?\(^3\)

---

New onset executive dysfunction in perimenopausal women

Decrement in immediate verbal memory

Decrement in delayed verbal memory

N=403 women followed longitudinally for 14 years; annual endocrine, behavioural and cognitive assessments.
## Effect Sizes in Psychiatry

<table>
<thead>
<tr>
<th>Category</th>
<th>Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atypical Neuroleptics (schiz.)</td>
<td>0.25</td>
</tr>
<tr>
<td>SSRI’s for Major Depression</td>
<td>0.50</td>
</tr>
<tr>
<td>ADHD Medication</td>
<td></td>
</tr>
<tr>
<td>Nonstimulants (as a group)</td>
<td>0.62</td>
</tr>
<tr>
<td>Extended Release Stimulants*</td>
<td>0.95</td>
</tr>
</tbody>
</table>

* Faraone SV. Using a meta-analysis to draw conclusions about ADHD medication effects. American Psychiatric Association; May 21, 2003; San Francisco, Calif.
# ADHD Medications Approved in Canada

<table>
<thead>
<tr>
<th>Class</th>
<th>Starting Dose</th>
<th>Manufacturer Maximum Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS STIMULANTS: MPH-based</td>
<td></td>
<td>(CADDRA max dose where differs)</td>
</tr>
<tr>
<td>Biphentin® (MLR methylphenidate)</td>
<td>10–20 mg qd am</td>
<td>Children and adolescents: 60 mg (80 mg); Adults: 80 mg</td>
</tr>
<tr>
<td>Concerta® (OROS methylphenidate)</td>
<td>18 mg qd am</td>
<td>Children: 54 mg (72 mg); Adolescents: 54 mg (90 mg); Adults: 72 mg (108 mg)</td>
</tr>
<tr>
<td>Foquest™ (MLR methylphenidate)</td>
<td>Adult: 25 mg qd am</td>
<td>Adults: 100 mg</td>
</tr>
<tr>
<td>Ritalin® (methylphenidate)</td>
<td>5 mg bid–tid; consider qid in adults</td>
<td>Children and adolescents: 60 mg; Adults: 60 mg (100 mg)</td>
</tr>
<tr>
<td>Ritalin® SR (methylphenidate)</td>
<td>20 mg qd am</td>
<td>Children: 60 mg; Adolescents: 60 mg (80 mg); Adults: 60 mg (100 mg)</td>
</tr>
<tr>
<td>CNS STIMULANTS: Amphetamines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexedrine® (dextroamphetamine)</td>
<td>2.5–5 mg bid</td>
<td>Children: 40 mg (20 mg); Adolescents: 40 mg (30 mg); Adults: 40 mg (50 mg)</td>
</tr>
<tr>
<td>Dexedrine® spansule® (dextroamphetamine)</td>
<td>10 mg qd am</td>
<td>Children/adolescents: 40 mg (30 mg); Adults: 40 mg (50 mg)</td>
</tr>
<tr>
<td>Vyvanse® (lisdexamfetamine)</td>
<td>20–30 mg qd am</td>
<td>Children: 60 mg; Adolescents: 60 mg (70 mg); Adults: 60 mg (70 mg)</td>
</tr>
<tr>
<td>Adderall XR® (mixed amphetamine salts)</td>
<td>5-10 mg qd am</td>
<td>Children: 30 mg; Adolescents/adults: 20–30 mg (50 mg)</td>
</tr>
<tr>
<td>NON-STIMULANTS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strattera® (atomoxetine)</td>
<td></td>
<td>Children/Adolescent s: 0.5 mg/kg/day; Adults: 40 mg qd</td>
</tr>
<tr>
<td>Intuniv® XR® (guanfacine)</td>
<td>1 mg</td>
<td>Children: Lesser of 1.4 mg/kg/day or 60 mg/day; Adolescents/Adults: Lesser of 1.4 mg/kg/day or 100 mg/day</td>
</tr>
</tbody>
</table>

First-line agents (CADDRA) are in bold; CADDRA maximum recommended doses are in parentheses when over or under the manufacturer’s recommendation.

MPH, methylphenidate; MLR, multilayer release; OROS, osmotic-controlled release oral delivery system; SR, sustained release.

A consensus decision has been made based on clinical use and research data. Doses per CADDRA that are over or under product monograph maximum or minimum doses should be considered off-label use.

B.i.d. refers to qam and qpm; t.i.d. refers to qa.m., qnoon, and q4p.m.
Bupropion XL in Adults With ADHD: Percent Responders

Responders, %

* * * *

Bupropion XL (n=81)
Placebo (n=81)

*p < 0.05

Teva-Methylphenidate ER-C
Pharmacokinetic Data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Teva-MPH ER-C</th>
<th>OROS MPH</th>
<th>Ratio of Geometric Means (%)</th>
<th>CI, 90%</th>
</tr>
</thead>
<tbody>
<tr>
<td>$AUC_{0-t}$ (ng•h/mL)</td>
<td>170.44</td>
<td>161.97</td>
<td>105.23</td>
<td>100.80–109.85</td>
</tr>
<tr>
<td>$C_{max}$ (ng/mL)</td>
<td>18.72</td>
<td>15.88</td>
<td>117.90</td>
<td>110.17–126.17</td>
</tr>
<tr>
<td>$T_{max}$ (h)*</td>
<td>4.61 (21)</td>
<td>7.58 (26)</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Teva-MPH ER-C</th>
<th>OROS MPH</th>
<th>Ratio of Geometric Means (%)</th>
<th>CI, 90%</th>
</tr>
</thead>
<tbody>
<tr>
<td>$AUC_{0-t}$ (ng•h/mL)</td>
<td>131.85</td>
<td>132.23</td>
<td>99.71</td>
<td>94.87–104.80</td>
</tr>
<tr>
<td>$C_{max}$ (ng/mL)</td>
<td>13.31</td>
<td>13.90</td>
<td>110.10</td>
<td>104.22–116.32</td>
</tr>
<tr>
<td>$T_{max}$ (h)*</td>
<td>3.81 (28)</td>
<td>7.20 (22)</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>
More Patients Destabilized with the Switch from OROS-MPH to MPH ER-C

Of the 46 destabilized MPH ER-C patients: 43% (21) indicated shorter duration of effect, and 78% (36) eventually restabilized when switched back to OROS MPH ER-C.
Medication Persistence and Duration of Treatment: OROS MPH vs MPH ER-C

Persistence at 12 months was 68% for those who continued OROS MPH and 39% for those who switched to generic product (chi-square, p < 0.001). Duration of treatment was a median of 365 days (IQR 294–365) and 243 days (IQR 90–365) for brand and generic drugs, respectively (median test, p < 0.001).

IQR = interquartile range
Patient Management: Reinforcing the Need for Behavioural Change

• 10% to 15% correctly identified patients will not be supported by the use of stimulants, hence the need for behavioural and educational initiatives

• Stimulants may enhance awareness and response to their perceived environment and may expose potential, previously unrecognized, complicating factors
Back to the Cases

- Richard: added long acting stimulant to his Wellbutrin XL with profound improvement in mood ADHD and social anxiety
- Meagan: focus on managing the Bipolar 2 first; Latuda partially effective, lithium added. Not yet addressing the ADHD. Referred to a DBT therapist
- Sheila: brain fog group emphasizing cognitive remediation strategies; Trintellix augmented by long acting stimulant; gradual improvement in brain fog and depression; targeting RTW
Additional Resources

- **Websites**
  - Canadian ADHD Resource Alliance (CADDRA): [www.caddra.ca](http://www.caddra.ca)
  - Centre for ADHD Awareness, Canada (CADDAC): [www.caddac.ca](http://www.caddac.ca)
  - Attention Deficit Disorder Association (ADDA): [www.add.org](http://www.add.org)
  - Quebec-based Dr Annick Vincent's ADHD website: [www.attentiondeficit-info.com](http://www.attentiondeficit-info.com)
  - Children and Adults with Attention-Deficit/Hyperactivity Disorder (CHADD): [www.chadd.org](http://www.chadd.org)
  - MyADHD, Connecting doctors, parents & teachers: [www.myadhd.com](http://www.myadhd.com)
  - Totally ADD: [www.totallyadd.com](http://www.totallyadd.com)
Additional Resources

- **Apps**
- Any to-do or task list (*Sticky Notes, Stickies, Evernote*)
- **Timeout, Workrave** (program-timed breaks)
- **Sleeptime, Shutdown Timer**
  - Set a timer to put your computer into sleep mode
- **30/30, Activity Timer**
  - Set up a task and assign it a set time
- **SelfControl, StayFocusd**
  - Block certain websites for a specified amount of time
- **Breathe2Relax**
  - Guided deep breathing
- **Sleep Cycle Alarm Clock**
  - Analyzes sleep patterns at night, wakes you up in your lightest sleep phase