Treatment of ADHD in Adults

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What predicts persistence of ADHD into adolescence & adult ?

- Family history of the ADHD
- Family adversity
- Presence of psychiatric comorbidity
- Genetic type
- Childhood ADHD severity
- Childhood treatment

Treatment

- ADHD: decreased social, educational, vocational and self-care functioning, Higher rates of accidental injury .
- The burden of untreated ADHD also includes the time and energy it requires individuals, and those that support them, to cope with ADHD-related challenges.

Treatment

- The high morbidity of ADHD makes it important that we also weigh risk of not treating ADHD
- Multimodal treatment plan:

  Medications , Educational and psychosocial interventions

Treatment:

- As in childhood ADHD, medication remains a key component of treatment for adult with ADHD
- Medication is first-line treatment for ADHD in adults with moderate to severe impairment

CADDRA

- CADDRA categorizes ADHD medications:
- First-line
- Second-line
- Third-line

First line medications:

Long-acting psychostimulants:

- ✓ Diminishes the need for multiple dosages and therefore augments compliance
- ✓ Symptom coverage and treatment response compared to immediate-release, may diminish diversion and rebound and is often associated with better tolerability

First line medications:

- Both classes of stimulants (methylphenidate and amphetamines) have similar efficacy and tolerability profiles at the population level.
- At the individual level, patients may respond to, or tolerate one class better than the other
- An adequate trial of both classes of long-actings before engaging in a trial of a second-line treatment.

Second line medications:

- ✓ Atomoxetine
- ✓ Guanfacine XR
- ✓ Short/intermediate acting psychostimulants

Second line medications:

- They may have lower effect sizes, sub optimal duration of action “compared to first-line treatment“, or reduced tolerability and risk benefit profile.
- They can be used for patients:

✓ significant side effects

✓ suboptimal response

✓ not access to first-line medications

Second line medications:

Second line Non-stimulants

- In combination with first-line agents as a potential augmentation for first-line treatment suboptimal responders.
- Where stimulant agents are contraindicated “ high risk of stimulant misuse”

Third line medications

Third-line medications: off -label

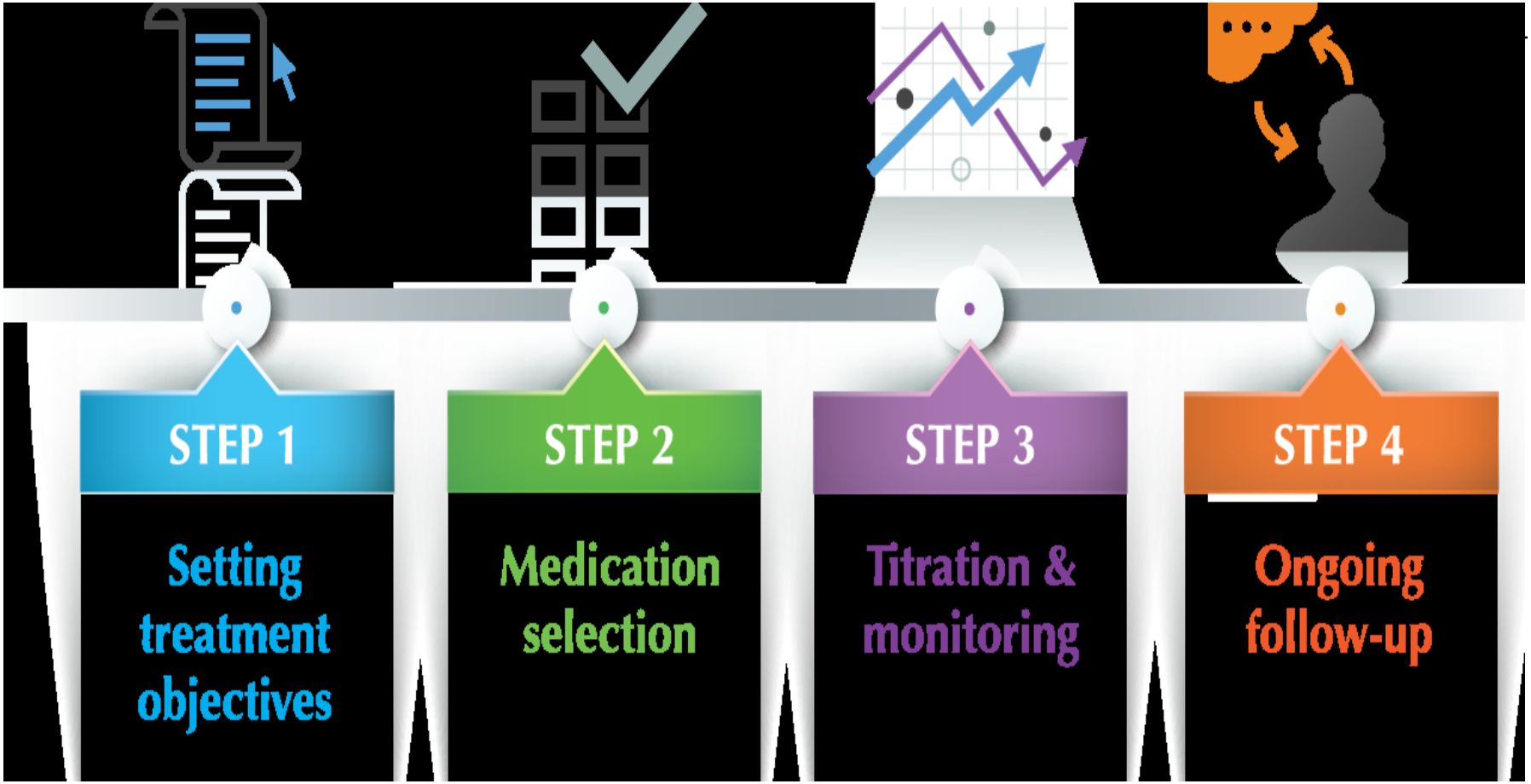
- Bupropion
- Clonidine
- Imipramine
- Modafinil

Atypical antipsychotics “for comorbidities often in combination with other agents”

Third line medications:

- Treatment-resistant cases
- They may require specialized care

Stepped Approach to Prescribing



Step 1: Setting Treatment Objectives

- Good treatment objectives are Specific, Measureable, Attainable, Relevant and Timely (SMART).

Step 2 - Medication Selection

Patient-related factors: *(*Age and Duration of effect required by timing of symptoms, Concurrent psychiatric and medical issues,…)

Medication-related factors: *(*Active ingredient /drug interactions/ onset of action / duration of action/ Available doses,…)

Special considerations: *(* Combining medication for adjunct effects/ Potential of abuse, misuse,…)

Patient-related factors:
Age and individual Variation

- ADHD medications could be used across the lifespan.
- There is no maximum age to treat ADHD - if the general health and cardiovascular status of the patient permits use of those treatments.
- Women of childbearing age: the effects of ADHD medications on the fetus and on the baby while breastfeeding are unknown.

Patient-related factors:
Age and individual Variation

- **Weight** of the patient does not predict optimal dosage for psychostimulants.
- At this time, there is insufficient evidence that **symptom profile, family history or genetic testing** can help predict which medication will work best for an individual in clinical practice.
- While patients respond differently, all medications approved for use in ADHD: reduce both inattention as well as impulsive/hyperactive symptoms of ADHD.

STEP 3 -Titration & Monitoring

- **Starting dose**: Start low and go slow but continue to increase the dose until:
- ✓ The desired goals of treatment
- ✓ Side effects preclude dose increases
- ✓ Maximum recommended dosage is reached.

STEP 3 -Titration & Monitoring

- **Optimal treatment:**
  - ✓ decrease of the symptoms
  - ✓ improvement in general functioning
- **Optimal dose:** is that dose above which there is no further improvement.

STEP 3 -Titration & Monitoring

- A stimulant medication's effects are likely to be stable at a given dose after one to three weeks
- For atomoxetine after four to six weeks

STEP 3 -Titration & Monitoring

- Full response may not even take effect until after three months on a particular dose.
- Some reports of loss of stimulant's effect over time.
- In some cases, taking breaks from stimulant treatment intermittently has reportedly allowed for the maintenance of effects at lower doses.

Step 4: Ongoing Follow-up

- It is crucial to treat ADHD proactively before long-term negative consequences occur (e.g.: school drop-out, delinquency, job loss, divorce, substances use issues, comorbidities).
- Active involvement of patients in own care: patients should be a partner in ADHD management.

Managing side effects:

- Usually, side effects are mild and temporary if dosage is appropriate and medications are taken as prescribed.
- Most side effects appear when the medication is started or dosages are modified.
- Often, they disappear over time (side effect tolerance), particularly when taken regularly.

Managing side effects:

- Analyzing timing of the side effects profile
- Monitoring of adverse changes in growth, sleep, nutrition, pre-existing conditions, blood pressure, heart rate, mood or anxiety distress, thought pattern, behaviour.

Managing side effects:

- The aim is to find a positive balance between clinical benefit versus adverse effects.

- Assess the comorbid disorders

When to Reduce the Dose, or Stop a Medication?

- If side effects require a period off medication (“drug holiday”) or a reduced dose, it could be done during vacation periods” summer vacations or on long weekends”, which minimize impact on critical role performance.

When to Reduce the Dose, or Stop a Medication?

- Tapering off or on the agent is needed to have less withdrawal effects: fatigue, or initiation effects such as sympathetic nervous symptom side effects.
- Clinically, it is observed that interrupting psychostimulants every weekend may in fact increase side effects.

When to Reduce the Dose, or Stop a Medication?

- Non-stimulant medications (atomoxetine, guanfacine XR, buproprion) need to be taken continuously for clinical effect.
- Alpha-2 agonist medications in particular, should be tapered "significant danger of withdrawal effects: hypertensive crisis for guanfacine XR and clonidine).

- decrements of no more than 1mg every three to seven days

Managing Changing Medication Effects Over time

- A pattern of escalating doses over time may reflect “tolerance”.
- Some patients confuse the energetic, mood or pleasure side effects of a stimulant from the attention and behaviour control clinical effects.

Managing Changing Medication Effects Over time

- While the energetic side effect tends to be reduced over time, the improvement of sustained attention is usually still there.

Managing Changing Medication Effects Over time

- Some clinical reports state that some individuals find that taking breaks from the stimulant medication may have a "rejuvenating" effect.
- Need to study
- It is advisable to have patients take breaks rather than to increase dose in a previously effective treatment

How to Stop Medication

- Some individuals may experience withdrawal from stopping psychostimulants, particularly if dosages are high.
- At robust doses, tapering these agents may avoid withdrawal.
- Atomoxetine is less likely to produce this withdrawal.

Unsatisfactory response to treatment

Reviewing the DATER diagram prior to second and third line medications:

- D:Dosage
- A: All
- T: Time
- E: Examine
- R: Review

DATER

D	**Dosage: Has the medication been tried on a high enough dose, is the duration of effect adequate? Side effects: Is the dosage too low or too high?**
A	**All : Have all medications within the higher line(s) been attempted? If not, explore why.**
T	**Time: Has enough time been given to examine patient response and for side effects to resolve?**
E	**Examine: Have specific targets for treatment and means to measure changes been determined ? Select standardized measures (teacher, parent, spouse and self-report)**
R	**Review: Review of potential comorbidity, psychosocial complications and lifestyle issues?**

Pharmacotherapy of Adult ADHD:

Drug treatments:

Stimulants (methylphenidate, dexamfetamine):

- ✓ Immediate action and can therefore be titrated more quickly.
- ✓ Have an appreciable positive effect on attention in those without ADHD, and a ‘therapeutic trial’ therefore has no diagnostic value
- ☐ Have more potential for diversion/misuse (immediate release preparations)

Pharmacotherapy of Adult ADHD:

Non-stimulants (atomoxetine, clonidine, bupropion etc.): A delayed onset of action

FDA-Approved Medication in Adults

- Dexmethylphenidate, XR (Focalin) (2005)
- Methylphenidate , OROS XR (Concerta) (2008)
- Lisdexamfetamine Dimesylate (LDX) (Vyvanse) (2008)
- Mixed Amphetamine salts (MAS) XR (Adderall) (2004)

- Atomoxetine (2002)

FDA-Approved Medication in Adults

- Only long-acting stimulants are FDA approved for adults with ADHD
- Although many treatments are not licensed in the adult population, this should not prevent medications being prescribed according to best practice.

Pre-treatment screening:

- Measuring baseline:
  - ✓ ADHD symptom severity
  - ✓ Impairment
  - ✓ Weight
  - ✓ Heart rate
  - ✓ Blood pressure
  - ✓ Sleeping pattern.

Pre-treatment screening:

- A history of tics and seizures (ADHD treatments can exacerbate both)
- ECG if :

✓ Family history or medical history of serious cardiac disease

✓ Family history of early cardiac death

✓ Abnormal findings on cardiac exam.

Pre-treatment screening:

- Routine ECG monitoring, either before drug administration or after starting therapy, is not recommended in young patients with no history of heart disease or normal physical examination.

Treatment

Stimulant treatment of adult ADHD

- ✓ Improve abnormal behaviors of ADHD ,self esteem ,cognition , social & family functioning

- ✓ Efficacy varied with age & psychiatric comorbidity

Treatment

- The average response rate : 50% (adult)

  70% (child & adol..)

- Plausible reasons:

  insufficient dosing

  uncertain diagnostic criteria

  psychiatric comorbidity

Methylphenidate:

- Recommended as the first line of treatment for ADHD in adults (NICE, 2008)
- Primarily a dopamine reuptake inhibitor, with some action on noradrenaline and other catecholamines
- Effect size of 0.5 (Castels *et al, 2011)*
- Immediate release preparations are cheaper and can allow greater fine-tuning of dosing.

Methylphenidate:

- Dose titration, using immediate or slow release preparations, should be done using the smallest available dose increments over intervals (e.g. every fortnight), until an adequate response is achieved or intolerable side-effects are experienced.

Methylphenidate:

- Typical starting dose (Immediate release) 5 mg once or twice a day, increased to three times daily after a week.
- Dosage increased by about 10–15 mg per week dependent on tolerability.

Methylphenidate:

- Modified release: start at 10 mg (27 or 36 mg if Concerta XL)
- Weekly increases by increments of 10–20 mg (18 mg if Concerta XL) to maximum effective tolerated dose.
- Monitor weight, blood pressure, pulse rate.

Dexamfetamine:

- Alternative stimulant treatment for adult ADHD with similar efficacy to methylphenidate.
- Used in patients with suboptimal response to methylphenidate.
- Promotes the release, and prevents the reuptake, of dopamine and noradrenaline.

Dexamfetamine:

- Dexamfetamine is considered to have more misuse/diversion potential than methylphenidate
- Although there is likely to be less misuse potential with lisdexamfetamine (Blick & Keating, 2007)
- Dose titration follows the same principles as for methylphenidate

Methylphenidate	Dexafetamine	Atomoxetine
Immediate release **• Ritalin/Medikinet:** 4h duration of action b.d. or t.d.s. 5,10, 20 mg tablets **max 100 mg/day**	**Short-acting** **• Dexamfetamine:** effect 4 h b.d. or t.d.s 5 mg tablets **max. 60 mg/day**	**Strattera:** 10, 18, 25, 40, 60, 80, 100 mg tablets usual dose 80 mg **max. 120 mg/day**
Modified release **• Concerta XL:** **22% IR: 78% MR)** **10–12 h duration of action** **18 mg tablets** **max. 108 mg/day** **Equasym XL:** **Medikinet XL**	**Long-acting** **• Lisdexamfetamine:** **effect 12–13 h** **30, 50, 70 mg tablets** **max. 70 mg/day**	

	Methylphenidate	Dexafetamine	Atomoxetine
Side effects	**Reduced appetite insomnia depressed mood, anxiety headache, irritability, tachycardia, tics, seizures, psychosis**	**Reduced appetite insomnia tachycardia, increased blood pressure, headache, depressed mood, anxiety, irritability, nasopharyngitis, tics, seizures**	**Reduced appetite, nausea, depressed mood, tachycardia, increased blood pressure, insomnia, dizziness, GI disturbance, sweating, sexual dysfunction, seizures, hepatitis**
Contraindications	**Cardiac disease, cerebrovascular disease, hyperthyroidism, phaeochromocytoma, vasculitis, some mental disorders (weigh risks *v. benefits)***	**Cardiovascular disease, hypertension, arteriosclerosis, hyperthyroidism, history of drug or alcohol misuse**	**Phaeochromocytoma**

- It is possible to combine a slow release preparation in the morning, with an immediate release preparation in the evening

Other pharmacological options:

Inadequate response to monotherapy:

- ✓ Combining a stimulant with atomoxetine
- ✓ Other potential treatment options, (less of an evidence base):
  - **Bupropion (Zyban):** dopamine and noradrenaline reuptake inhibitor
  - **Modafinil (Provigil):** dopamine reuptake inhibitor
  - **Clonidine**: alpha agonist
  - **Nortriptyline or desipramine:** potent inhibitors of noradrenaline reuptake.

Adverse effects of stimulants:

- **Common**: appetite, headache, stomach ache, trouble sleeping, weight loss, dry mouth, nervousness, mood swings, dizziness, fast heart beat.
- **Also**: agitation, not indicated in highly anxious, agitated, or psychotic patients

Adverse effects of stimulants:

- Small increases in blood pressure.
- Patients with narrow angle glaucoma should avoid stimulants.
- Stimulants may worsen tic or Tourette's syndrome.

Adverse effects of stimulants:

- Blood pressure and pulse should be monitored with stimulant treatment and may be of greater clinical significance in the treatment of adults with ADHD

STIMULANTS AND SUBSTANCE ABUSE

- No evidence: stimulant use increases the chances of substance abuse or dependence.
- In fact: stimulant use in the successful treatment of adults with ADHD can actually reduce the chances of a person developing a substance use disorder in comparison to adults untreated for ADHD.

Potential for Abuse, Misuse and Diversion

Individuals who abuse stimulants:

- Trying to mask fatigue
- Believing that the non-medical use of stimulants will increase academic performance.
- Higher in short-acting formulations

Atomoxetine:

- Non-stimulant treatment for ADHD which is usually considered in adults unresponsive or intolerant to stimulant treatments, or when misuse/diversion of stimulants is a concern.
- A noradrenaline reuptake inhibitor
- Delayed onset of action of several weeks with effect size of 0.4 (Asherson *et al 2014).*

Atomoxetine:

- Does not require the same individuald fine-tuning of dose that stimulants require and has the advantage of once-daily dosing.
- Side-effects are usually avoided by a gradual dose titration, for example starting at 40 mg and increasing by 20 mg per week.

Atomoxetine:

- Doses above 80 mg have not shown any additional benefit.
- Some individuals are poor metabolisers of atomoxetine and are sensitive to side-effects at low doses.
- Acute liver failure and suicidality are rare but significant potential side-effects. All patients should be advised of symptoms of these adverse events.

Atomoxetine:

- Monitor weight, blood pressure and pulse rate at baseline, after each dose change and long-term every 3 months, with weight every 6 months.
- Increased risk of ventricular arrhythmias has been described when used with drugs that prolong the QTc interval.

Adverse effects of Atomoxetine

- Common: constipation, dry mouth, nausea, fatigue, decreased appetite, insomnia, erectile dysfunction, urinary hesitation and/or urinary retention and/or dysuria, dysmenorrhea, and hot flush.
- May: sedation, GI complaints, mild increases in blood pressure (blood pressure and pulse should be monitored)

Adverse effects of Atomoxetine

- Rare: allergic reaction(skin rash, drug should be discontinued)
- Patients with pre-existing **heart disease or cardiac abnormalities, hypertension, hypotension, liver disease** should avoid atomoxetine.

Atomoxetine

- Atomoxetine as the first medication for ADHD in individuals with an **active substance abuse problem, co morbid anxiety or tics**
- Starting dose: Children and adolescents <70kg:0.5mg/kg/day
- Adults: 40 mg/d

Atomoxetine

- FDA Max/Day: Lesser of 1.4mg/kg or 100mg
- Off-label Max/Day: Lesser of 1.8 mg/kg or 100 mg

Dosage & Administration

Initial, Target and Maximum Daily Dose

Body Weight	Initial Daily Dose	Target Total Daily Dose	Maximum Total Daily Dose
Children and adolescents up to 70 kg	0.5 mg/kg	1.2 mg/kg	1.4 mg/kg
Children and adolescents over 70 kg and adults	40 mg	80 mg	100 mg

Stramox® should be administered either as a single daily dose in the morning or as evenly divided doses in the morning and late afternoon/early evening.

Atomoxetine

- may be taken with or without food.
- can be discontinued without being tapered.
- capsules are not intended to be opened, they should be taken whole.

Off-label medications

- **Modafinil**
- ✓ It does not activate the areas of reward and abuse in the brain
- ✓ Increased efficacy with higher dosages(340-425mg/day)
- ✓ Significant improvement were observed in a large RCT (Biederman et al-2005)
- ✓ Risk of srious Stevens-Johnson-like rashes

Guanfacine XR

- Only guanfacine XR has been approved by Health Canada for the adjunctive treatment of ADHD in combination with psychostimulants.
- However, other combinations are frequently used in clinical practice (e.g. atomoxetine and psychostimulants).

Viloxazine

- Selective norepinephrine reuptake inhibitor (NRI)
- It was used as an antidepressant in some European countries, and produced a stimulant effect that is similar to the amphetamines, except without any signs of dependence

Viloxazine

- It does not produce sedative anticholinergic or adrenergic effects
- It is structurally distinct from conventional tri- or tetra-cyclic antidepressants

Psycho social treatment

- Time management, Organization, Planning, Task-completion, Anger management, CBT, Coaching, Social skills training, Money management, Relationship counseling, Vocational counseling….
- And very importantly, self-education about ADHD.

Monitoring of medication

At each dose titration review and every 6 months:

- ✓ Weight, blood pressure and heart rate
- ✓ Side-effect monitoring

Monitoring treatment in ADHD

Name:	Date:	Medication:	Dose:	BP: Pulse: Weight:
Physical health check				
Side-effect	**Frequency**			
	Not at all often	**Sometimes**	**Often**	**Very Often**
Headache				
Dizziness				
Nausea				
Vomiting				
Sweating				
Loss of appetite				
Sexual dysfunction				
Weight loss				
Diarrhoea				
Tics				
Sleep difficulties				
Mood instability				
Agitation				
Sadness				
Palpitations				
Other				

Duration of treatment

- Once an acceptable dose has been achieved that balances efficacy with side-effects, this dose should be continued and reviewed at least annually.
- With stimulants, the need for ongoing treatment can be evaluated by ‘drug holidays’.
- Often this occurs naturally through omission of doses.

Effective treatment significantly improves quality of life