Whitepaper: ADHD medication for adults

Overview for specialist doctors who wish to start ADHD medication in their patients.

Medication should:

- Be considered as first choice, unless the person prefers a psychological approach
- Always be part of a broader treatment offer that also addresses psychological, behavioural, educational and/or work-related needs

1. Before starting ADHD medication

Required before starting:

- Physical history and examination
  - Presence of exertion-related fainting, shortness of breath and other cardiovascular complaints/diseases
  - Pulse and blood pressure
  - Weight
- Family history
  - Cardiovascular disease
  - Sudden death without clear cause <50 years
- ECG or referral to a cardiologist if there are cardiac concerns in the patient or in the family history
- Ask about risk of substance misuse and misuse of medication

2. Choice of medication

Methylphenidate or (Lis)dexamfetamine

- Both are first choice in the Belgian guideline
- The guideline primarily recommends the long-acting preparations (12 h)
- Lisdexamfetamine is the safest choice when there is a risk of medication misuse

Not effective/poorly tolerated?

- Switch to the other first-choice option
- Stimulants not effective: Atomoxetine
- Atomoxetine also not effective: off-label alternatives (or re-evaluate for a missed diagnosis)

Good to know: Guanfacine is not yet formally approved in Belgium for adults with ADHD, although it is approved for children and adolescents. It may be a possible off-label alternative, but be aware that there is currently insufficient research demonstrating its effectiveness in adults. Clonidine and Modafinil have also been studied, so far likewise with insufficient research to recommend them for adults.

3. Dose titration

Starting dose

MEDICATION	STARTING DOSE
Methylphenidate	± 20 to 30 mg divided over 1-3 doses per day
Lisdexamfetamine	30 mg, in the morning only
Dexamfetamine sulphate	Week 1: 2 × 2.5 mg/d Week 2: 2 × 5 mg/d Week 3: 2 × 7.5 mg/d Week 4: 2 × 10 mg/d
Atomoxetine	40 mg/day for 7 days, then increase to 80 mg/day

20 mg dexamfetamine sulphate ≈ 50 mg lisdexamfetamine ≈ 40 mg methylphenidate

Evaluating the dose

AFTER 1 MONTH	Evaluate effects	Consider using the ASRS scale for a structured comparison
	Evaluate side effects	Monitor weight if needed
	Blood pressure and pulse measurement	
	Decide on dose increase	Yes: increase the dose and re-evaluate after 1 month No: continue monitoring blood pressure/pulse once every 6 months and weight if needed
AFTER 1-2 YEARS	Evaluate whether tapering the medication is possible	Consider tapering in consultation with the patient The safety and effectiveness of medication use beyond 2 years in adults remain insufficiently studied

4. Types of ADHD medication

Stimulants

Methylphenidate

- Mechanism: Increases dopamine and noradrenaline by blocking synaptic reuptake
- Treatment effect from the first dose, maximum effect after a few weeks
- Maximum dose according to the guideline: 60-70 mg/day

DIFFERENT BRANDS OF METHYLPHENIDATE			
PRODUCT	**RELEASE**	**TMAX**	**T1/2**
Concerta	Extended 22% immediate 78% controlled	Biphasic 1st: 1-2 hours 2nd: 6-8 hours	3.5 hours
Equasym	Extended 30% immediate 70% controlled	Biphasic 1st: 1.5 hours 2nd: 4.5 hours	2 hours
Medikinet	Immediate	1-2 hours	2 hours
	Extended 50% immediate 50% controlled	Biphasic 1st: 1-2 hours 2nd: 4 hours	3.2 hours
Methylphenidate Retard	Extended 22% immediate 78% controlled	Biphasic 1st: 1-2 hours 2nd: 6-8 hours	3.5 hours
Rilatine	Immediate	1-2 hours	2 hours
	Extended 50% immediate 50% controlled	Biphasic 1st: 1-2 hours 2nd: 4 hours	3.5 hours

(Lis)dexamfetamine

- Mechanism: Increases dopamine and noradrenaline by stimulating their release and blocking synaptic reuptake
- Treatment effect from the first dose, maximum effect after a few weeks
- Daily intake not always necessary
    - Lisdexamfetamine: metabolised to dexamfetamine by an enzyme in the blood; this is a rate-limiting step, which limits peak exposure in the brain
- Maximum dose according to the guideline
    - Dexamfetamine sulphate: 30 mg/day, exceptionally 40 mg/day
    - Lisdexamfetamine: 70 mg/day

SHORT- AND LONG-ACTING	
Short	▪ More flexibility in the time course of the effect ▪ More control and smaller steps possible when building up the dose
Long	▪ Convenience of once-daily dosing; often improves adherence ▪ Reduces the risk of misuse

Occasional side effects

- Insomnia, loss of appetite, weight loss
- Headache, dry mouth, gastrointestinal complaints (nausea, abdominal pain), restlessness, tremor, nervousness
- With methylphenidate also possible worsening of comorbid psychiatric symptoms (anxiety, depression, emotional blunting, autism)

Rare, serious side effects

- Increased heart rate and blood pressure: risk of arrhythmias or sudden cardiac problems in patients with underlying heart disease
- Worsening of anxiety, OCD symptoms, tics/Tourette syndrome, depressive symptoms
- Possible agitation or (very rarely) psychotic/manic symptoms at high doses

Contraindications

- Known serious structural cardiac abnormalities or arrhythmias, untreated hypertension, untreated hyperthyroidism, glaucoma, phaeochromocytoma
- Concomitant use of MAO inhibitors
- Active psychosis, untreated bipolar disorder
- Pregnancy and breastfeeding

Non-stimulants

Atomoxetine

- Selective norepinephrine reuptake inhibitor
- Mechanism: Inhibits the presynaptic norepinephrine (NE) transporter, increasing NE + a possible indirect increase in dopamine
- The full therapeutic effect may require 6–8 weeks of continuous use
- Daily intake is always necessary
- Has no significant abuse potential
- Maximum dose: 100 mg/day

Occasional side effects

- Nausea
- Insomnia, reduced appetite
- Headache, agitation or anxiety (especially at the start), tremor, sweating
- Increased heart rate and/or blood pressure
- Orthostatic hypotension (rather rare)
- Sexual dysfunction (rather rare)

Good to know: Most side effects wear off after the first days/weeks. It is advisable for the patient to stay on the dose and to drink and eat enough.

Rare, serious side effects

- Liver damage
- Increased suicidality
- Urinary retention (especially in older men)

Contraindications

- If a cardiologist advises against it because the noradrenergic effect on blood pressure and/or heart rate is medically contraindicated
- Untreated hyperthyroidism, glaucoma, phaeochromocytoma
- Concomitant use of MAO inhibitors
- Caution in patients with impaired liver function
- Pregnancy and breastfeeding

Plus point: Atomoxetine may be preferred in comorbid anxiety or tic disorders, as it can sometimes improve these conditions (or at least is less likely than stimulants to worsen them)

Off-label alternatives

Bupropion

- Type: Atypical antidepressant (off-label for ADHD)
- Chemical: norepinephrine-dopamine reuptake inhibitor (NDRI)
- Mechanism: Blocks the reuptake of dopamine and norepinephrine
  - Mechanism overlaps with that of ADHD stimulants, but is weaker and more diffuse
- Maximum dose according to the guideline: 450 mg/day

Occasional side effects

1. Insomnia, reduced appetite, weight loss
2. May increase blood pressure and/or pulse rate
3. Dry mouth, headache, nausea, agitation/anxiety, tremor, sweating, constipation

Rare, serious side effects

- Seizures, especially above 300 mg/day or in people with a history of epilepsy or eating disorders (lowers the seizure threshold)

Contraindications

- Caution with a history of epilepsy, bulimia or anorexia nervosa (due to increased seizure risk)
- Concomitant use of MAO inhibitors, or withdrawal from alcohol/benzodiazepines
- Use caution with untreated anxiety disorders or psychosis

Further reading

- https://www.adhd-traject.be/nl/pagina/behandeling-adhd
  Website for children and young people under 18 (in Dutch), widely used as a reference source in child and adolescent psychiatry

- Cortese, Samuele et al. “Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis.” *The lancet. Psychiatry* vol. 5,9 (2018): 727-738. doi:10.1016/S2215-0366(18)30269-4

- Zhang L, Li L, Andell P, et al. Attention-Deficit/Hyperactivity Disorder Medications and Long-Term Risk of Cardiovascular Diseases. *JAMA Psychiatry.* 2024;81(2):178–187. doi:10.1001/jamapsychiatry.2023.4294

Sources

- Belgian Superior Health Council (Hoge Gezondheidsraad): guideline on the pharmacological treatment of ADHD
  https://www.health.belgium.be/sites/default/files/uploads/fields/fpshealth_theme_file/20210308_hgr-9547_adhd_vweb_0.pdf

- Bcfi.be (Belgian Centre for Pharmacotherapeutic Information) and the associated package leaflets of the medications listed above

- The Maudsley “Prescribing Guidelines in Psychiatry” book, 13th edition

- Prescribers Guide Stahls Essential Psychopharmacology