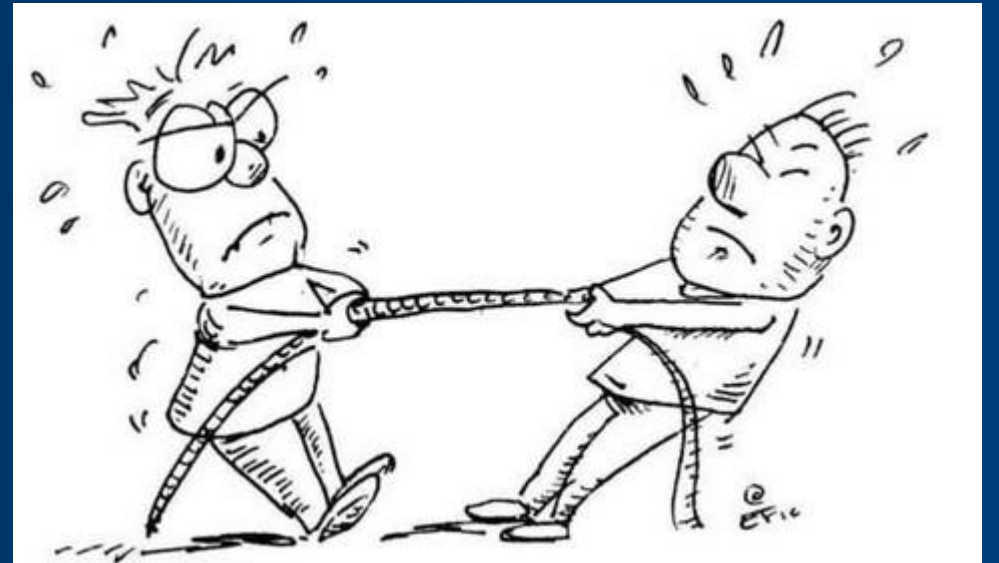


# The Good, the Bad & Everything In Between: ADHD-medicatie in de praktijk



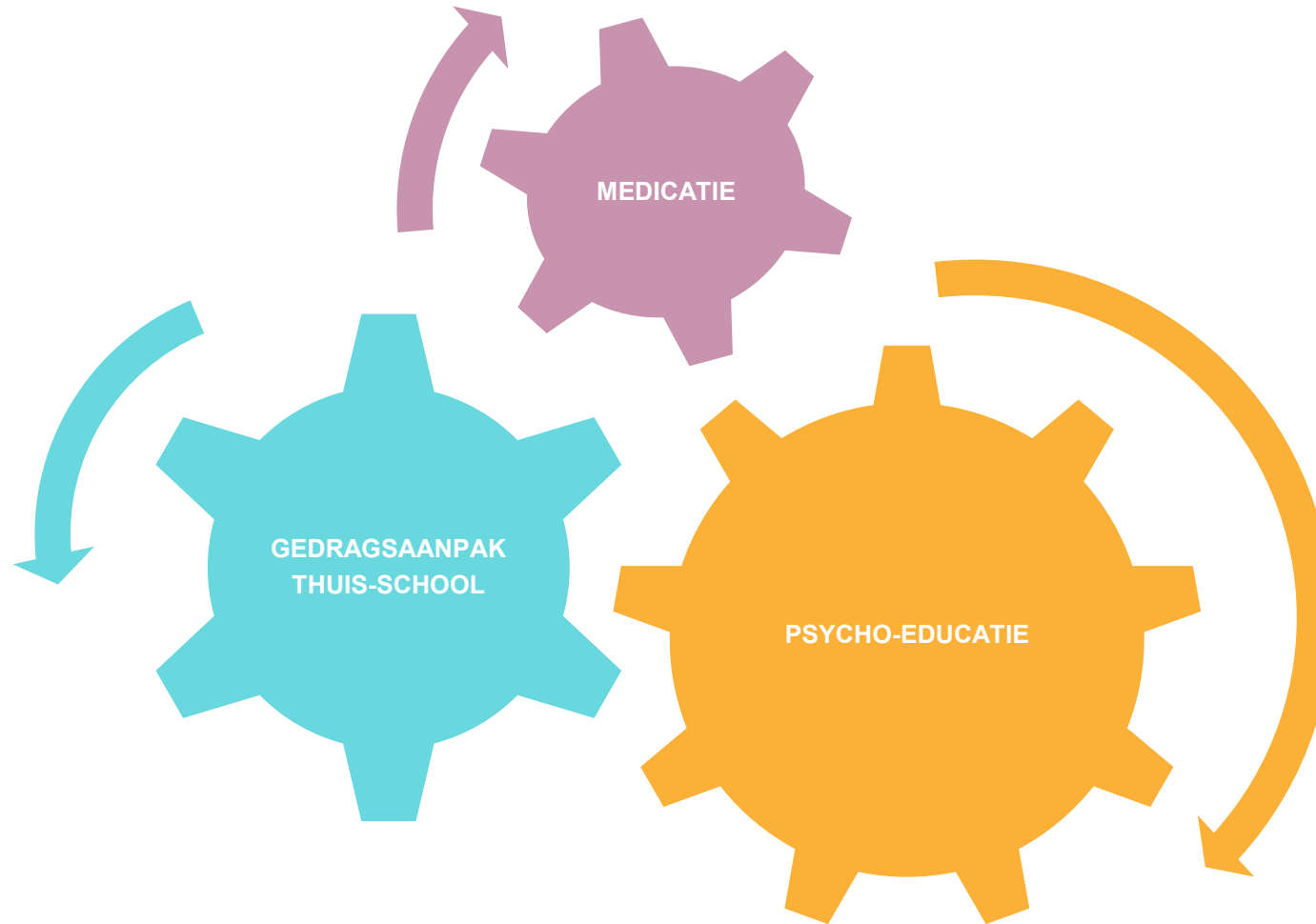
Prof.dr. Karen Vertessen

## Conflict of interest Karen Vertessen

| Type of activity                                                  | Company                                                                         |
|-------------------------------------------------------------------|---------------------------------------------------------------------------------|
| <ul style="list-style-type: none"><li>• Research grants</li></ul> | <ul style="list-style-type: none"><li>• Takeda</li><li>• Infectopharm</li></ul> |

# Intro

# Geïntegreerd geïndividualiseerd behandelplan



# ADHD-medicatie (in België)

## MEDICATIE

**STAP 1:** Methylfenidaat (Rilatine®, Medikinet®, Equasym®, Concerta®...) +/- 70%

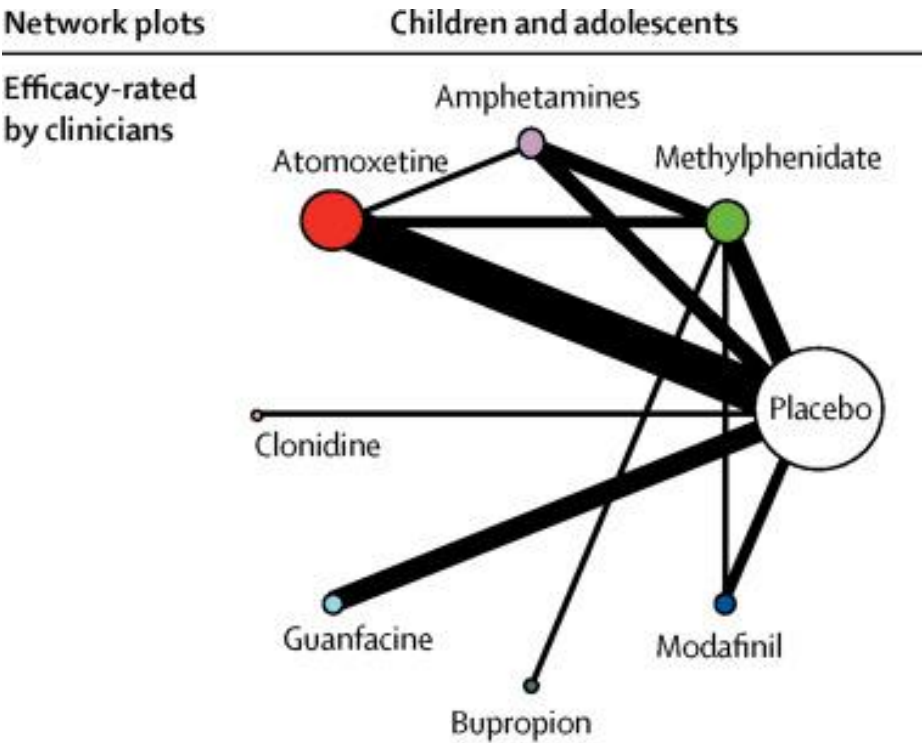
**STAP 2:** Dexamfetaminesulfaat/ Lisdexamfetamine (Dexamfetaminesulfaat, Elvanse®)

**STAP 3:** Atomoxetine of Guanfacine (Intuniv®)

+/- 90%

# THE GOOD

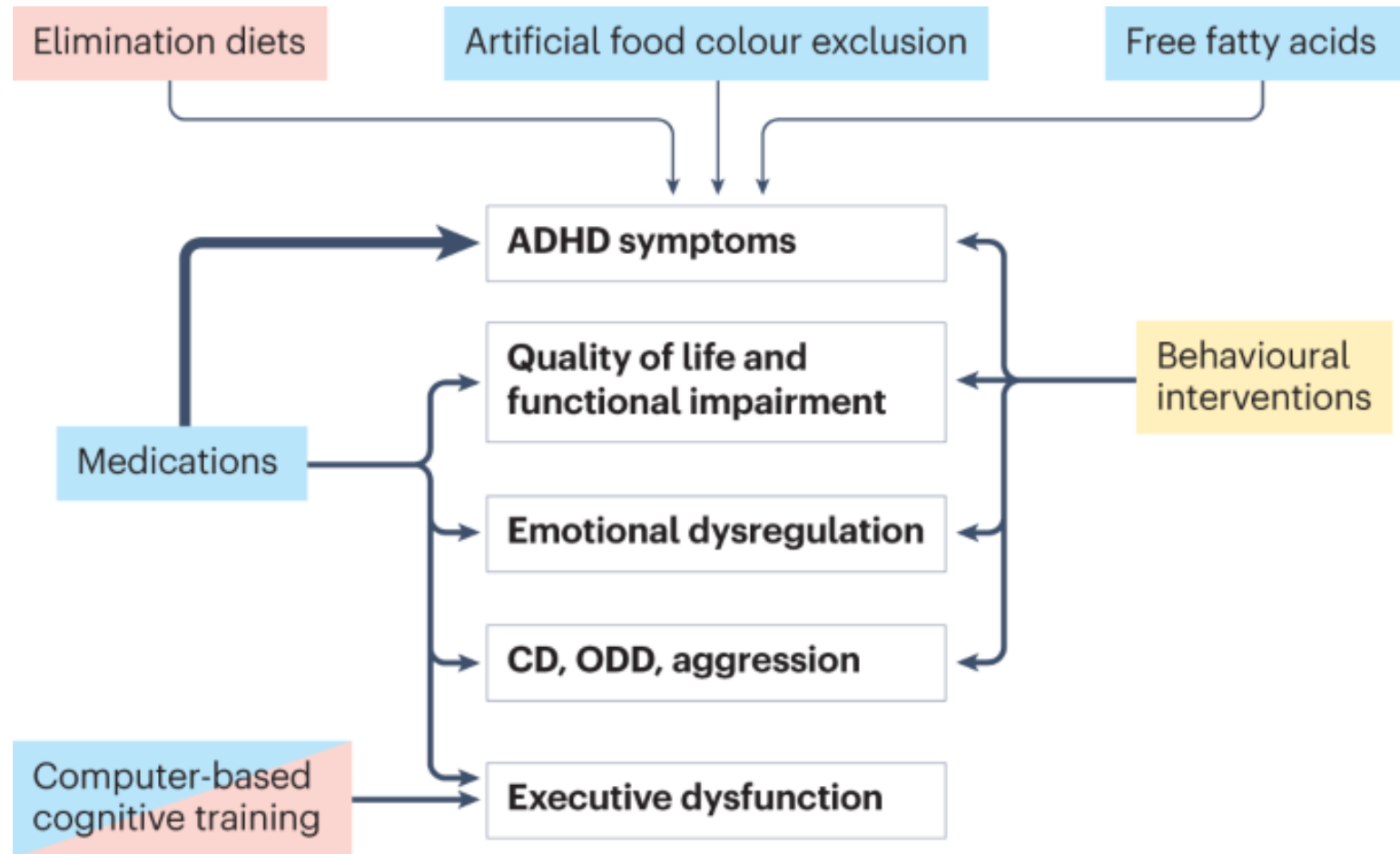
# Effectiviteit is goed onderbouwd



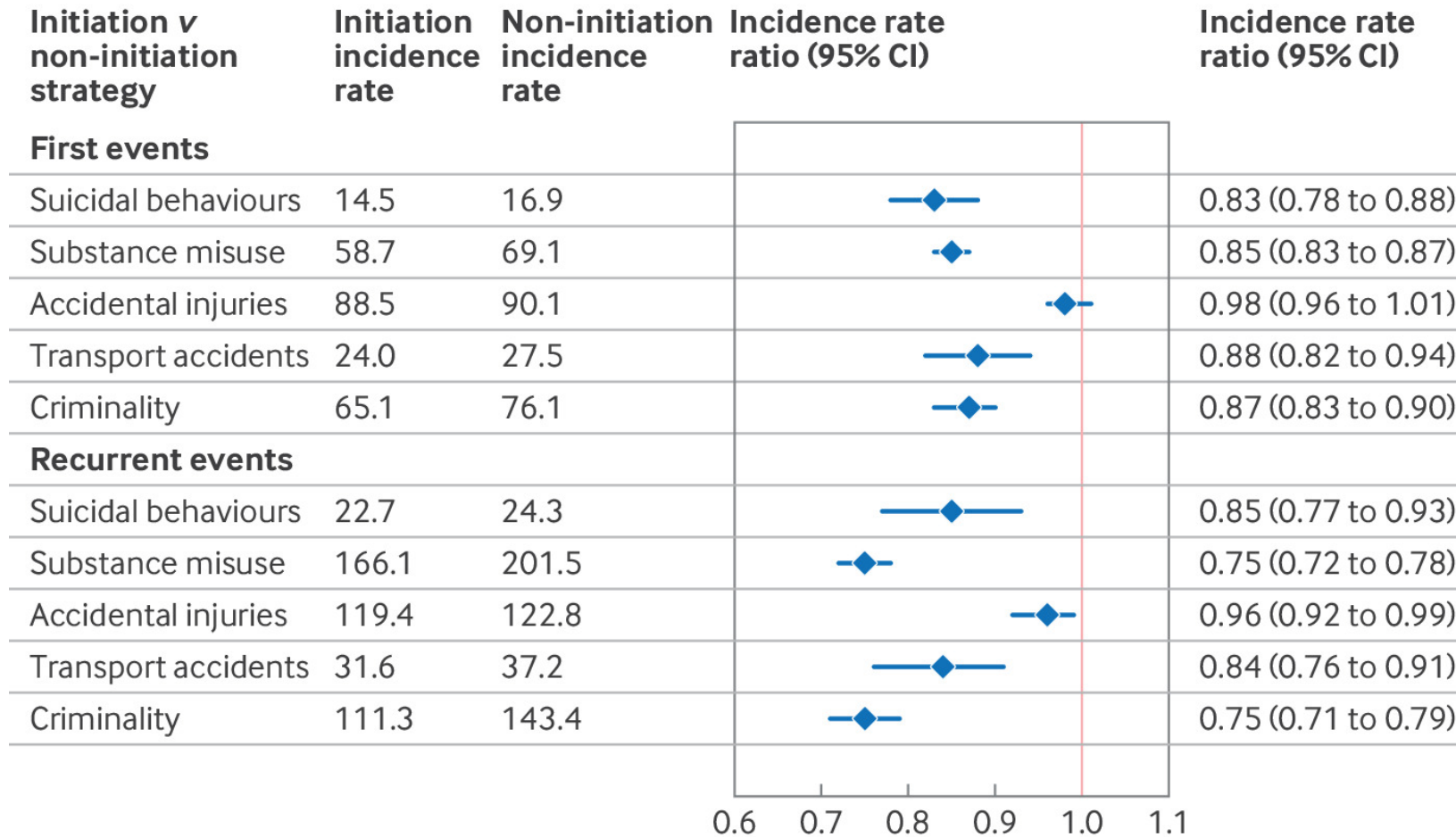
|                | K&A<br>(clanicus) | K&A<br>(Leerkracht) | Volwassenen<br>(clanicus) |
|----------------|-------------------|---------------------|---------------------------|
| Amphetamines   | 1.02              | -                   | 0.79                      |
| Methylfenidaat | 0.78              | 0.82                | 0.49                      |
| Guanfacine     | 0.67              | 0.63 (B)            | -                         |
| Atomoxetine    | 0.56              | 0.32 (B)            | 0.45                      |
| Clonidine      | 0.71 (B)          | -                   | -                         |
| Bupropion      | 0.96 (B)          | 0.32 (B)            | 0.46                      |
| Modafinil      | 0.62              | 0.76                | - 0.16 (B)                |

| effectgrootte      | het verschil is |
|--------------------|-----------------|
| $E > 0,8$          | groot           |
| $0,4 < E \leq 0,8$ | middelmatig     |
| $E \leq 0,4$       | gering          |

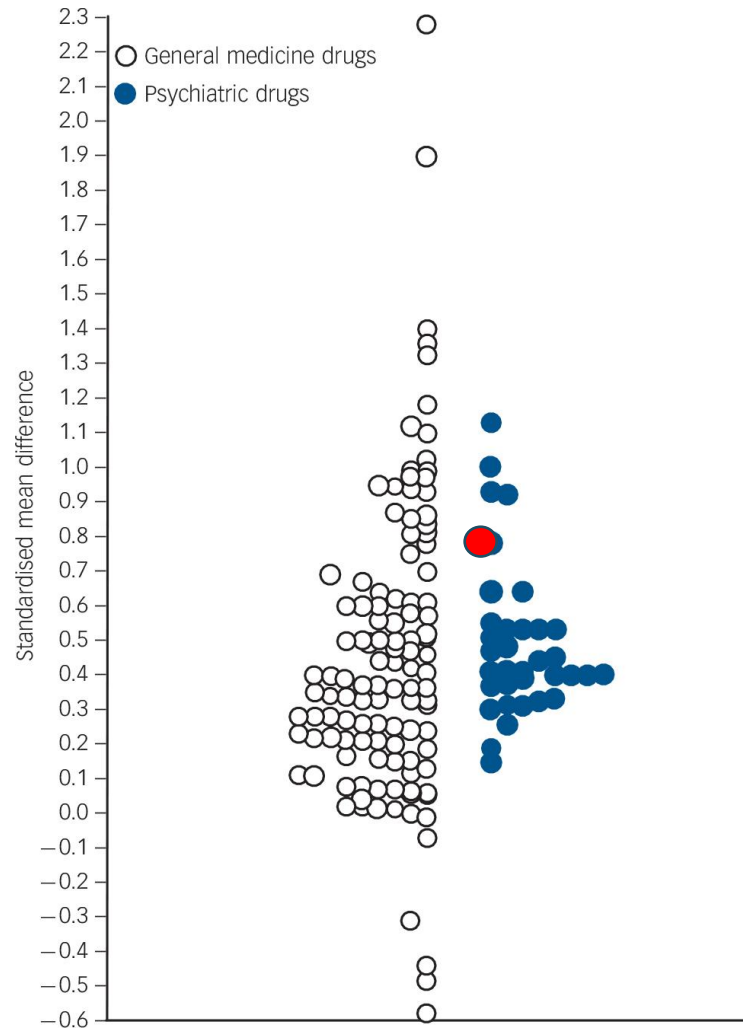
# Bredere effecten dan enkel op ADHD-symptomen



# Bredere effecten



# Effecten van medicatie



Heel effectieve medicatie tov andere medicatie

# Lange termijn gebruik is veilig

## Summary

**Background** Methylphenidate is the most frequently prescribed medication for the treatment of ADHD in children and adolescents in many countries. Although many randomised controlled trials support short-term efficacy, tolerability, and safety, data on long-term safety and tolerability are scarce. The aim of this study was to investigate the safety of methylphenidate over a 2-year period in relation to growth and development, psychiatric health, neurological health, and cardiovascular function in children and adolescents.

**Methods** We conducted a naturalistic, longitudinal, controlled study as part of the ADDUCE research programme in 27 European child and adolescent mental health centres in the UK, Germany, Switzerland, Italy, and Hungary. Participants aged 6–17 years were recruited into three cohorts: medication-naïve ADHD patients who intended to start methylphenidate treatment (methylphenidate group), medication-naïve ADHD patients who did not intend to start any ADHD medication (no-methylphenidate group), and a control group without ADHD. Children with ADHD diagnosed by a qualified clinician according to the DSM-IV criteria and, in the control group, children who scored less than 1·5 on average on the Swanson, Nolan, and Pelham IV rating scale for ADHD items, and whose hyperactivity score on the parent-rated Strengths and Difficulties Questionnaire was within the normal range (<6) were eligible for inclusion. Participants were excluded if they had previously taken any ADHD medications but remained eligible if they had previously taken or were currently taking other psychotropic drugs. The primary outcome was height velocity (height velocity SD score; estimated from at least two consecutive height measurements, and normalised with reference to the mean and SD of a population of the same age and sex).

**Findings** Between Feb 01, 2012, and Jan 31, 2016, 1410 participants were enrolled (756 in methylphenidate group, 391 in no-methylphenidate group, and 263 in control group). 1070 (76·3%) participants were male, 332 (23·7%) were female, and for eight gender was unknown. The average age for the cohort was 9·28 years (SD 2·78; IQR 7–11). 1312 (93·0%) of 1410 participants were White. The methylphenidate and no-methylphenidate groups differed in ADHD symptom severity and other characteristics. After controlling for the effects of these variables using propensity scores, there was little evidence of an effect on growth (24 months height velocity SD score difference –0·07 (95% CI

ADHD medications are effective, and for most patients their adverse effects are acceptable and manageable, supporting their use as first-line treatments when indicated (Cortese et al , 2018)

**Interpretation** Our results suggest that long-term treatment with methylphenidate for 2 years is safe. There was no evidence to support the hypothesis that methylphenidate treatment leads to reductions in growth. Methylphenidate-related pulse and blood pressure changes, although relatively small, require regular monitoring.

Adduce  
studies

# Goed uitgeschreven Belgische richtlijnen

The screenshot displays the 'ZORGPAD ADHD' website. At the top, there is a search bar labeled 'Zoeken...' and language selection buttons for 'NL' and 'FR'. Below the header, a navigation bar includes links for 'WIE BEN IK?', 'OVER ZORGPAD ADHD', and 'ADRESSEN'. The main content area is titled 'TITRATIESCHEMA'S EN VOORSCHRIJFREGELS'. A sidebar on the left lists various treatment options under 'BEHANDELING ADHD', with 'MEDICAMENTEUZE BEHANDELING' selected. The main text explains that methylphenidate and dexamfetamine are controlled substances ('verdovende middelen') and provides specific dosing guidelines for methylphenidate, including immediate release formulations like Rilatine and Medikinet. A red banner at the bottom shows a treatment flowchart with steps: 'WANNEER AAN ADHD DENKEN?', 'PREDIAGNOSTISCHE FASE', 'DIAGNOSTISCHE FASE', and 'BEHANDELING ADHD'.

ZORGPAD ADHD

Zoeken...

NL FR

WIE BEN IK? OVER ZORGPAD ADHD ADRESSEN

Home » BEHANDELING ADHD » Medicamenteuze behandeling » Opstarten medicatie » Titratieschema's » Titratieschema's en voorschriftregels

**BEHANDELING ADHD**

- PSYCHO-EDUCATIE
- GEÏNTEGREERD BEHANDELPLAN
- NIET-MEDICAMENTEUZE BEHANDELING
- **MEDICAMENTEUZE BEHANDELING**
  - ▶ Opstarten medicatie
    - Geïnformeerde beslissing en toestemming
    - Checklist medicatie opstarten
    - Basislijn en vooronderzoeken
    - Welke medicatie kiezen?
      - › ADHD zonder comorbiditeit

**TITRATIESCHEMA'S EN VOORSCHRIJFREGELS**

**TITRATIESCHEMA'S**

Methylfenidaat en dexamfetamine vallen onder de reglementering van de "verdovende middelen". Dat betekent dat alle getallen voluit moeten geschreven worden.

**1. METHYLFENIDAAT**

**1.1. Kortwerkende Methylfenidaat IR (Immediate Release)**

Rilatine® 10 mg Medikinet® 5 mg, 10 mg, 20 mg

Maximum dosis: 60 mg/d

Bij uitzondering kan in oudere adolescenten verhoogd worden tot 100 mg

Bij kinderen onder 25 kg: 45 mg/d

Tijdens de titratiefase wordt aangeraden medicatie 3 x dag te geven en tijdens het weekend, zodat

ZORGPAD

WANNEER AAN ADHD DENKEN?

PREDIAGNOSTISCHE FASE

DIAGNOSTISCHE FASE

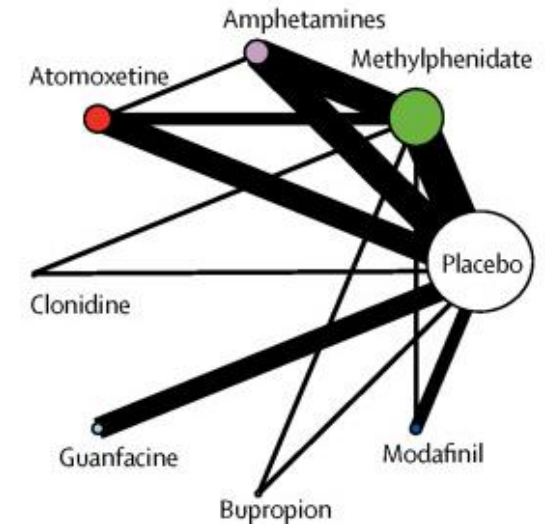
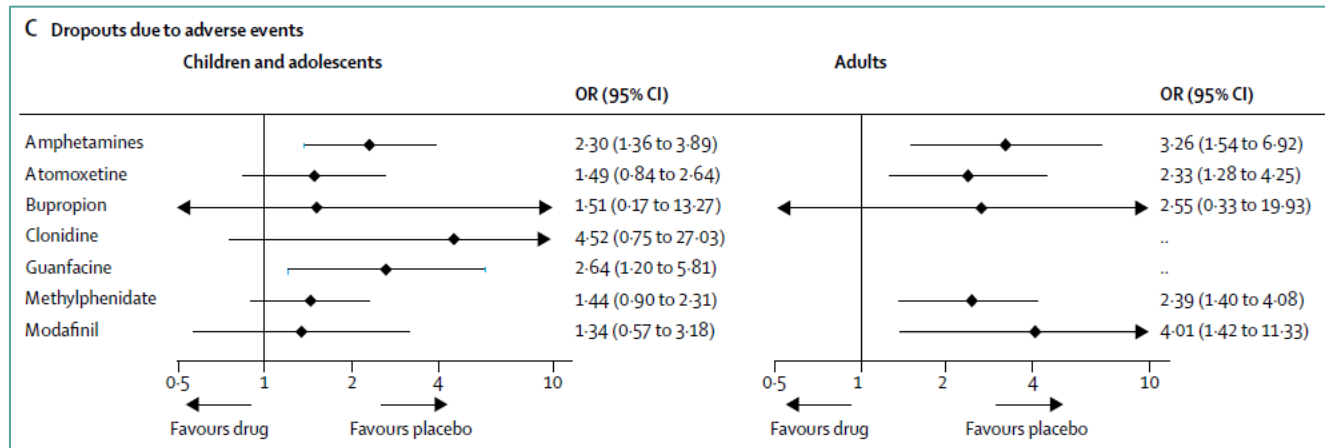
BEHANDELING ADHD

# THE BAD

# Bijwerkingen

**Nevenwerkingen** leiden vaker tot stoppen met medicatie dan placebo

Tolerability



# Bijwerking

## MEEST VOORKOMENDE BIJWERKINGEN

- Eetlustvermindering
- Gewichtsstagnatie of –verlies
- Beperkte groei achterstand
- Misselijkheid/buikpijn, hoofdpijn
- Slaapmoeilijkheden
- Emotionele nevenwerkingen
- Lichte verhoging van de bloeddruk en pols

**GERT-JAN** «De rilatine maakt me geremder, minder sociaal en minder spraakzaam. Vrienden op school zeiden soms: 'Je bent zo anders, je zegt zo weinig.' Dat raakte me wel.

»In het begin had ik ook veel last van bijwerkingen. Ik voelde me somber en had weinig eetlust, in de eerste maand ben ik bijna 10 kilo afgevallen. Ik werd gelukkig goed begeleid,



Veel nevenwerkingen treden voornamelijk op bij de opstart van de medicatie

- Bij **lichte nevenwerkingen**:
  - Wacht enkele dagen af en neem eventueel pijnstilling in.
- Bij **storende en/of aanhoudende nevenwerkingen**:
  - Stop de inname van de medicatie en neem contact op met de behandelaar

# Lange termijn neveneffecten

- Bloeddruk verhoging – risico vasculaire problemen (zeer beperkt)
- Effect op lengte groei is beperkt
- Geen negatieve effecten op hersenontwikkeling
- Niet verslavend – wel oppassen voor misbruik van kortwerkende stimulantia

# Niet medisch gebruik van ADHD-medicatie

- Ongeveer één op de negen studenten (11,5%) geeft aan ooit stimulerende medicatie genomen te hebben. Het aandeel studenten dat in de afgelopen twaalf maanden stimulerende medicatie gebruikte, bedraagt 7,6%.  
→ [Lees meer](#)
- Studenten gebruiken stimulerende medicatie voornamelijk tijdens de blok- en examenperiodes (84,3% van de studenten die in het laatste jaar gebruikten, deed dit minstens 1 keer per week).  
→ [Lees meer](#)
- Van de totale studentenpopulatie heeft 7,0% van de studenten ooit stimulerende medicatie gebruikt om de studieprestaties te verbeteren, en 4,4% van alle studenten heeft dit in de afgelopen twaalf maanden gedaan.  
→ [Lees meer](#)
- Ongeveer acht op de tien studenten (79,8%) die ooit stimulerende medicatie gebruikten om de studieprestaties te verbeteren, rapporteerden minimaal één negatieve bijwerking van de medicatie.  
→ [Lees meer](#)
- Het aandeel studenten dat in de afgelopen twaalf maanden stimulerende medicatie gebruikte om de studieprestaties te verbeteren, verschilt significant tussen mannen en vrouwen (4,9% vs. 2,7%) en tussen zelfstandig wonende studenten (5,1%), kotstudenten (4,0%) en thuis wonende studenten (3,0%).  
→ [Lees meer](#)

# Niet medisch gebruik van ADHD-medicatie

Inconsistent effect van ADHD-medicatie op cognitieve prestaties bij gezonde volwassenen

- Effecten zijn **klein** en **specifiek voor onderzoekssetting**

Verbetering werk- studieresultaten is vaak motief

- **Geen positieve invloed** aangetoond
- Sommige studies laten een negatieve invloed zien
- Indien positief effect lijkt vooral gekoppeld aan verwachting

Niet medisch gebruik van stimulantia bij studenten: **rode vlag** voor andere problemen

# EVERYTHING IN BETWEEN



# Waar lopen we tegen aan?

1. Several clinically relevant areas lack sufficient evidence, including how to personalise treatment and identify practical predictors of treatment response.
2. Some existing evidence has not yet been adequately translated into clinical guidelines or routine practice, particularly regarding comparative treatment effects and dose–response relationships relevant to medication titration.
3. Some respondents reported needs that are already addressed in existing international guidelines, suggesting that language barriers may limit access to guidance and underscoring the importance of developing country-specific recommendations in local languages.

European Child & Adolescent Psychiatry  
<https://doi.org/10.1007/s00787-026-03161-w>

## RESEARCH



### Clinical practices in ADHD management across Europe: findings from the ESCAP research academy survey

Héloïse Young<sup>1,2</sup> · Alexis Revet<sup>3,4</sup> · Julie Hagstrøm<sup>5</sup> · Burçin Özlem Ates<sup>6</sup> · Astrid Brænden<sup>7</sup> · Markella Grigoriou<sup>8</sup> · Irina Jarvers<sup>9</sup> · Moa Jederström<sup>10,11</sup> · Lucie Jurek<sup>12,13</sup> · Konstantinos Kotsis<sup>14</sup> · Sanja Lestarevic<sup>15</sup> · Matthias Liebrand<sup>16</sup> · Emilia Matera<sup>17</sup> · Dorottya Öri<sup>18,19</sup> · Asilay Seker<sup>20</sup> · Gordana Nikolova<sup>21</sup> · Tetiana Skrypnyk<sup>22,23</sup> · Mireia Solerdelcoll<sup>24,25</sup> · Christine Lykke Thousttrup<sup>5,26</sup> · Karen Vertessen<sup>27,28</sup> · European ADHD Guidelines Group (EAGG)\* · Paul Klauser<sup>29,30</sup> · Samuele Cortese<sup>31,32,33,34,35</sup>



# Waar lopen we tegen aan?

| Topics                                                      | Major findings                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Limitations                                                                                                                                                                                                                                                                                            | Further reviews needed                                                                                                                                                                                                            |
|-------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Pharmacological treatment                                   | <p>Stimulants were recommended as first-line medication both for children (methylphenidate preferred) and adults (amphetamine preferred)</p> <p>Nonstimulants were also found effective in treating ADHD in children (atomoxetine, guanfacine) and adults (atomoxetine, bupropion), though less effective than stimulants</p> <p>Side-effects were common and include reduced appetite, sleep problems, headache, increased heart rate and increased blood pressure</p> | <p>Most trials have <u>short follow-up time</u> (weeks and months rather than years) and focus mainly on core symptoms of ADHD as outcome</p> <p>There is no review evidence of pharmacological treatment effect on life-trajectory in ADHD over more than few months follow-up</p>                    | Reviews of pharmacological treatment effects in ADHD on long-term prognosis with real-life outcomes including educational attainment, welfare dependency and employment, criminality, injuries, and mortality are urgently needed |
| Pharmacological versus nonpharmacological treatment in ADHD | <p>Stimulants were superior to nonpharmacological treatment in reducing core symptoms among children and adolescents with ADHD</p> <p>While medications improved ADHD symptoms, psychosocial treatments were beneficial for academic and organizational skills in adolescents</p> <p>Pharmacological treatment was found to be cost-effective compared to nonpharmacological treatment or no treatment</p>                                                              | <p>Reviews compared medication with groups of different nonpharmacological intervention rather than comparing medication with one particular nonpharmacological intervention</p> <p>There is no review evidence of long-term effect of pharmacological versus nonpharmacological treatment on ADHD</p> | Reviews comparing the long-term effects of pharmacological versus nonpharmacological treatment on ADHD are needed                                                                                                                 |

European Psychiatry

[www.cambridge.org/epa](http://www.cambridge.org/epa)

## Review/Meta-analysis

**Cite this article:** Chaulagain A, Lyhmann I, Halmøy A, Widding-Havneraas T, Nytingnes O, Bjelland I, Mykletun A (2023). A systematic meta-review of systematic reviews on attention deficit hyperactivity disorder. *European Psychiatry*, 66(1), e90, 1–92 <https://doi.org/10.1192/j.eurpsy.2023.2451>

## A systematic meta-review of systematic reviews on attention deficit hyperactivity disorder

Ashmita Chaulagain<sup>1,2</sup> , Ingild Lyhmann<sup>1,2</sup> , Anne Halmøy<sup>2,3</sup> , Tarjei Widding-Havneraas<sup>1,2</sup> , Olav Nytingnes<sup>1</sup> , Ingvar Bjelland<sup>2,3</sup>  and Arnstein Mykletun<sup>1,4,5,6</sup> 

<sup>1</sup>Centre for Research and Education in Forensic Psychiatry, Haukeland University Hospital, Bergen, Norway; <sup>2</sup>Department of Clinical Medicine, University of Bergen, Bergen, Norway; <sup>3</sup>Division of Psychiatry, Haukeland University Hospital, Bergen, Norway; <sup>4</sup>Division for Health Services, Norwegian Institute of Public Health, Oslo, Norway; <sup>5</sup>Department of Community Medicine, UiT – The Arctic University of Norway, Tromsø, Norway and <sup>6</sup>Centre for Work and Mental Health, Nordland Hospital, Bodo, Norway

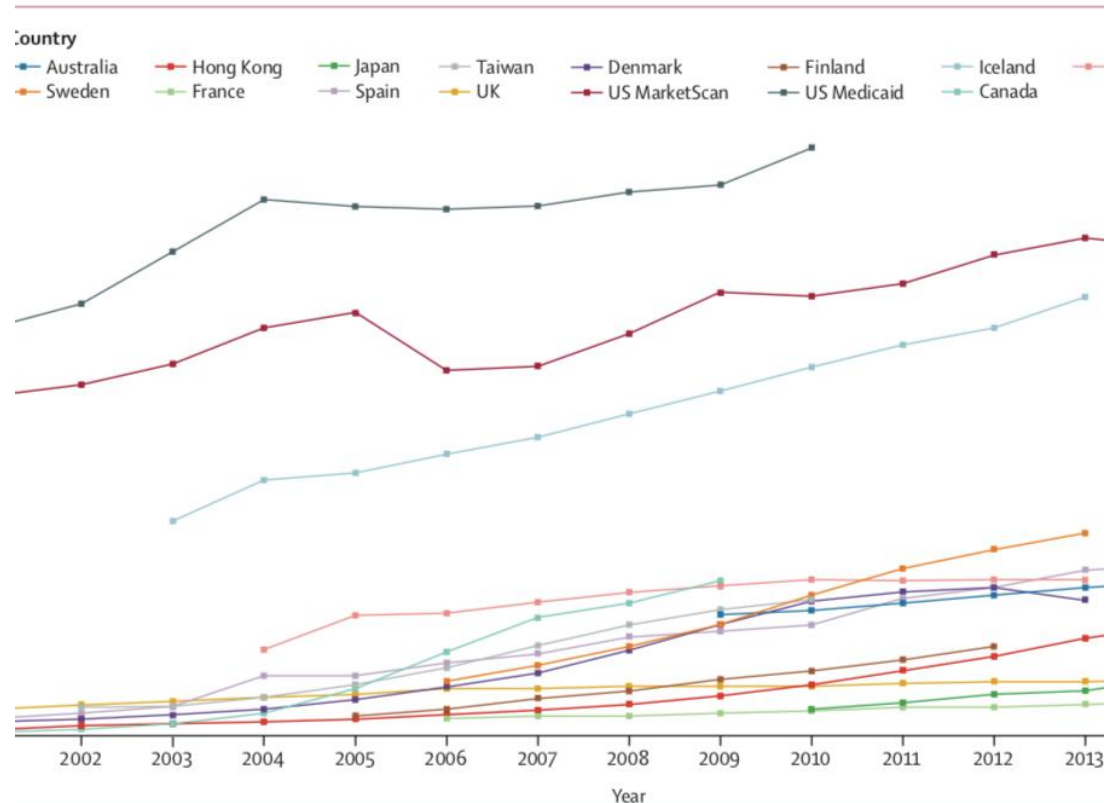
# Waar lopen we tegen aan?



EVERYTHING IN BETWEEN

Wie start er met medicatie?

# Toenemend gebruik



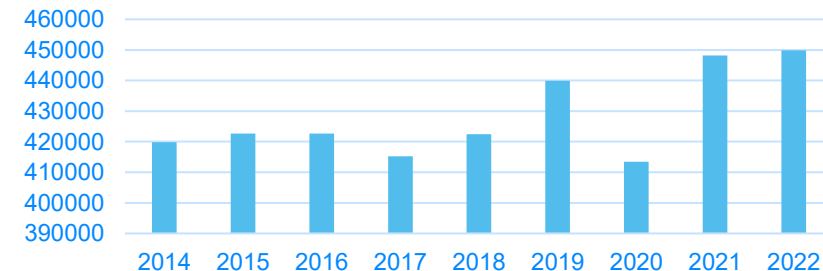
all annual prevalence of attention deficit hyperactivity disorder medication use in children aged 3-18 years

## CM waarschuwt voor overgebruik Rilatine

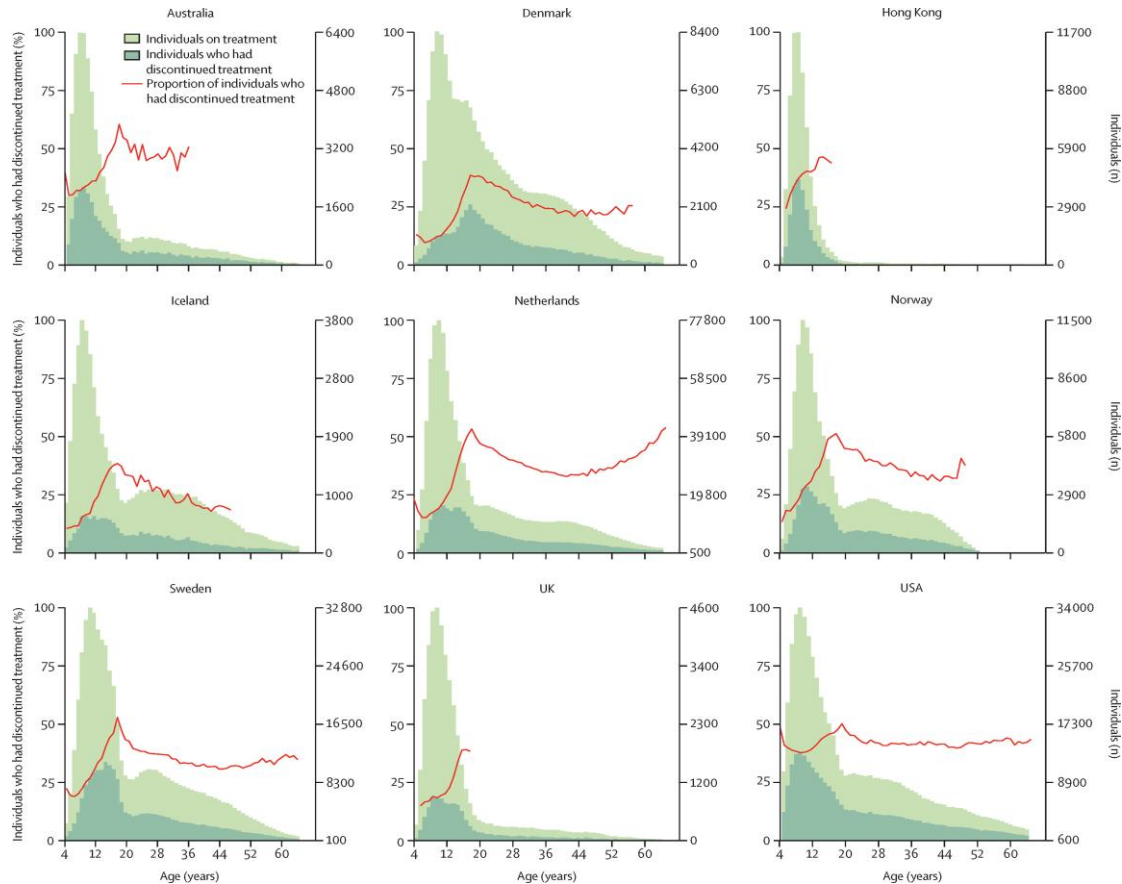


©Saskia Vanderstichele

## Aantal verpakkingen methyfenidaat per jaar



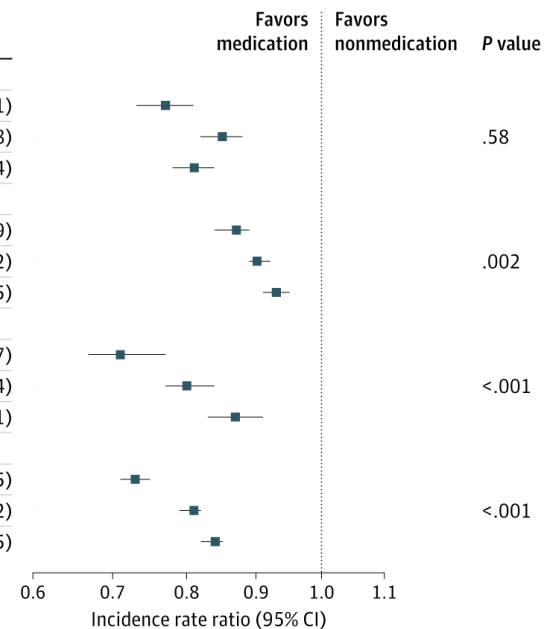
# Velen stoppen snel ...



- Veel personen die starten met ADHD medicatie stoppen er ook snel weer mee (Brikell et al; 2024)
- Ervaren van weinig effect meest voorkomende reden om te stoppen (Titheradge et al., 2022)

# Stijgend voorschrijven ~ kleinere effecten

| Study                | With medication |              | No medication |              | Incidence rate ratio (95% CI) |
|----------------------|-----------------|--------------|---------------|--------------|-------------------------------|
|                      | Events, No.     | Person-years | Events, No.   | Person-years |                               |
| Self-harm            |                 |              |               |              |                               |
| 2006-2010            | 2696            | 12634.96     | 16236         | 108157.46    | 0.77 (0.73-0.81)              |
| 2011-2015            | 7185            | 30555.45     | 18646         | 93063.10     | 0.85 (0.82-0.88)              |
| 2016-2020            | 11286           | 40355.69     | 21331         | 78961.54     | 0.81 (0.78-0.84)              |
| Unintentional injury |                 |              |               |              |                               |
| 2006-2010            | 9162            | 52187.10     | 76130         | 494717.26    | 0.87 (0.84-0.89)              |
| 2011-2015            | 27477           | 138895.33    | 99632         | 492271.63    | 0.90 (0.89-0.92)              |
| 2016-2020            | 40505           | 218581.36    | 84404         | 426325.72    | 0.93 (0.91-0.95)              |
| Traffic crashes      |                 |              |               |              |                               |
| 2006-2010            | 1551            | 10563.48     | 16103         | 94968.63     | 0.71 (0.67-0.77)              |
| 2011-2015            | 4252            | 31264.83     | 16746         | 102841.98    | 0.80 (0.77-0.84)              |
| 2016-2020            | 5806            | 45288.43     | 16795         | 103046.04    | 0.87 (0.83-0.91)              |
| Crime                |                 |              |               |              |                               |
| 2006-2010            | 9556            | 18523.63     | 94432         | 154631.06    | 0.73 (0.71-0.75)              |
| 2011-2015            | 20279           | 52780.13     | 88020         | 172326.78    | 0.81 (0.79-0.82)              |
| 2016-2020            | 21130           | 74554.05     | 78829         | 182772.84    | 0.84 (0.82-0.85)              |

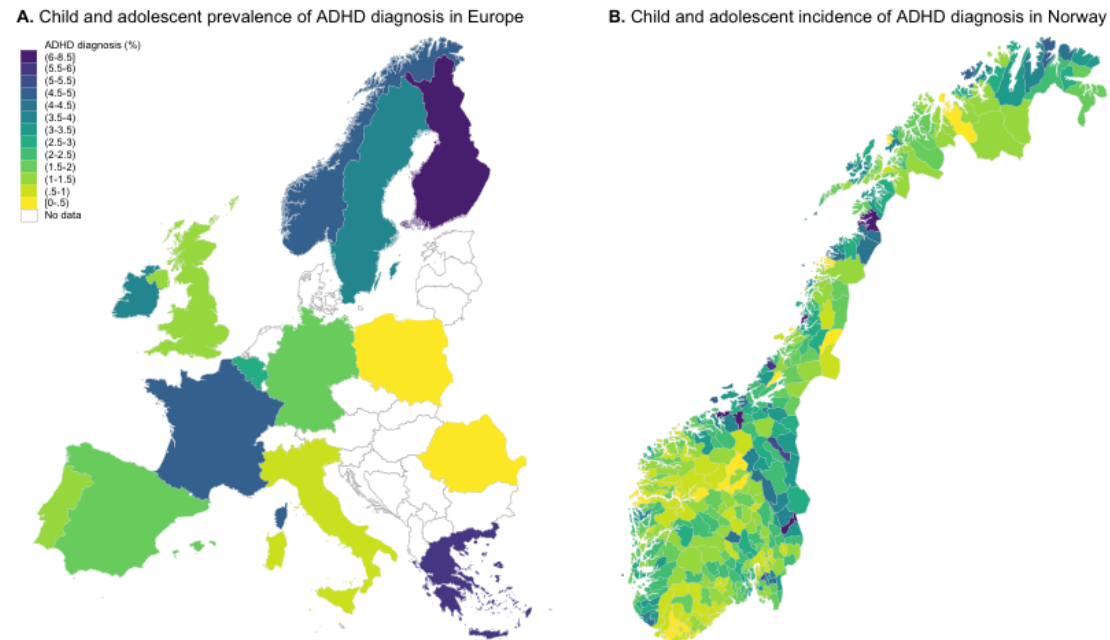


- Zweeds registeronderzoek naar ADHD-medicatie en reële uitkomsten.
- Vergeleek periodes mét en zonder medicatie binnen dezelfde personen in verschillen tijdsperiodes
- Stijgend medicatie gebruik in populatie over de tijd

# ADHD Controversy Project



# Grote verschillen in ADHD diagnoses tussen en binnen landen



**Fig.1** Geographical variation in ADHD diagnosis in Europe and Norway. Panel **A** Prevalence rate of ADHD diagnosis in children and adolescents across European countries. Panel **B** Incidence rate of

ADHD diagnosis in Norway, 0–18 years, 2011–2016. ADHD diagnoses registered in the Norwegian Patient Registry by municipality ( $n=428$ )

European Child & Adolescent Psychiatry (2023) 32:1795–1803  
<https://doi.org/10.1007/s00787-022-01996-7>

## ORIGINAL CONTRIBUTION

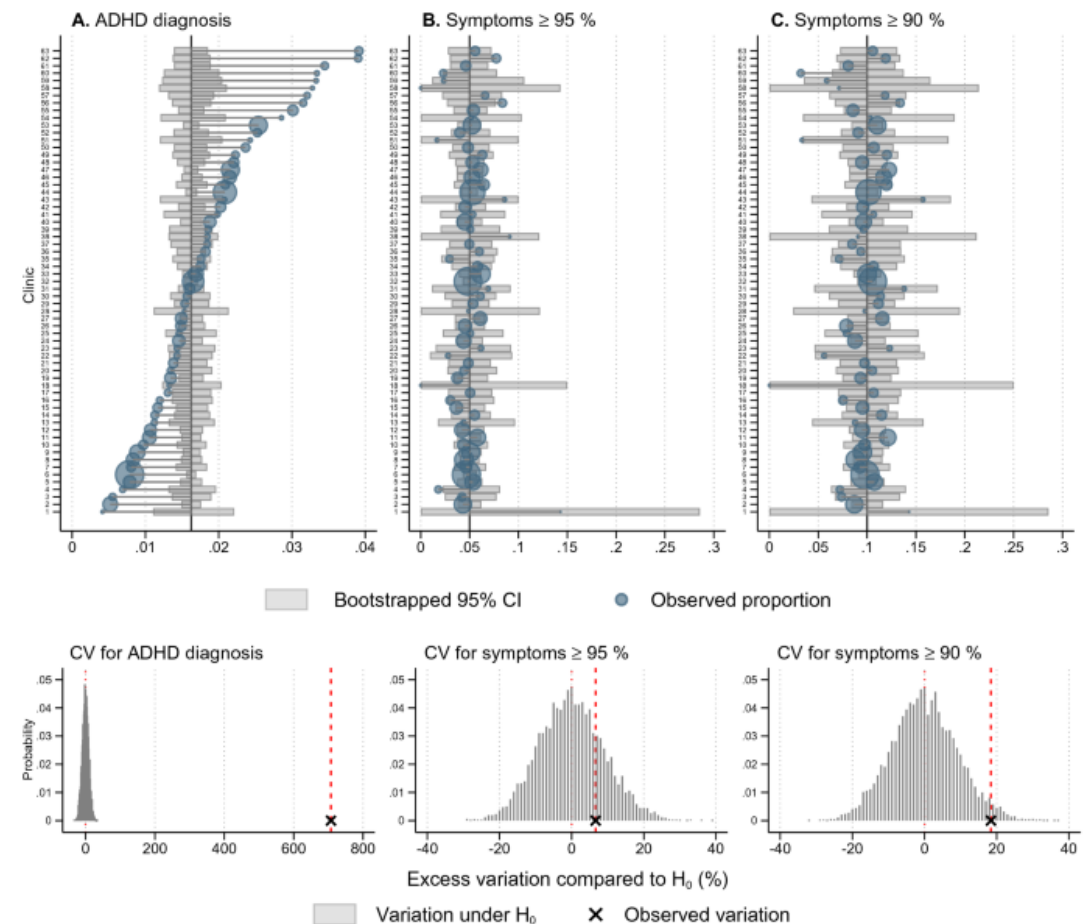
### Geographical variation in ADHD: do diagnoses reflect symptom levels?

Tarjei Widding-Havneraas<sup>1,2</sup> · Simen Markussen<sup>3</sup> · Felix Elwert<sup>4</sup> · Ingvild Lyhmann<sup>1,2</sup> · Ingvar Bjelland<sup>1,5</sup> · Anne Halmøy<sup>1,5</sup> · Ashmita Chaulagain<sup>1,2</sup> · Eivind Ystrom<sup>6,7</sup> · Arnstein Mykletun<sup>2,8,9,10</sup> · Henrik Daae Zachrisson<sup>11</sup>

Received: 5 April 2022 / Accepted: 23 April 2022 / Published online: 18 May 2022  
© The Author(s) 2022

# Grote verschillen in ADHD diagnoses

- Veel variatie in hoeveelheid ADHD diagnoses
- Weinig variatie in ADHD symptomen in de populatie



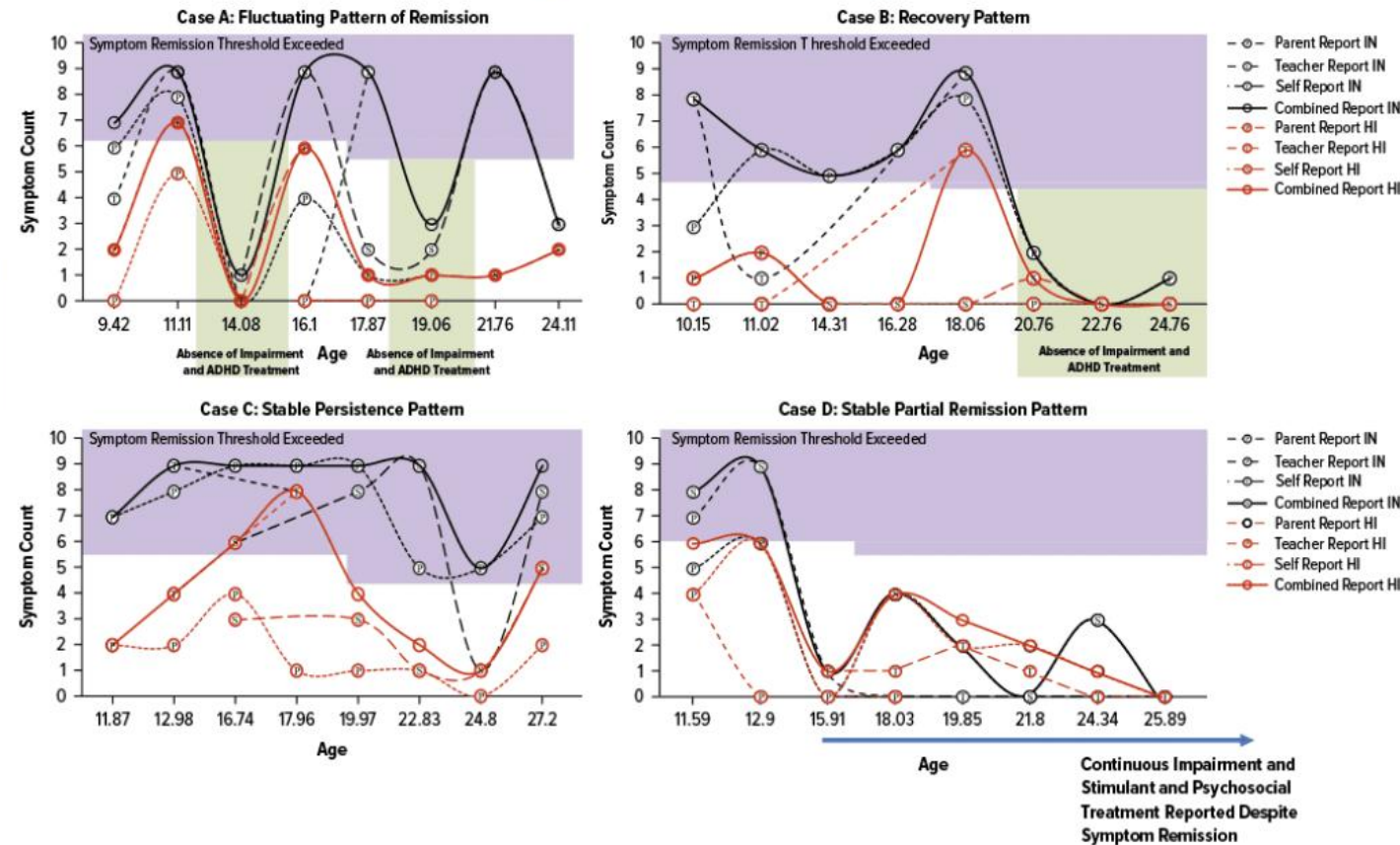
EVERYTHING IN BETWEEN

# Lange termijn

# Lange termijn verloop van klachten

Figure 1.

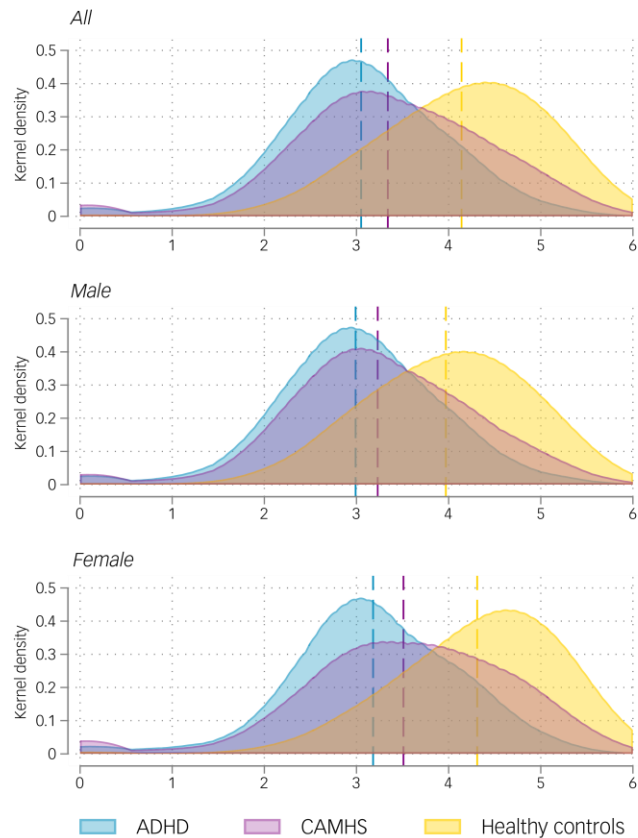
## Case Examples and Definitions of Longitudinal Remission Subgroups<sup>a</sup>



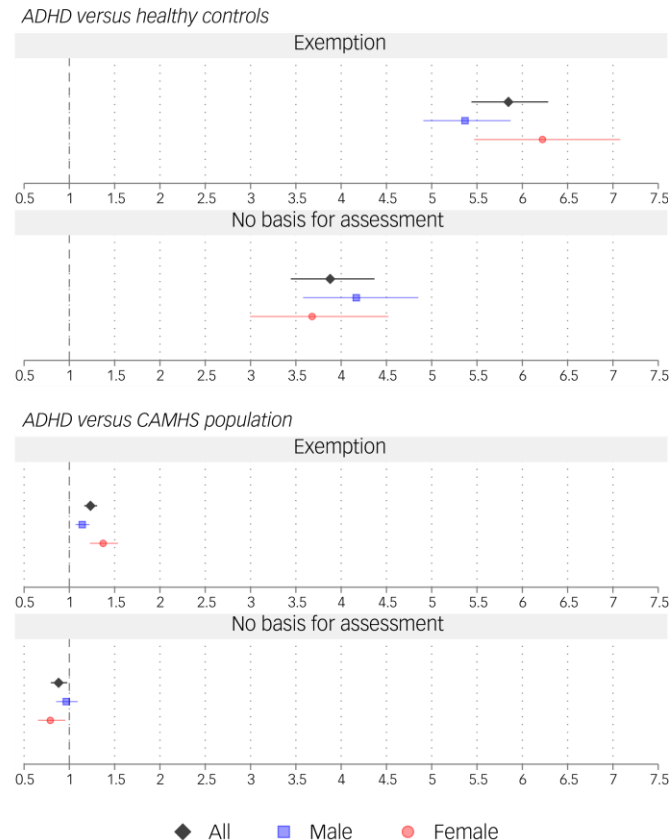
- Veel variatie in verloop van symptomen en impact
- Weinig studies onderzoeken langer dan 2 jaar
- Lange termijn onderzoek is niet evident

# Lange termijn effect op schoolse resultaten

(a) Grade point average distribution



(b) Risk ratios for 'Exemption' and 'No basis for assessment'



BJPsych

The British Journal of Psychiatry (2026)  
1-8. doi: 10.1192/bjp.2026.10754

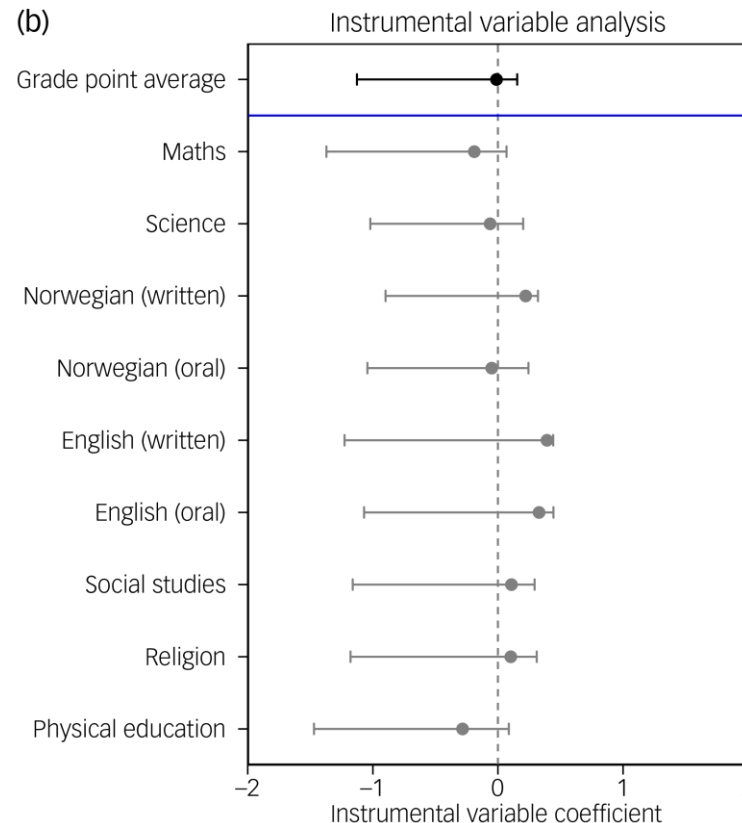
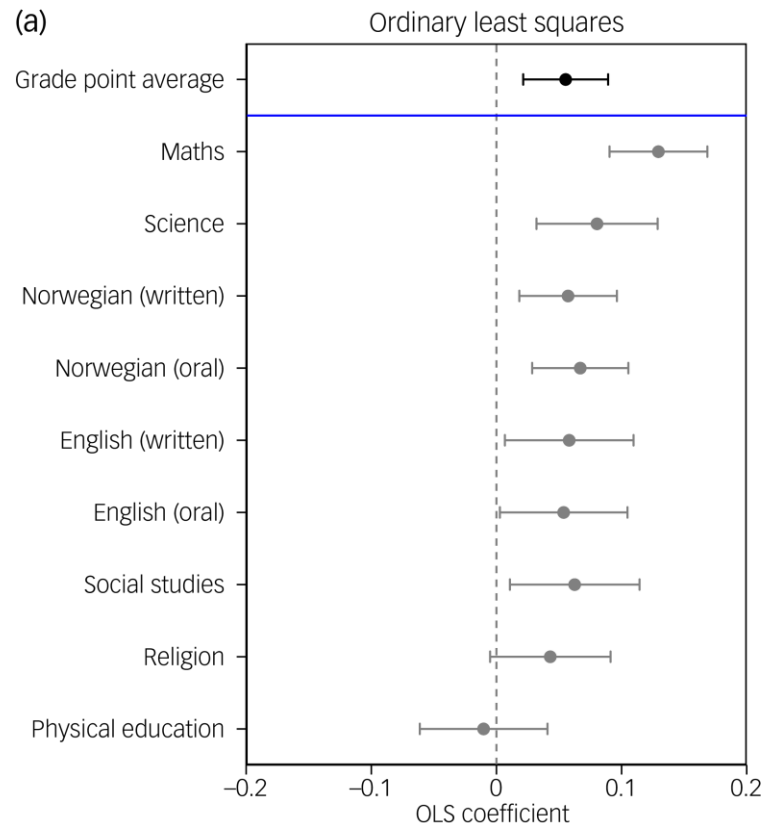
## Original Article

### Effect of pharmacological treatment of attention-deficit hyperactivity disorder on academic performance: registry-based population study

Ingvald Lyhmann, Tarjei Widding-Havneraas, Simen Markussen, Henrik Daae Zachrisson, Felix Elwert, Ashmita Chaulagain, Ingvar Bjelland, Anne Halmøy and Arnstein Mykletun

- Noorse register studie
- 6255 kinderen met ADHD diagnose
- Verschil in voorschrijfgedrag tussen de centra
- Opvolging tot 10 jaar lang

# Lange termijn effect op schoolse resultaten

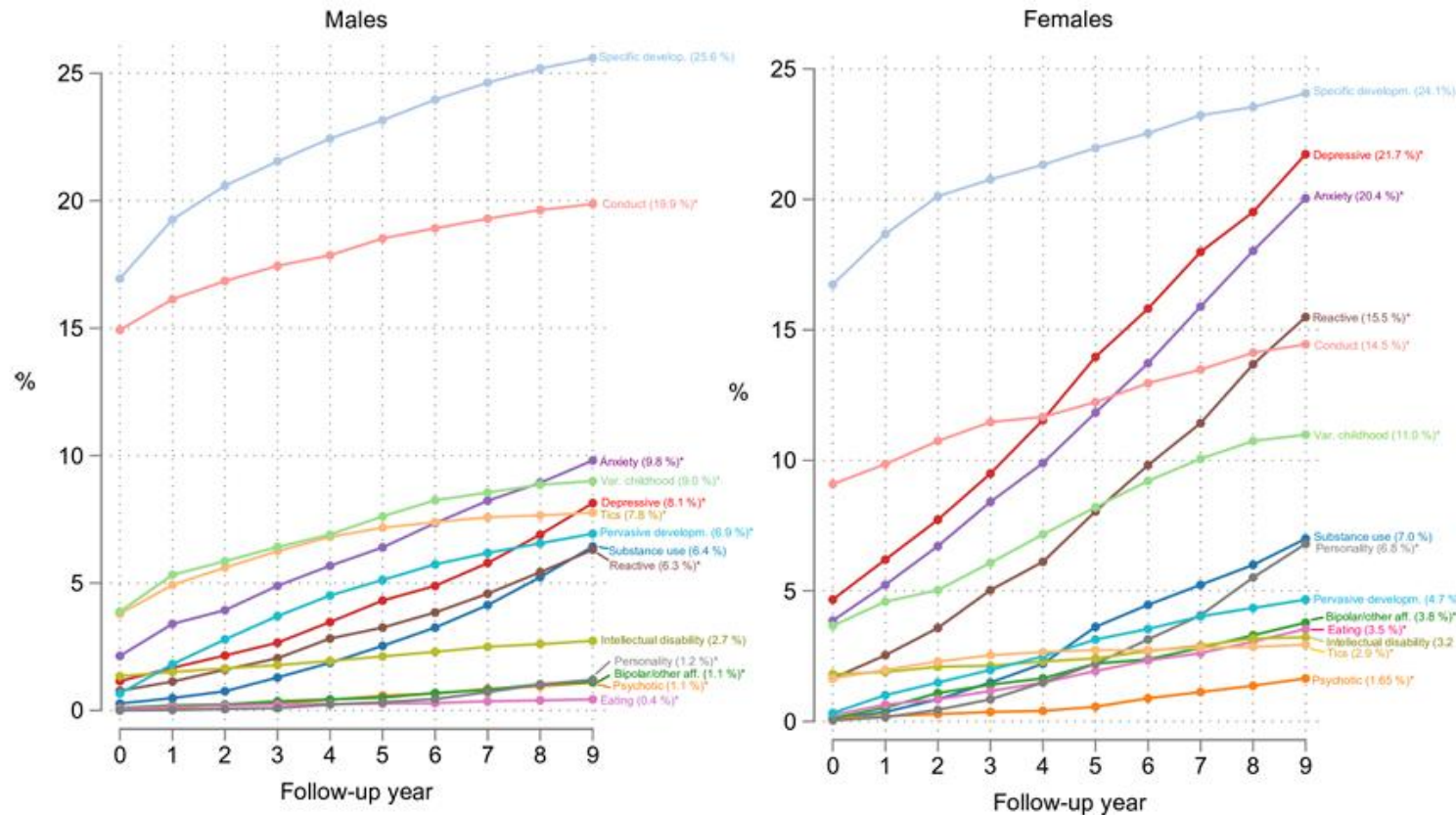


Instrumental variable analyse:

- Kleine voordelen van medicatie verdwijnen als rekening gehouden wordt met het centrum
- Belangrijk info voor jongeren op de grens voor medicatie

Dit betekent niet dat er geen effect is op schoolse resultaten

# Lange termijn effect op comorbiditeit

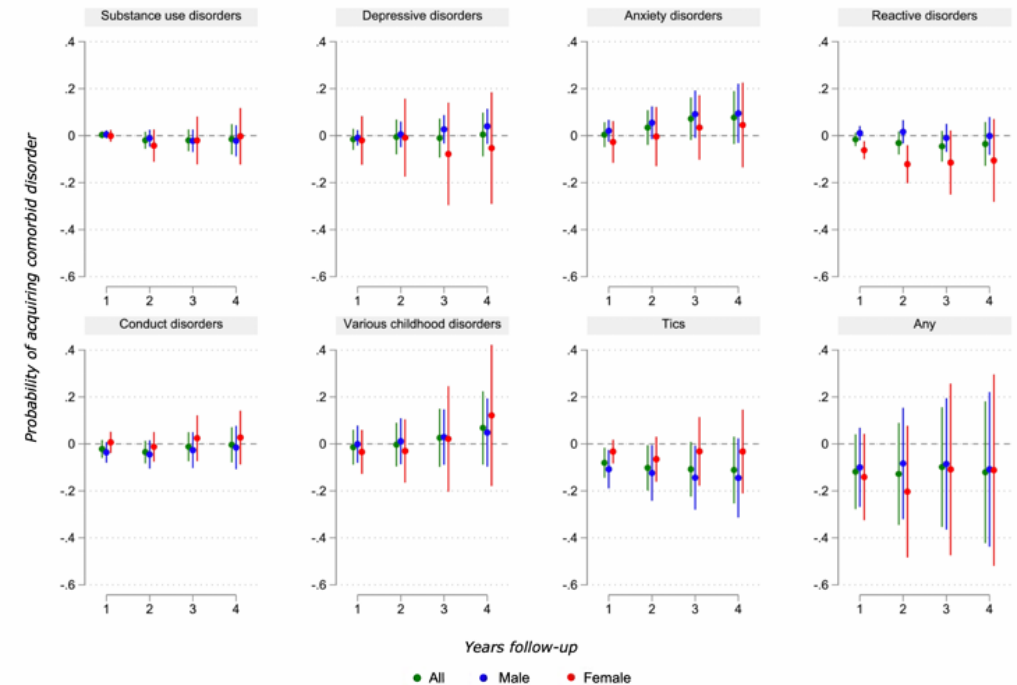


Veel bijkomende problemen

**Figure 1** Cumulative incidence of comorbidity by years of follow-up. Year 0 signifies time of attention-deficit/hyperactivity disorder (ADHD) diagnosis; registered comorbid disorders at this baseline may include incident or prevalent cases.

# Lange termijn effect op comorbiditeit

- Geen evidentie dat ADHD – medicatie op lange termijn de comorbiditeit verlaagt
- Wel:
  - minder stressgerelateerde stoornissen bij meisjes gedurende de eerste 2 jaar behandeling
  - minder ticstoornissen bij jongens gedurende de eerste 3 jaar behandeling.



**Figure 3** Results from instrumental variable (IV) analyses: effect estimates of attention-deficit/hyperactivity disorder (ADHD) medication on psychiatric comorbidities. Patients diagnosed with ADHD in Norway in 2009–2011, aged 5–18 at time of diagnosis. Coefficient plots for regressions with 95% CIs. Two-stage least squares (2SLS) estimates adjusted for patient mix.

# Een andere cohort

European Neuropsychopharmacology 113 (2026) 113861



ELSEVIER

Contents lists available at ScienceDirect

European Neuropsychopharmacology

journal homepage: [www.sciencedirect.com/journal/european-neuropsychopharmacology](http://www.sciencedirect.com/journal/european-neuropsychopharmacology)



## Long-term outcomes of childhood ADHD stimulant use trajectories

Noa E. van der Plas<sup>a,b,\*</sup>, Siri D.S. Noordermeer<sup>a,b</sup>, Catharina A. Hartman<sup>c,d</sup>,  
Pieter J. Hoekstra<sup>d,e</sup>, Nanda N.J. Rommelse<sup>e,f</sup>, Emma Sprooten<sup>f,g</sup>, Jaap Oosterlaan<sup>a,b,h,i</sup>,  
Marjolein Luman<sup>a,b,j</sup>

<sup>a</sup> Vrije Universiteit Amsterdam, Amsterdam, the Netherlands

<sup>b</sup> Amsterdam Public Health Research Institute, Amsterdam University Medical Centers, Amsterdam, the Netherlands

<sup>c</sup> Rijksuniversiteit Groningen, Groningen, the Netherlands

<sup>d</sup> Universitair Medisch Centrum Groningen, Groningen, the Netherlands

<sup>e</sup> Universiteit Utrecht, Utrecht, the Netherlands

<sup>f</sup> Donders Institute for Brain, Cognition and Behaviour, Radboud University, Nijmegen, the Netherlands

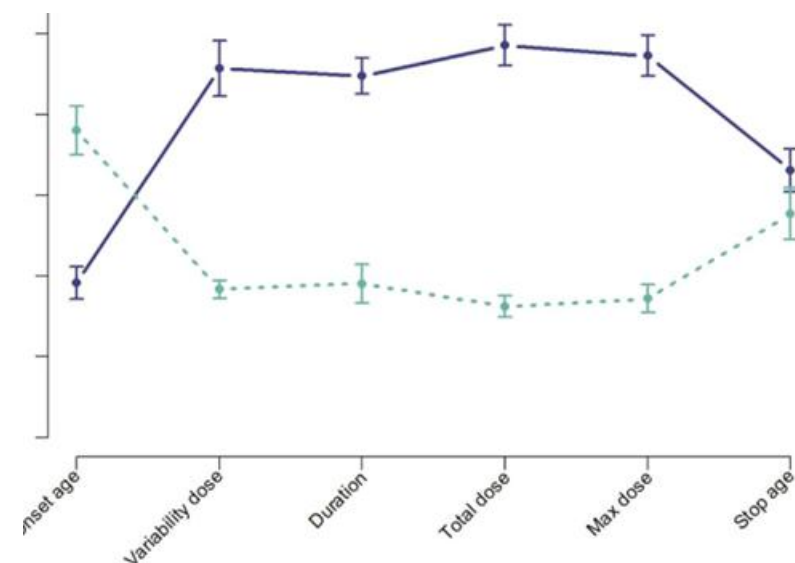
<sup>g</sup> Radboud University Medical Center, department of Medical Neuroscience, Nijmegen, the Netherlands

<sup>h</sup> Emma Children's Hospital Amsterdam UMC, location University of Amsterdam, Amsterdam, the Netherlands

<sup>i</sup> Amsterdam Reproduction and Development Research Institute, Amsterdam, the Netherlands

<sup>j</sup> Levvel, Academic Center for Child and Adolescent Psychiatry, Amsterdam, the Netherlands

- 143 volwassenen uit de IMAGE Cohort
- Outcomes na >12 jaar



stimulant treatment trajectory groups at NeuroIMAGE wave II using K-Means clustering.

l stimulant treatment trajectory groups, early-and-intense (solid purple;  $n_{\text{wave II}}=138$ ) and late-and-moderate (dotted green;  $n_{\text{wave II}}=122$ ) consisted of participants that were stimulant-naïve in childhood. The error bars reflect the 95% confidence interval.

# Lange termijn....

Table 1

Follow-up NeuroIMAGE Wave IV measures for stimulant treatment trajectories: early-and-intense, late-and-moderate, and stimulant-naïve.

| Early-and-intense<br>(n = 46) | Late-and-moderate<br>(n = 63) | Stimulant-naïve<br>(n = 34) | Wald $\chi^2$ of group effect | Post-hoc significant group differences |
|-------------------------------|-------------------------------|-----------------------------|-------------------------------|----------------------------------------|
|-------------------------------|-------------------------------|-----------------------------|-------------------------------|----------------------------------------|

3 groepen: vroeg en intens medicatiegebruik – Laat en gematigd medicatiegebruik – Geen stimulantia gebruikt

Op volwassen leeftijd **geen verschil** in 51 verschillende outcomes:

- Voldoen aan criteria psychiatrische diagnoses
- Gedrags- of emotionele problemen
- Academisch en professioneel functioneren
- Adaptief functioneren
- Neurocognitief functioneren
- Lichamelijke gezondheid
- Gebruik van gezondheidszorg

**Behalve:** na correctie voor sexe en leeftijd: beter score op callous unemotional traits voor de medicatie groepen

# Lange termijn effectiviteit

CONTINUED BENEFITS OF METHYLPHENIDATE AFTER 2 YEARS

**TABLE 2. Change in ADHD Rating Scale (ADHD-RS) and Clinical Global Impressions improvement scale (CGI-I) scores in a randomized placebo-controlled discontinuation study of methylphenidate in ADHD**

| Measure                         | Discontinuation Group (N=47) |      |           | Continuation Group (N=47) |      |           | Analysis                             |            |           |
|---------------------------------|------------------------------|------|-----------|---------------------------|------|-----------|--------------------------------------|------------|-----------|
|                                 | Mean                         | SD   | 95% CI    | Mean                      | SD   | 95% CI    |                                      |            |           |
| Baseline                        |                              |      |           |                           |      |           |                                      |            |           |
| ADHD-RS                         |                              |      |           |                           |      |           |                                      |            |           |
| Total score                     | 19.6                         | 8.9  | 16.9–22.2 | 21.4                      | 9.7  | 18.7–24.1 |                                      |            |           |
| Inattention score               | 12.0                         | 5.7  | 10.3–13.7 | 13.8                      | 6.2  | 12.1–15.5 |                                      |            |           |
| Hyperactivity-impulsivity score | 7.6                          | 5.0  | 6.1–9.0   | 7.6                       | 5.2  | 6.1–9.0   |                                      |            |           |
| 7 weeks                         | Mean                         | SD   | 95% CI    | Mean                      | SD   | 95% CI    | Δ Change between groups <sup>a</sup> | 95% CI     | Cohen's d |
| ADHD-RS                         |                              |      |           |                           |      |           |                                      |            |           |
| Total score                     | 24.7                         | 11.4 | 21.6–27.9 | 21.9                      | 10.8 | 18.7–25.1 | –4.6*                                | –8.7, –0.6 | –0.23     |
| Inattention score               | 14.8                         | 6.0  | 13.0–16.5 | 13.5                      | 6.3  | 11.7–15.2 | –3.1*                                | –5.4, –0.9 | –0.29     |
| Hyperactivity-impulsivity score | 10.0                         | 6.8  | 8.2–11.8  | 8.5                       | 5.8  | 6.7–10.3  | –1.5                                 | –3.7, –0.7 |           |
|                                 | N                            | %    |           | N                         | %    |           |                                      |            |           |
| CGI-I <sup>b</sup>              |                              |      |           |                           |      |           |                                      |            |           |
| Not worsened                    | 28                           | 59.6 |           | 37                        | 84.1 |           |                                      |            |           |
| Very much improved              | 0                            | 0.0  |           | 0                         | 0.0  |           |                                      |            |           |
| Much improved                   | 2                            | 4.3  |           | 3                         | 6.4  |           |                                      |            |           |
| Minimally improved              | 5                            | 10.6 |           | 2                         | 4.3  |           |                                      |            |           |
| No change                       | 9                            | 19.1 |           | 25                        | 53.2 |           |                                      |            |           |
| Minimally worse                 | 12                           | 25.5 |           | 7                         | 14.9 |           |                                      |            |           |
| Worsened                        | 19                           | 40.4 |           | 7                         | 15.9 |           |                                      |            |           |
| Much worse                      | 17                           | 36.2 |           | 7                         | 14.9 |           |                                      |            |           |
| Very much worse                 | 2                            | 4.3  |           | 0                         | 0.0  |           |                                      |            |           |

<sup>a</sup> Indicates the difference (Δ) in mean change from baseline to endpoint between the discontinued and continued treatment groups, by mixed models for repeated measurements analysis. The main effect for time was significant for ADHD-RS total score (F=7.81, df=92, p=0.006), inattention score (F=4.54, df=92, p=0.036), and hyperactivity-impulsivity score (F=9.19, df=92, p=0.003).

<sup>b</sup> On the CGI-I scale, there was a significant difference between worsened compared with not worsened (p=0.010).

\*p<0.05

## MASK: Methylfenidaat Afbouw Studie bij Kinderen

- 94 kinderen & adolescenten
- > 2 jaar MPH gebruik
- RCT: afbouw en continueringsgroep
- Afbouw in 3 weken naar placebo

# EVERYTHING IN BETWEEN

# Wat werkt voor wie?



# ADHD-medicatie (in België)

## MEDICATIE

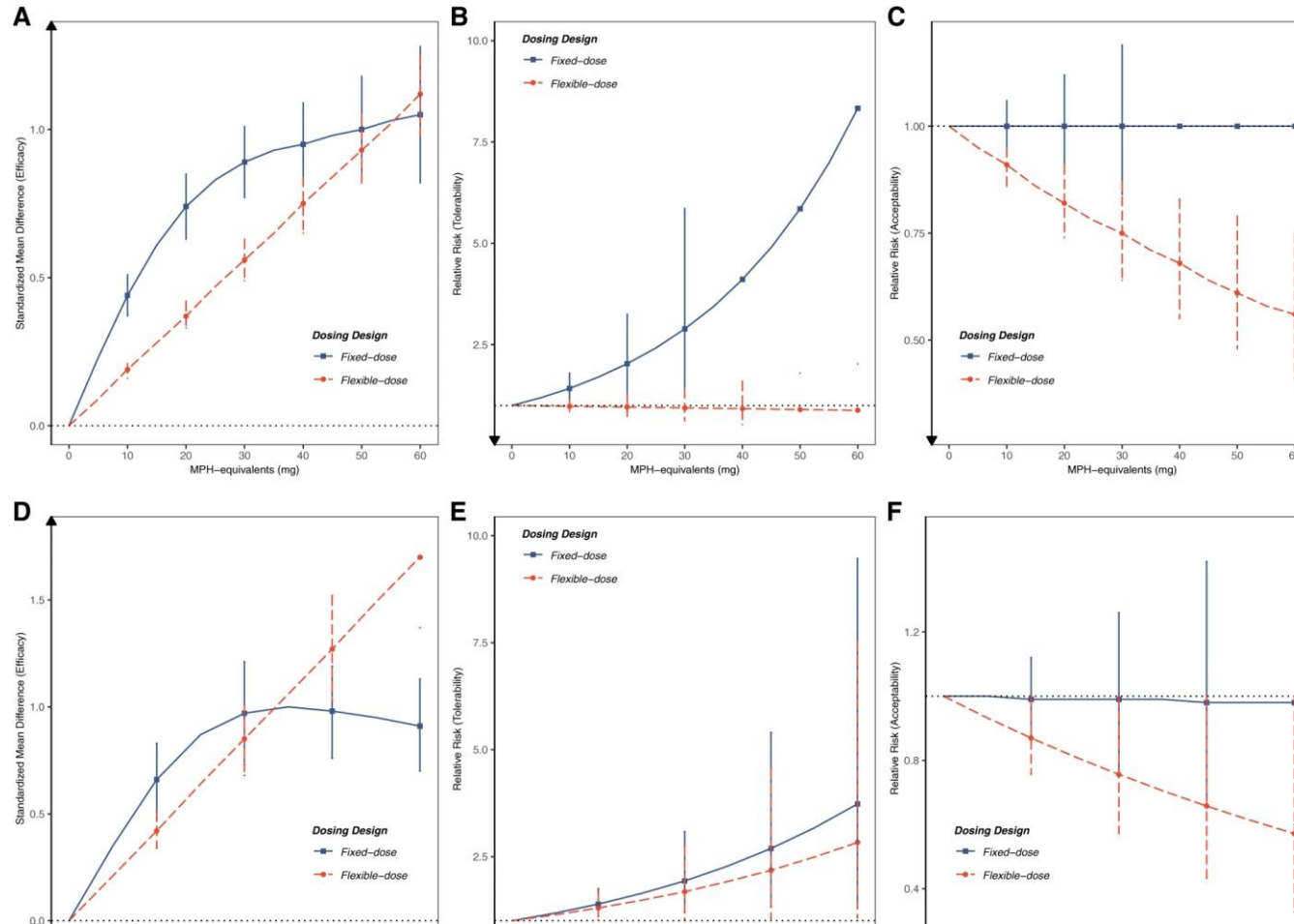
**STAP 1:** Methylfenidaat (Rilatine®, Medikinet®, Equasym®, Concerta®...) +/- 70%

**STAP 2:** Dexamfetaminesulfaat/ Lisdexamfetamine (Dexamfetaminesulfaat, Elvanse®)

**STAP 3:** Atomoxetine of Guanfacine (Intuniv®)

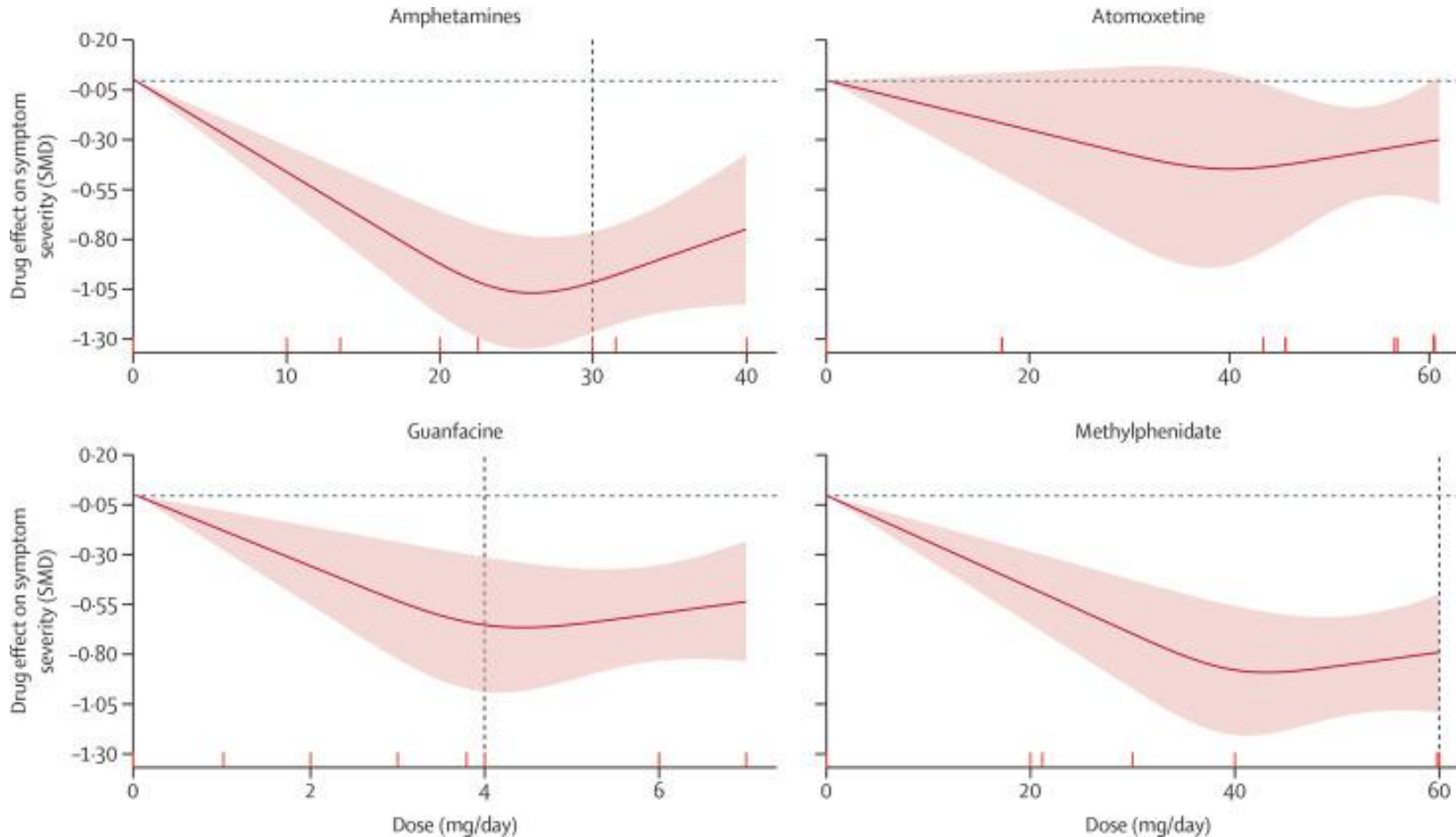
+/- 90%

# One size does not fit all



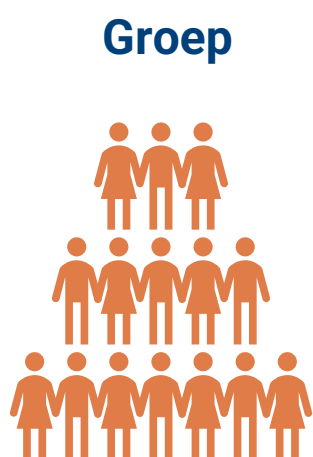
- Meta-analyse: **fixed-dose** versus **flexible-dose**
- Hogere doses geven gemiddeld meer symptoomverbetering.
  - **Fixed-dose** studies vlakt de extra winst af boven: ~30 mg methylfenidaat ~20 mg amfetamine
  - **Flexible-dose** studies blijft de verbetering toenemen over het volledige aanbevolen dosisbereik
- Flexible - dose: betere aanvaardbaarheid en minder uitval

# Dosis effect meta-analyse

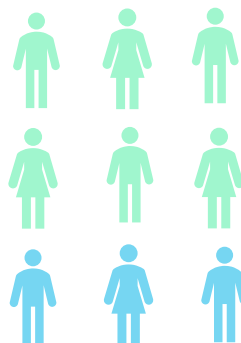


- Dose–effect network meta-analyse van ADHD-medicatie
- Hogere dosissen: meer uitval door bijwerkingen
- Boven de maximaal vergunde dosis : geen duidelijk betere gemiddelde resultaten.
- **De resultaten pleiten zowel tegen:**
  - onder doseren
  - onbeperkt dosisverhogen wanneer de baten waarschijnlijk niet meer opwegen tegen de risico's.

# Groepseffecten ~ Individuele effecten



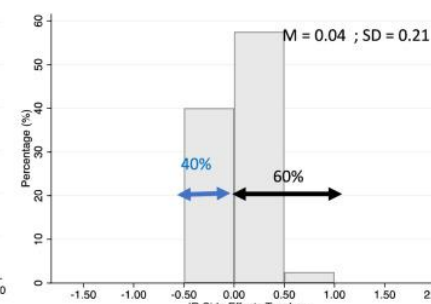
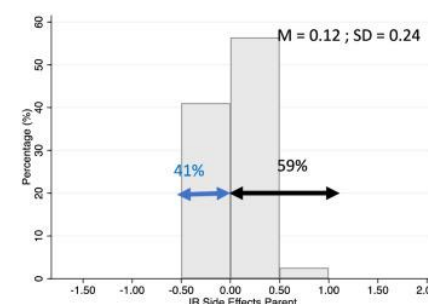
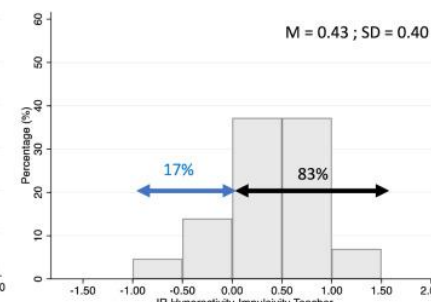
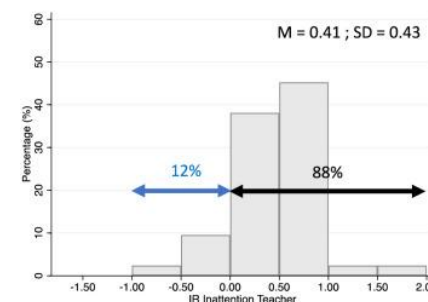
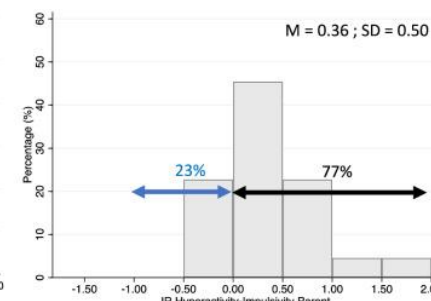
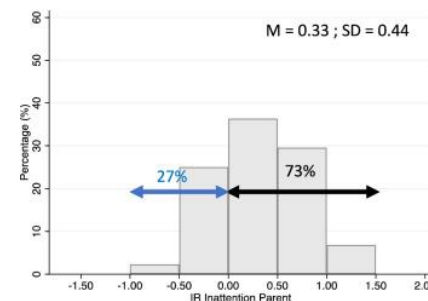
**Individueel**



Hogere doseringen

NIET ALTIJD

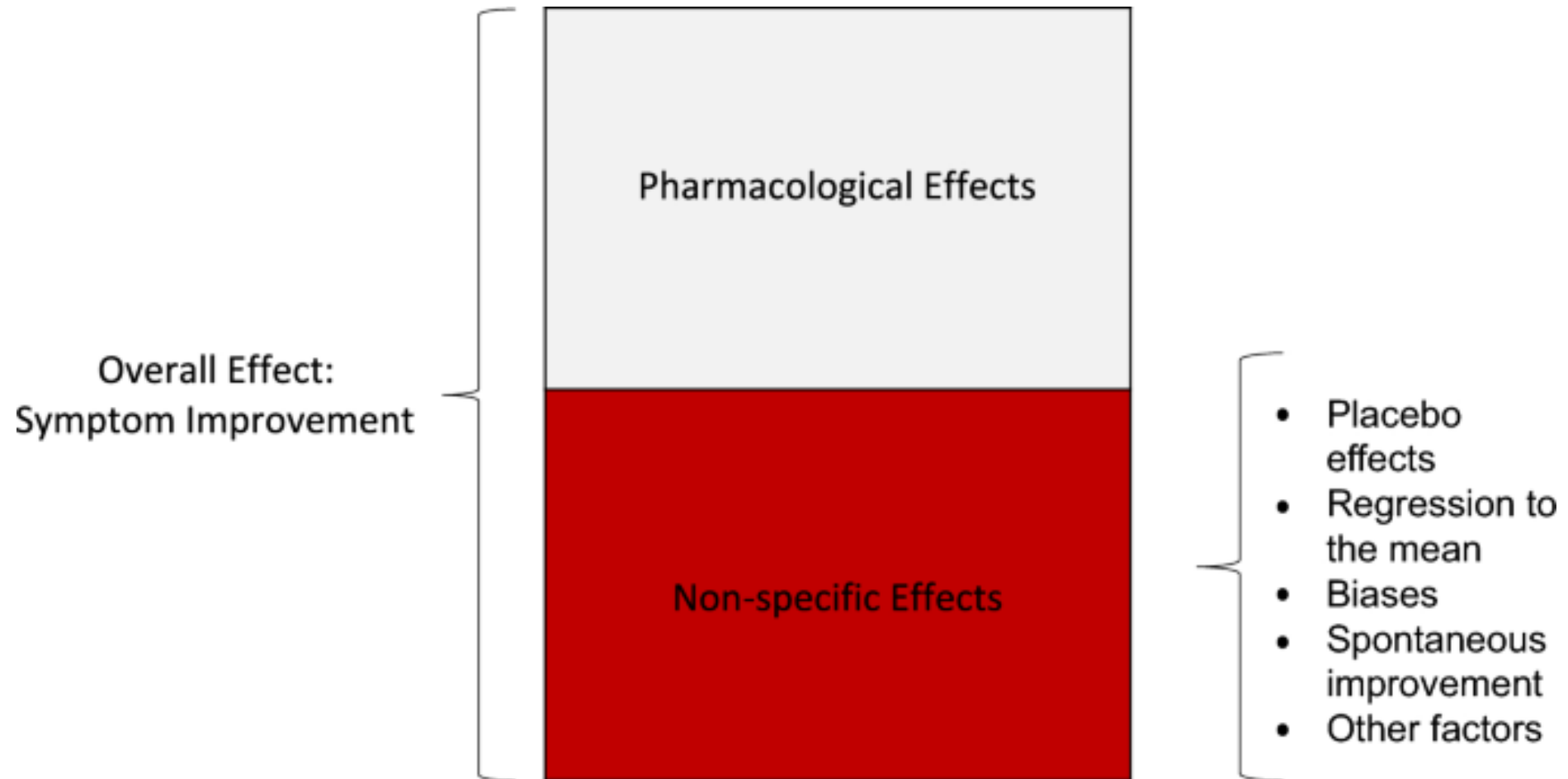
- Betere effecten
- Meer bijwerkingen



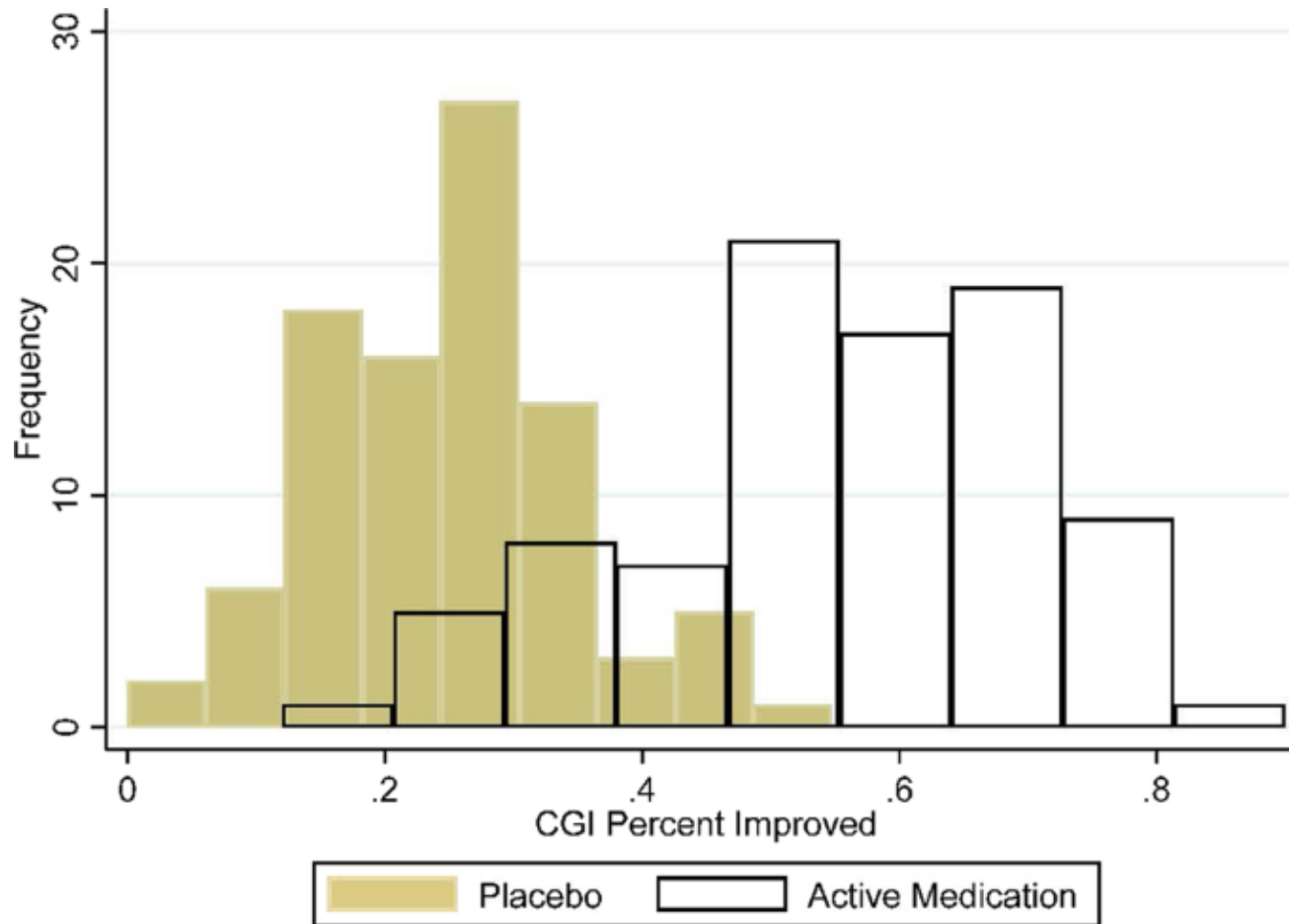
EVERYTHING IN BETWEEN

# De rol van verwachting

# Niet alle effecten zijn farmacologisch

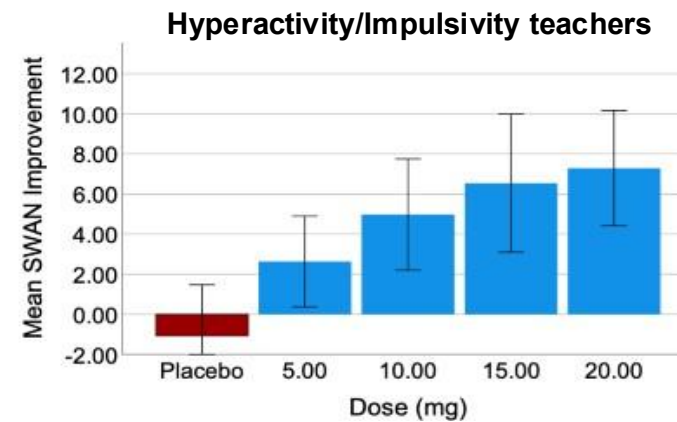
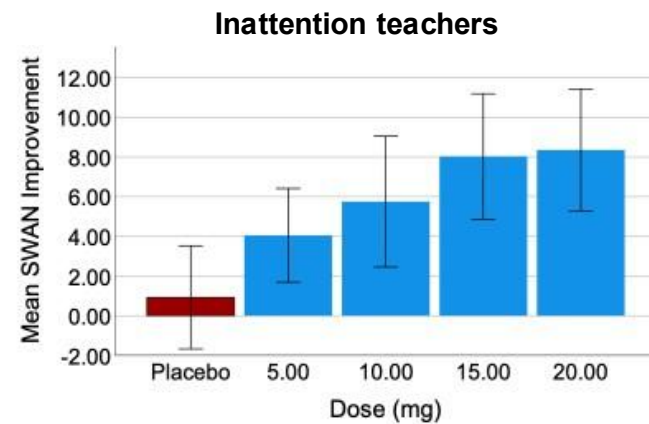
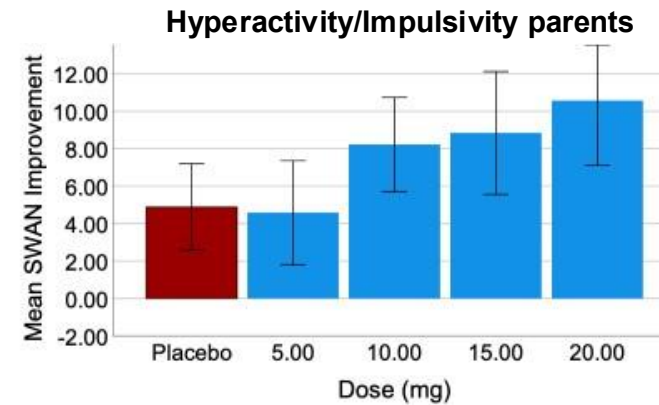
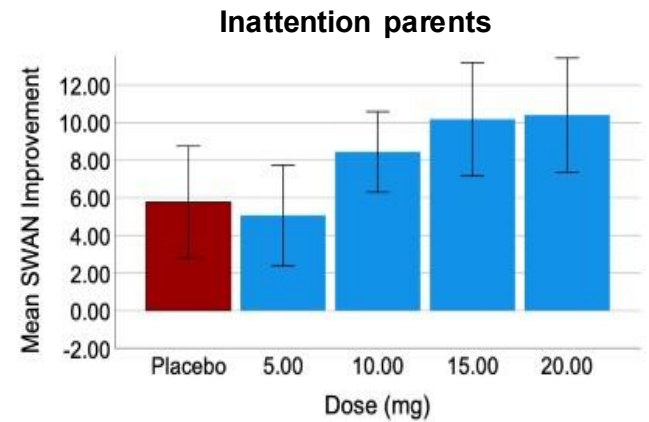


# Placebo-Nocebo



- Meta-analyse van 128 placebo-gecontroleerde ADHD-studies.
- Placebo: substantiële symptomatische verbetering
- Gemiddeld ~25% verbetering onder placebo.
- Verbetering is groter onder actieve medicatie (~47-60%).
- Behandelcontext en verwachtingen dragen mee bij aan het uiteindelijke effect

# Titratie: placebo effecten- verschillende informanten



# Factoren die bijdragen aan medicatierouw

| Factors                                               | N of study | N of patients | Effect model | Results of meta |            | Heterogeneity      |       |
|-------------------------------------------------------|------------|---------------|--------------|-----------------|------------|--------------------|-------|
|                                                       |            |               |              | OR              | 95%CI      | I <sup>2</sup> (%) | P     |
| Patient-related                                       |            |               |              |                 |            |                    |       |
| Genders                                               | 3          | 74,485        | Random       | 1.07            | 1.03–1.11  | 89.20              | <0.01 |
| Medication-related                                    |            |               |              |                 |            |                    |       |
| Fewer medications                                     | 2          | 949           | Random       | 0.45            | 0.27–0.75  | 0.00               | <0.01 |
| Parental approval of drug treatment                   | 2          | 526           | Random       | 1.87            | 1.16–3.02  | 91.00              | 0.01  |
| Caregiver-related                                     |            |               |              |                 |            |                    |       |
| Parents had received medication education or training | 3          | 1,304         | Random       | 6.34            | 3.97–10.12 | 63.10              | <0.01 |
| Number of children in a family                        | 2          | 1,167         | Random       | 1.80            | 1.29–2.52  | 0.00               | <0.01 |

OR, odds ratio.

- Meta-analyse over medicatietrouw bij kinderen en adolescenten met ADHD: 63 studies met 450.759 deelnemers
- Gemiddelde medicatietrouw bedroeg slechts 43,6%.

# Waarom stoppen jongeren met hun medicatie

**Results:** Reasons given by young people for stopping ADHD medication included the following: the perceived balance between benefits and adverse effects of medication; perceptions of ADHD as a childhood or educational disorder; life circumstance of the young person and challenges young people faced in accessing services.

*'They were turning out to be more bad than good'*

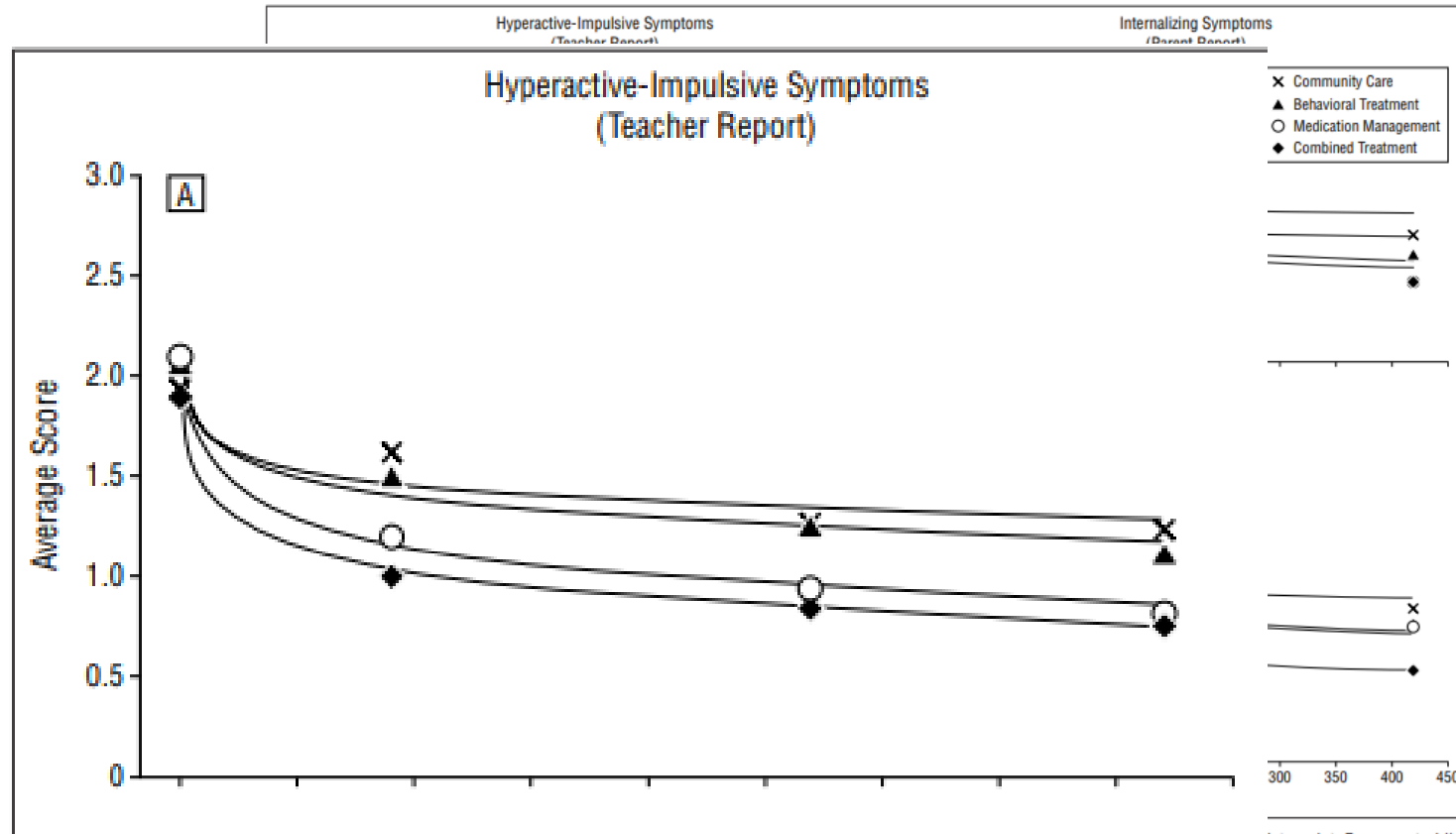
*'So the medication, it helps but it's the side effects of the medication that I didn't really like. That's why I was very rebellious against taking the medication at some points'*

*'The first day I went into school after taking the medication and I remember we had a test and my teacher got the results from this test, I think it was in maths, and they were, like, "Is this yours?" It was perfect. Every answer was right'*

- Kwalitatief onderzoek
- Adolescentie is vaak een kwetsbare periode
- Medicatiegebruik daalt fors en is niet in verhouding met afnemen van de ernst van ADHD

EN NU ....

# Gestandaardiseerde titratie geeft belangrijke voordelen



For internalizing symptoms (parent reported), combined treatment and medication management symbols overlapped at the 14-month data point. For parent-child arguing (power assertion, parent reported), medication management and intensive behavioral treatment symbols overlapped at the 3-month and 14-month data points. A, Combined treatment and medication management were more effective than community care. B, Combined treatment was more effective than behavioral treatment and community care. C, Combined treatment and medication management were more effective than community care. D, Combined and behavioral treatment were more effective than community care.

Community care (meestal met medicatie) minder goede outcome tov medicatie in de study

# Gestandaardiseerde titratie geeft belangrijke voordelen

## The Dundee ADHD Clinical Care Pathway (DACCP) :

- klinische praktijk gebaseerd op MTA-studie
- standaard protocollen voor assessment, titratie en routine monitoring van zorg en behandeling

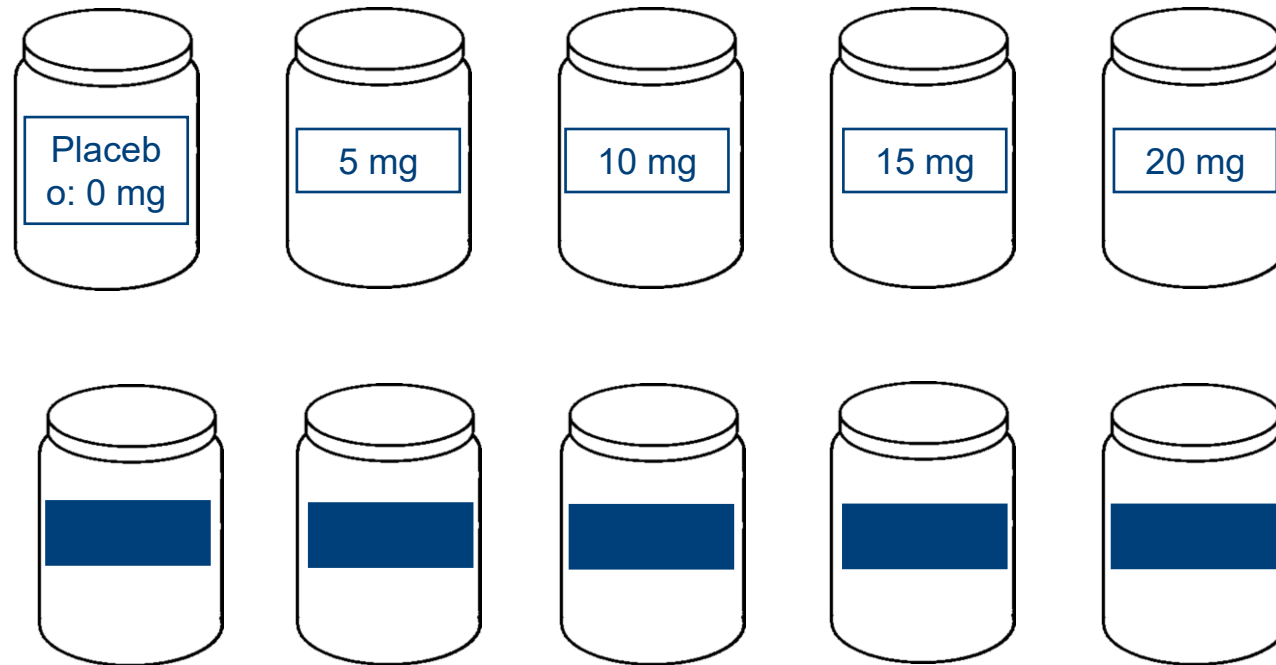
⇒ responders van 44 naar 67%

# Medicatie voor ADHD

INSTELLEN VAN DE MEDICATIE: Klassieke titratie (kan ook met langwerkend)

| Normale titratie                                                                                | Voorzichtige titratie                                                                          |
|-------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|
| Week 1 : 3 x 5 mg /d<br>Week 2 : 3 x 10 mg /d<br>Week 3 : 3 x 15 mg /d<br>Week 4 : 3 x 20 mg /d | Week 1 : 2 x 2,5 mg /d<br>Week 2: 2 x 5 mg /d<br>Week 3: 2 x 7,5 mg /d<br>Week 4: 2 x 10 mg /d |

# Placebo gecontroleerde titratie



# Wat als medicatie niet werkt?

## Management of stimulant-refractory ADHD<sup>298</sup>

Prior to changing to non-stimulants or adding medications consider the following:

- Has the dose been titrated correctly to the maximum tolerated dose?
- Should the dose or preparation be changed for a more balanced effect?
- Are the right symptoms and time of day being targeted?
- Has the patient become tolerant to the medication?
- Does the patient have any life circumstances contributing to the poor response?
- Have any comorbidities been missed?
- Is the diagnosis correct?

Use of second-line medications (atomoxetine, guanfacine extended-release (ER), clonidine ER, viloxazine ER).

Augmenting agents (combine stimulants with other immediate release or ER stimulants, guanfacine ER or clonidine ER).

Use of other agents (off-label) under specialist advice and/or supervision.

# Aanbevelingen voor de klinische praktijk

- Neem **kritische houding** aan – zeker bij een milder ADHD profiel
- Test **alle doseringen** (ook de hoge): individuele verschillen
- **Registreer** symptomen/bijwerkingen **systematisch**
- Betrek **leerkrachten**: minder niet-specifieke effecten
- Breng symptomen voor start in kaart
- **Jaarlijkse evaluatie** medicatie meerwaarde

# Praktisch

## Advies hoge gezondheidsraad (2021)

The screenshot shows the ZORGPAD ADHD website. At the top, there is a search bar and language options (NL, FR). Below the navigation bar, the main content area is titled 'MEDICAMENTEUZE BEHANDELING'. On the left, a sidebar lists treatment options: PSYCHO-EDUCATIE, GEïNTEGREERD BEHANDELPLAN, NIET-MEDICAMENTEUZE BEHANDELING, and MEDICAMENTEUZE BEHANDELING (which is highlighted). Under MEDICAMENTEUZE BEHANDELING, there are sub-points: Opstarten medicatie, Geïnformeerde beslissing en toestemming, Checklijst medicatie opstarten, Basislijn en vooronderzoeken, Welke medicatie kiezen? (with sub-points for ADHD zonder comorbiditeit, ADHD met comorbiditeit, and ADHD-medicatie en cardiovasculaire risico's), and Opstarten medicatie. The main content area contains text explaining that medication is not for every child with an ADHD diagnosis and lists three scenarios for when medication might be considered: 1. Bij kinderen **onder zes jaar** is gebruik van medicatie niet aangewezen. 2. Bij kinderen **vanaf zes jaar** met een **lichte of matige vorm** van ADHD wordt ook eerst begonnen met psychosociale en opvoedingsinterventies thuis en op school. 3. Bij kinderen **vanaf zes jaar** met een **ernstige vorm** van ADHD, biedt starten met medicatie van bij het begin van de behandeling in combinatie met psychosociale en opvoedingsinterventies de beste kansen op succes. At the bottom, a red navigation bar shows the flow: ZORGPAD -> WANNEER AAN ADHD DENKEN? -> PREDIAGNOSTISCHE FASE -> DIAGNOSTISCHE FASE -> BEHANDELING ADHD.

## Zorgpad ADHD

- [https://www.health.belgium.be/sites/default/files/uploads/fields/fpshealth\\_t\\_heme\\_file/20210308\\_hgr-9547\\_adhd\\_vweb\\_0.pdf](https://www.health.belgium.be/sites/default/files/uploads/fields/fpshealth_t_heme_file/20210308_hgr-9547_adhd_vweb_0.pdf)

# Dank u!