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TREATMENT OF ADHD IN PATIENTS WITH SUD: NEW EVIDENCES

4 March 2018

Frieda Matthys MD PhD



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An overview

- Where we come from
- Where are we now
- Where are we going



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WHERE WE COME FROM

The history

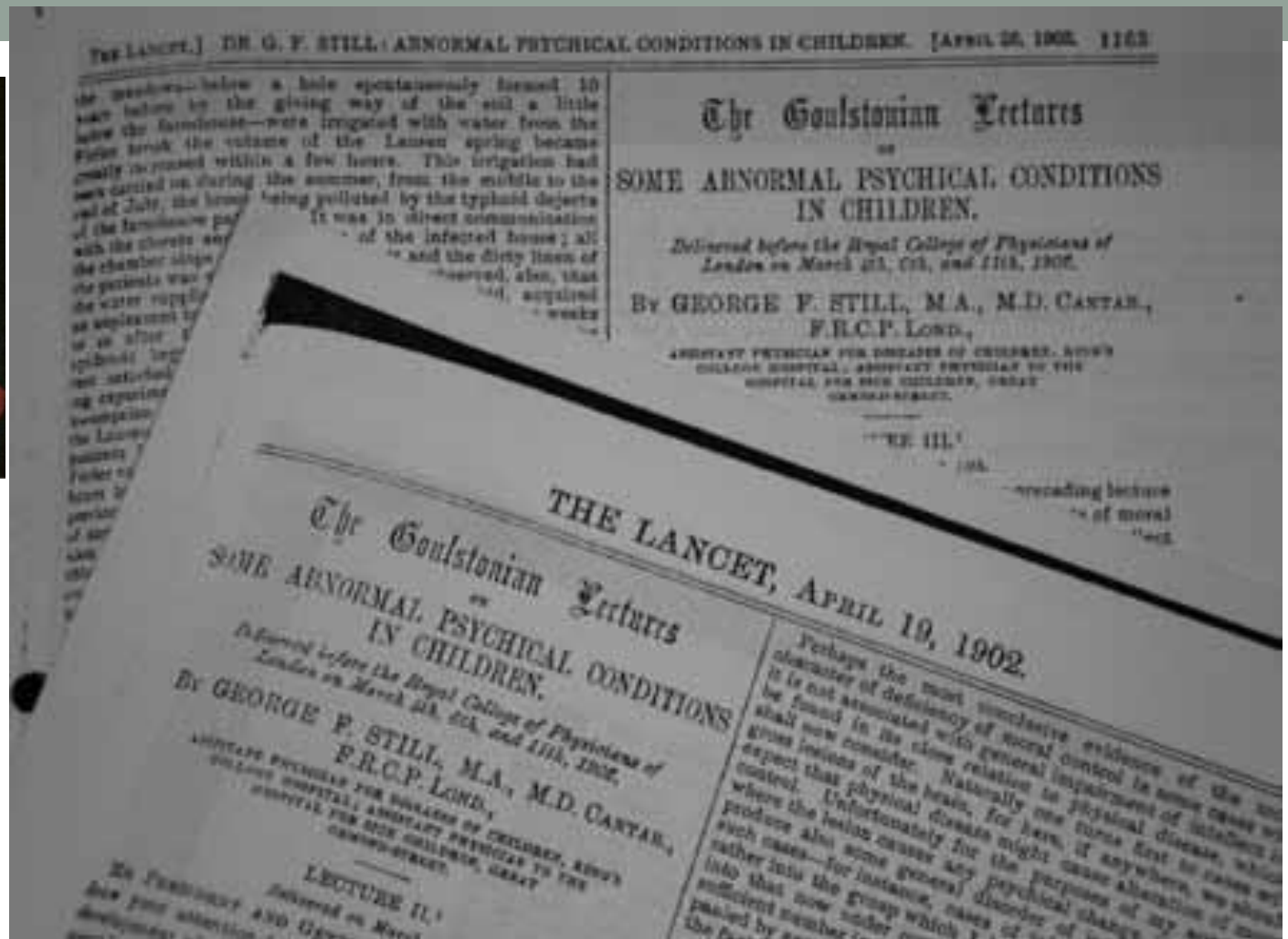
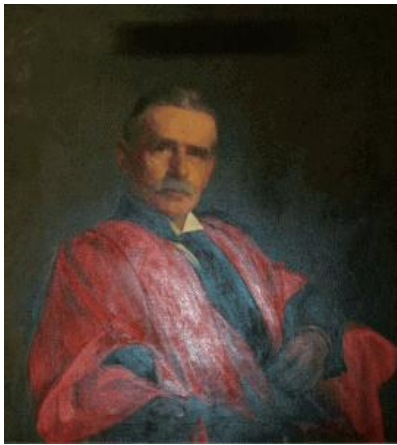
The risk for SUD

Scarcity of research data

The first guideline

The history

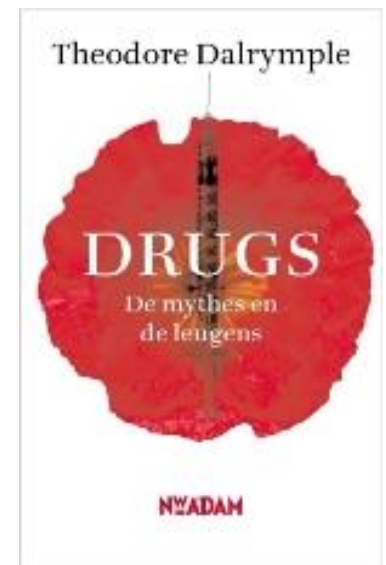




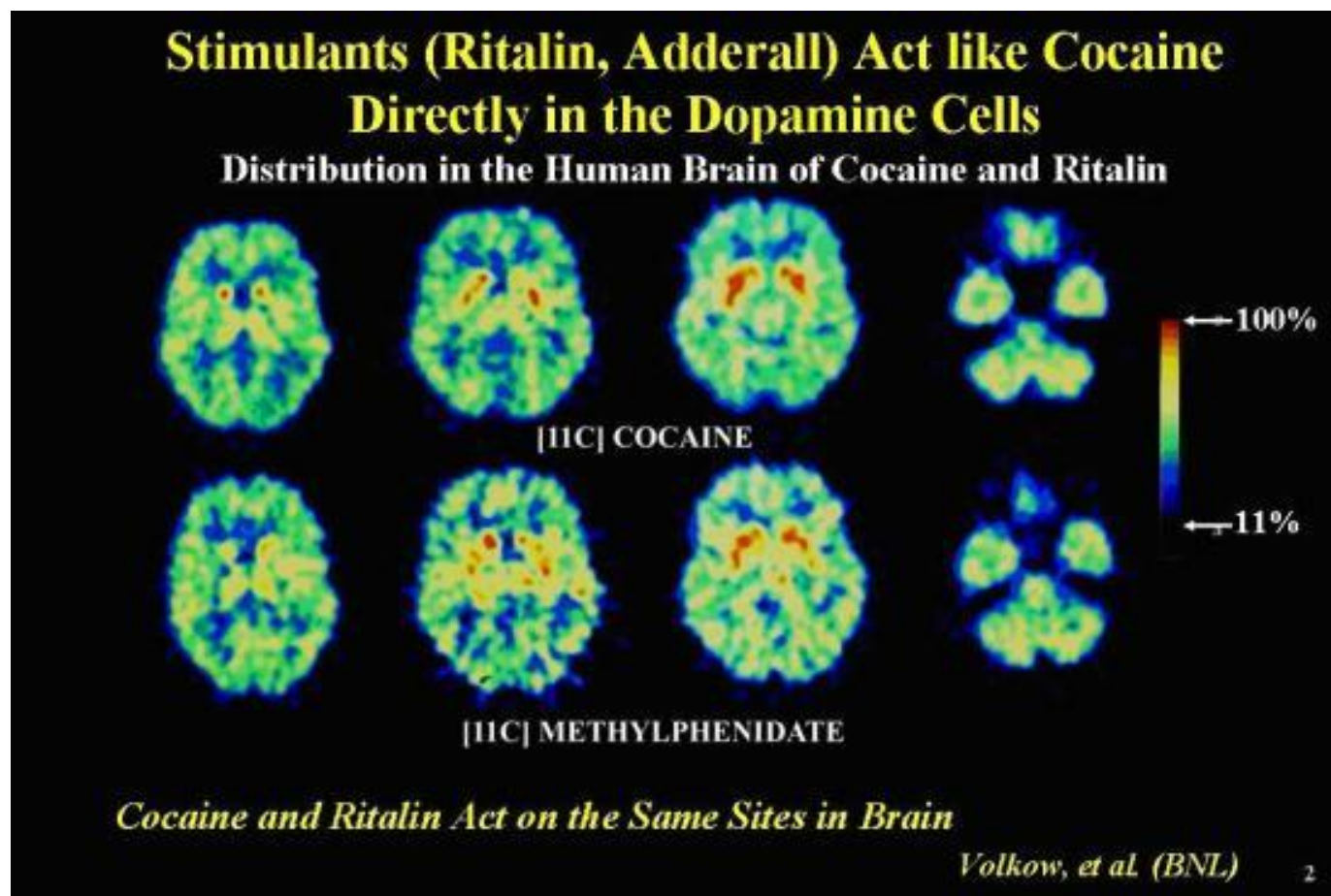
he describes 43 children who exhibit 'defects of inhibitory volition',
accompanied by 'stealing, lying, violence, and sexual chicanery'.
He considered it a 'defect of moral control'.



Vulnerability



Pay Attention: Ritalin Acts Much Like Cocaine



ADHD treatments: non-pharmacological



Restrictive Elimination Diet
Hypo-allergic food
individually adapted



**Artificial food colour
exclusion diet**



**Fatty Acid
supplementation**



Cognitive training :
working memory training /
attention training / Executive
function training



**Neurofeedback
(EEG-biofeedback)
training**



Behavioural Interventions:
based on social learning or
operant techniques

ADHD treatments: non-pharmacological

Meta-analysis of RCT of psychological and dietary treatments, in ADHD subjects, effects on ADHD symptoms

Standardized Mean Difference	Most proximal rater	Most blinded rater
Restricted Elimination Diet	1.48	0.51 (p<0.06)
Artificial Food Colour Exclusions	0.32	0.42
Free Fatty Acid Supplementation	0.21	0.16
Cognitive training	0.64	0.24 NS
Neurofeedback	0.59	0.29 NS
Behavioural Interventions	0.40	0.02 NS

Conclusion: Better evidence for efficacy from blinded assessments is required

Table 1

Clinical trials on stimulant medication in adults with ADHD

Simulants' study	N	Method	Outcome	Conclusion
<i>Short-acting stimulants</i>				
MPH* (Spencer et al 1995)	23	Duble-blind crossover study	ADHD symptoms ↓ (78%)	MPH is significantly more effective than placebo
MPH (Spencer et al 2005)	146	Duble-blind randomized study	ADHD symptoms ↓ (76%) No serious CV adverse events	MPH is significantly more effective than placebo Good tolerability
<i>Long-acting stimulants</i>				
Controlled release MPH/Biphentin/ (Jain et al 2007)	39	Double-blind placebo-controlled crossover study	ADHD symptoms ↓ Weight loss	Successful in symptoms control Well tolerated
OROS-MPH/Concerta/ (Fallu et al 2006)	32	Uncontrolled, open label study	ADHD symptoms ↓ Functional improvements (Sheehan scale)	Successful control of symptoms Less functional disability
OROS-MPH/Concerta/ (Biederman et al 2006)	141	Double-blind, randomized, placebo controlled study	ADHD symptoms ↓ ↑Systolic and diastolic blood pressure and heart rate	Successful control of symptoms Concerns about CV tolerability
OROS-MPH/Concerta/ (Reimherr et al 2007)	47	Double-blind, placebo-controlled, crossover study	ADHD symptoms ↓ (41%–42% symptoms reduction)	Less remarkable improvement than in other comparable studies
Mixed amphetamine salts XR/Adderall XR/ (Biederman et al 2005)	223	Double-blind, placebo-controlled study	ADHD symptoms ↓ (sustained improvement up to 24 months) Good tolerance	Sustained symptomatic improvement Well tolerated

Guideline for Screening, Diagnosis and Treatment of ADHD in Adults with Substance Use Disorders

Frieda Matthys, Steven Stes, Wim van den Brink, Peter Joostens, David Möbius, Sabine Tremmery & Bernard Sabbe

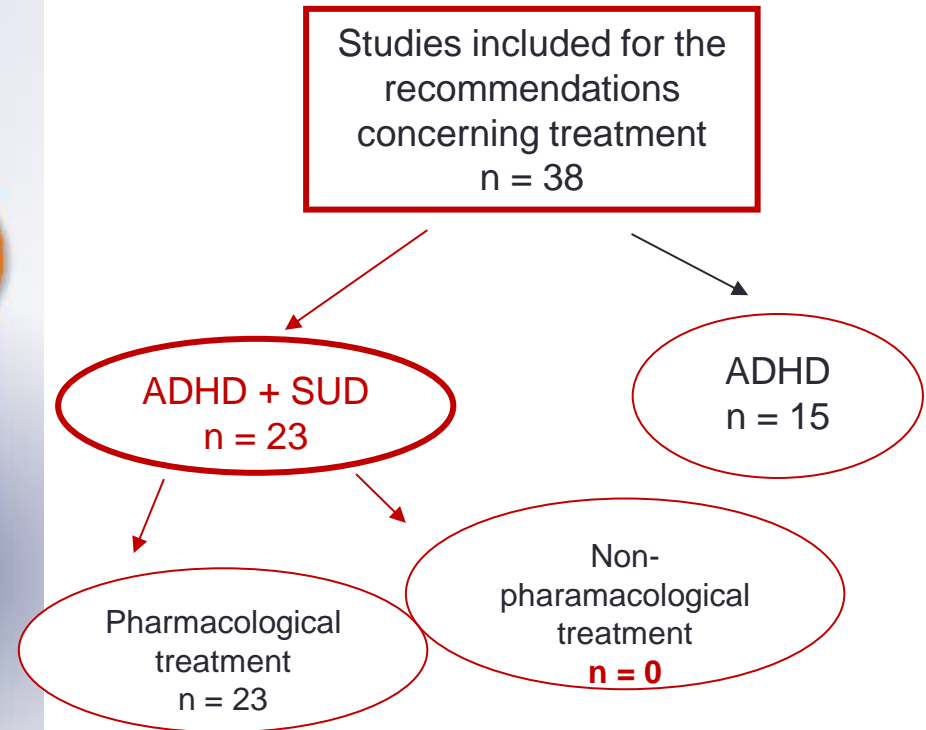
International Journal of Mental Health and Addiction

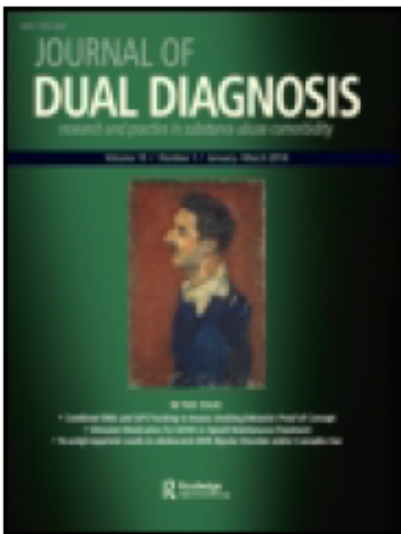
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Journal of Dual Diagnosis

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Barriers to Implementation of Treatment Guidelines for ADHD in Adults With Substance Use Disorder

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WHERE ARE WE NOW

The risk for SUD

An international consensus

Pharmacological treatment

Non-pharmacological treatment

International consensus statement on diagnosis and treatment of SUD patients with comorbid ADHD

Cleo L. Crunelle, Wim van den Brink, Franz Moggi, Maija Konstenius, Johan Franck, Frances R. Levin, Geurt van de Glind, Zsolt Demetrovics, Corné Coetzee, Mathias Luderer, Arnt Schellekens, ICASA consensus group, Frieda Matthys, *EAR, accepted 2018*

The International Collaboration on ADHD and Substance Abuse (ICASA) is an organization of clinicians and researchers with the aim of developing evidence based procedures for screening, diagnosis and treatment of patients with comorbid ADHD and SUD. This Consensus Statement was developed by clinicians and researchers from **13 European countries, Australia, South Africa and the USA**, and is based on a comprehensive literature search, own studies, and clinical experience.



Principles for medical treatment

- Cost of medications
- The time of day of impairment (of most concern)
- Tolerance of adverse events (such as insomnia)
- Risk of substance abuse
- Comorbid disorders
- Capacity for adherence
- Urgency of response
- The patient's choice upon reviewing the risks and benefits of each medication option.

Risk for SUD

Stimulant ADHD medication and risk for substance abuse

Zheng Chang,¹ Paul Lichtenstein,¹ Linda Halldner,^{1,2} Brian D’Onofrio,³ Eva Serlachius,⁴ Seena Fazel,⁵ Niklas Langstrom,¹ and Henrik Larsson¹

¹Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden; ²Karolinska Institutet Center of Neurodevelopmental Disorders (KIND), Stockholm, Sweden; ³Department of Psychological and Brain Sciences, Indiana University, Bloomington, IN, USA; ⁴Department of Clinical Neuroscience, Centre for Psychiatric Research and Education, Karolinska Institutet, Stockholm, Sweden; ⁵Department of Psychiatry, University of Oxford, Oxford, UK

Risk for SUD

The American Journal of
Psychiatry

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Volume 174, Issue 9, September 01, 2017, pp. 877-885

[Next Article](#)

ADHD Medication and Substance-Related Problems

Patrick D. Quinn, Ph.D., Zheng Chang, Ph.D., Kwan Hur, Ph.D., Robert D. Gibbons, Ph.D., Benjamin B. Lahey, Ph.D., Martin E. Rickert, Ph.D., Arvid Sjölander, Ph.D., Paul Lichtenstein, Ph.D., Henrik Larsson, Ph.D., Brian M. D'Onofrio, Ph.D.

<https://doi.org/10.1176/appi.ajp.2017.16060686>

Pooled random effects meta-analysis estimates of the prevalence of psychiatric disorders co-existing with ADHD

	≤18years		Adults	
	Rate	95% CI	Rate	95% CI
Psychiatric co-morbidity				
Conduct disorder	0.61	0.43–0.80	0.29	0.21–0.37
Substance use disorders	0.70	0.59–0.80	0.74	0.52–0.96
Mood disorders	0.25	0.16–0.34	0.66	0.50–0.81
Depressive disorder	0.13	0.05–0.21	0.55	0.35–0.76
Anxiety disorders	0.21	0.03–0.40	0.68	0.48–0.88
Personality disorders ^a	–	–	0.60	0.41–0.78

TREATMENT ADHD & SUD

OPEN TRIAL

Somoza et al. 2004	MPH 60 mg	41 pat.	cocaine
Castaneda et al. 2000	MPH SR 20-120 mg	19 pat.	cocaine
Levin et al. 1998:	MPH SR 40-80 mg	12 pat.	cocaine
Riggs et al. 1996:	Pemoline 37,5-75 mg	10 pat.	cocaine

Non-randomized studies showed some promise for the improvement of both ADHD and SUD

TREATMENT ADHD & SUD

DOUBLE- BLIND, PLACEBO-CONTROLLED

Biederman 2008	MPH SR	112 pat.	several
Levin 2007	MPH 60 mg/d	106 pat.	cocaine
Carpentier 2005:	MPH 0.6 mg/kg/d	25 pat.	several
Collins 2005:	MPH 40 mg	14 pat.	cocaine
Levin 2006:	MPH vs BPR	96 pat.	MMT + coca.
Schubiner 2002:	MPH 90 mg	48 pat.	Cocaine
Konstenius 2010:	MPH OROS 72mg/d	24 pat.	amph
Riggs 2011:	MPH OROS up to 72 mg/d	303 ado	several
Konstenius 2014:	MPH OROS up to 180 mg/d	54 pat.	amph
Winhusen 2010:	MPH OROS up to 72 mg/d	255 pat.	nicotine

Studies show that medication is only moderately

TREATMENT ADHD & SUD

OPEN TRIAL

Levin et al. 2009	ATX 80 mg/d	20 pat.	cocaine
Tirado et al. 2008	ATX 25-80 mg/d	13 pat.	cannabis
Levin et al. 2002:	BPR 250-400 mg	11 pat.	cocaine
Upadhayaya et al. 2001	VLF 75-300 mg	10 pat.	cocaine / OH

TREATMENT ADHD & SUD

DOUBLE- BLIND, PLACEBO-CONTROLLED

Cantinelena et al. 2012	ATX 80-100 mg/d	20 pat.	cocaine
Wilens et al., 2008	ATX 25-100 mg/d	147 pat.	alcohol
Thurnstone et al. 2010	ATX up to 100 mg/d	70 pat.	several
McRae Clark et al 2010	ATX up to 100 mg/d	38 pat.	THC
Levin 2006	Bupropion 400mg	98 pat	MMT

In several studies, ADHD symptoms improves across all groups, indicating an important placebo effect associated with either expectation and/or the effect of the psychotherapy provided in all treatment conditions.

Recommendations

Table 8. Consensus.

1. Stimulants are first-line treatment for adults with ADHD (A)
2. Atomoxetine is considered first-line treatment in patients with substance use disorders (S)
3. Drug treatment should be continued as long as clinically useful (S)
4. Careful titration and monitoring of side effects is required, particularly when using stimulants (A)
5. Drug holidays may be useful to ascertain the need of continuation of treatment (S)
6. Co-administration of drugs is relatively common in clinical practice for resistant cases but there is a lack of studies investigating its efficacy(S)


Research needs

1. More studies are required to elucidate the effects of 'flexible' dosing and co-administration of drugs
2. More pharmacological studies in humans are necessary to understand the full range of actions of ADHD medications in the brain and the individual variations that may limit efficacy or cause side effects

BRITISH ASSOCIATION OF PSYCHOPHARMACOLOGY

Level of recommendation C	Atomoxetine is preferred due to the absence of abuse potential
Level of recommendation C	Long-acting methylphenidate may also be used, provided that it is dose delivered and/or under adequate supervision
Level of recommendation C	Bupropion or imipramine are possible choices for the treatment of ADHD
Level of recommendation C	Because of its abuse potential short-acting methylphenidate can only have a place in the start-up phase in a residential treatment program to assess its impact

NON PHARMACOLOGICAL TREATMENT RECOMMENDATIONS



A complex problem requires a complex treatment

- A **multimodal** treatment is preferable
- The first phase consists of **psycho-education**
- In the second phase, **CBT and skills training** (individually or group-based), individual coaching and peer support are recommended in addition to medication
- The treatment of ADHD should be **integrated** into the treatment of addiction
- Dialectical behavior therapy (DBT) and mindfulness training can also be helpful
- Peer and family support enhances the effect of the treatment. Relationship therapy should be considered
- Remaining comorbid disorders should be treated

INTERNATIONAL CONSENSUS STATEMENT

Summary of the recommendations (2018)

- Screening tools allow for a good recognition of possible ADHD in adults with SUD, and should be used routinely.
- For individuals in SUD treatment, the ADHD diagnostic process should be started as soon as possible.
- In diagnosed patients, simultaneous and integrated treatment of ADHD and SUD, using a combination of pharmacotherapy and psychotherapy, is recommended.
- Long-acting methylphenidate, extended-release amphetamines, and atomoxetine are effective in the treatment of comorbid ADHD and SUD, and **up-titration** to higher dosages may be considered in patients unresponsive to standard doses.
- Caution and careful clinical management is needed to prevent abuse and diversion of prescribed stimulants.

PROMISING RESULTS...

- Trials that found significant improvement looking at primary or secondary outcome measures:
 - Wilens et al., 2008; Riggs et al., 2011
- Trials that seem promising looking at Subgroups
 - Levin et al., 2007; Winhusen et al., 2011
 - Secondary analyses (Nunes et al., 2013; Covey et al., 2012; Tamm et al., 2013)
- Shortest List: Trials that Found Significant Improvement in ADHD and SUD for Primary Outcome Measures:
 - Konstenius et al., 2014; Levin et al., 2015



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MENTAL HEALTH
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WHERE ARE WE GONING

Other molecules

Higher doses

Integrated psychotherapy

LDX-COCAINE: PILOT STUDY



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Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcddep



Pilot study of the effects of lisdexamfetamine on cocaine use: A randomized, double-blind, placebo-controlled trial[☆]



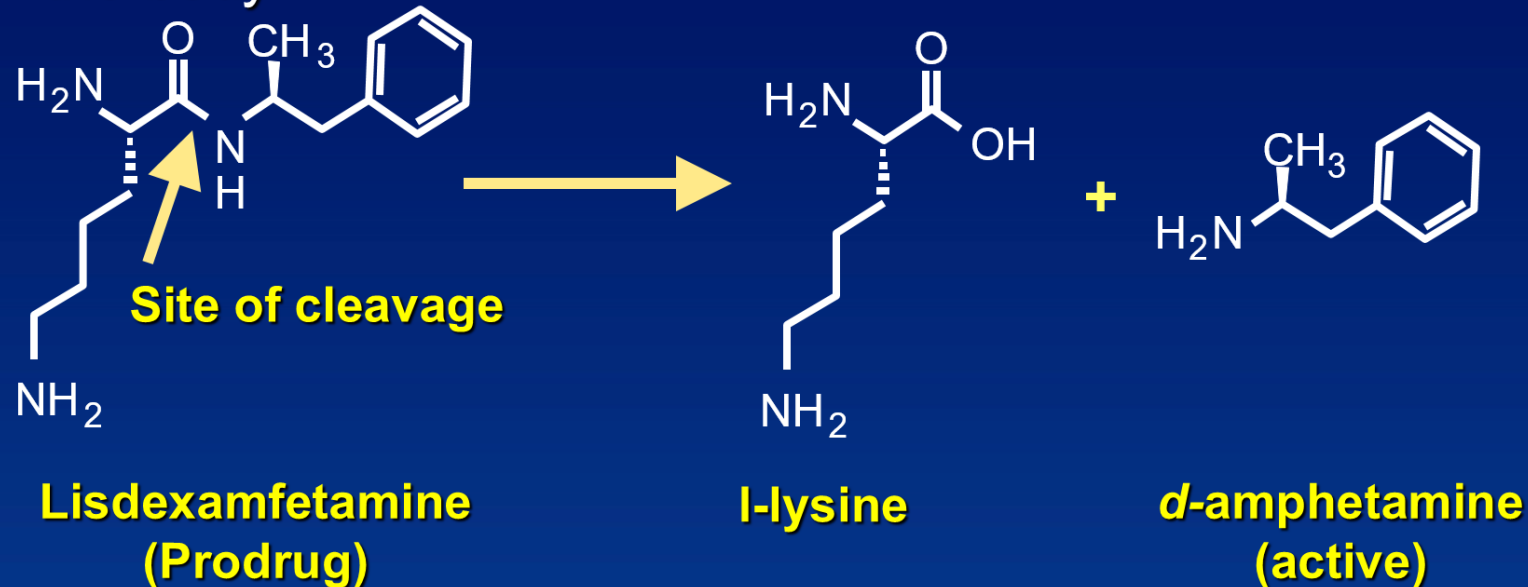
Marc E. Mooney^{a,*}, David V. Herin^a, Sheila Specker^a, David Babb^a, Frances R. Levin^b,
John Grabowski^a

^a Department of Psychiatry, University of Minnesota, Minneapolis, United States

^b New York State Psychiatric Institute & Department of Psychiatry, Columbia University, United States

LISDEXAMPHETAMINE

- Lisdexamfetamine is a prodrug that is therapeutically inactive until it is converted to active *d*-amphetamine in the body



Release of the active ingredient in LDX does not rely on gastrointestinal factors such as GI transit time or Gastric pH

LDX-COCAINE: PILOT STUDY

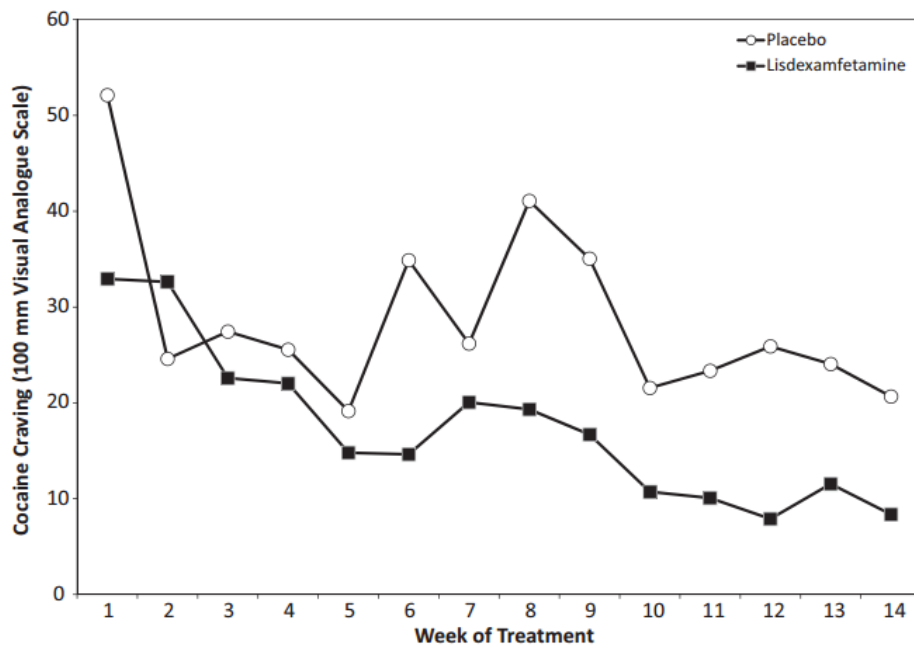


Fig. 5. Cocaine craving since last visit, “Needing Cocaine” rated on a 100-mm visual analog scale. Cocaine craving was significantly lower in those receiving LDX compared to placebo.

LDX-treated subjects reported significantly less craving for cocaine.
No significant differences between treatment groups in cocaine use rates.

Research

Original Investigation

Extended-Release Mixed Amphetamine Salts vs Placebo for Comorbid Adult Attention-Deficit/Hyperactivity Disorder and Cocaine Use Disorder A Randomized Clinical Trial

Frances R. Levin, MD; John J. Mariani, MD; Sheila Specker, MD; Marc Mooney, PhD; Amy Mahony, LMHC; Daniel J. Brooks, MA; David Babb, BA; Yun Bai, MS; Lynn E. Eberly, PhD; Edward V. Nunes, MD; John Grabowski, PhD

IMPORTANCE Adult attention-deficit/hyperactivity disorder (ADHD) is prevalent but often unrecognized, in part because it tends to co-occur with other disorders such as substance use disorders. Cocaine use disorder is one such disorder with high co-occurrence of ADHD.

OBJECTIVE To examine whether treatment of co-occurring ADHD and cocaine use disorder with extended-release mixed amphetamine salts is effective at both improving ADHD symptoms and reducing cocaine use.

DESIGN, SETTING, AND PARTICIPANTS Thirteen-week, randomized, double-blind, 3-arm, placebo-controlled trial of participants meeting DSM-IV-TR criteria for both ADHD and cocaine use disorder conducted between December 1, 2007, and April 15, 2013, at 2 academic health center substance abuse treatment research sites. One hundred twenty-six adults diagnosed as having comorbid ADHD and cocaine use disorder were randomized to extended-release mixed amphetamine salts or placebo. Analysis was by intent-to-treat population.

INTERVENTIONS Participants received extended-release mixed amphetamine salts (60 or 80 mg) or placebo daily for 13 weeks and participated in weekly individual cognitive behavioral therapy.

MAIN OUTCOMES AND MEASURES For ADHD, percentage of participants achieving at least a 30% reduction in ADHD symptom severity, measured by the Adult ADHD Investigator Symptom Rating Scale; for cocaine use, cocaine-negative weeks (by self-report of no cocaine use and weekly benzoylgonine urine screens) during maintenance medication (weeks 2-13) and percentage of participants achieving abstinence for the last 3 weeks.

RESULTS More patients achieved at least a 30% reduction in ADHD symptom severity in the medication groups (60 mg: 30 of 40 participants [75.0%]; odds ratio [OR] = 5.23; 95% CI, 1.98-13.85; $P < .001$); and 80 mg: 25 of 43 participants [58.1%]; OR = 2.27; 95% CI, 0.94-5.49; $P = .07$) compared with placebo (17 of 43 participants [39.5%]). The odds of a cocaine-negative week were higher in the 80-mg group (OR = 5.46; 95% CI, 2.25-13.27; $P < .001$) and 60-mg group (OR = 2.92; 95% CI, 1.15-7.42; $P = .02$) compared with placebo. Rates of continuous abstinence in the last 3 weeks were greater for the medication groups than the placebo group: 30.2% for the 80-mg group (OR = 11.87; 95% CI, 2.25-62.62; $P = .004$) and 17.5% for the 60-mg group (OR = 5.85; 95% CI, 1.04-33.04; $P = .04$) vs 70% for placebo.

CONCLUSIONS AND RELEVANCE Extended-release mixed amphetamine salts in robust doses along with cognitive behavioral therapy are effective for treatment of co-occurring ADHD and cocaine use disorder, both improving ADHD symptoms and reducing cocaine use. The data suggest the importance of screening and treatment of ADHD in adults presenting with cocaine use disorder.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00553319

JAMA Psychiatry doi:10.1001/jamapsychiatry.2015.41
Published online April 18, 2015.

Supplemental content at
jamapsychiatry.com

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Corresponding Author: Frances R. Levin, MD, New York State Psychiatric Institute, 1061 Riverside Dr, Unit 66, New York, NY 10032 (fl2@columbia.edu).

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JAMA Psychiatry

FR Levin and coauthors

Extended-Release Mixed Amphetamine Salts vs Placebo for Comorbid Adult Attention-Deficit/Hyperactivity Disorder and Cocaine Use Disorder: A Randomized Clinical Trial

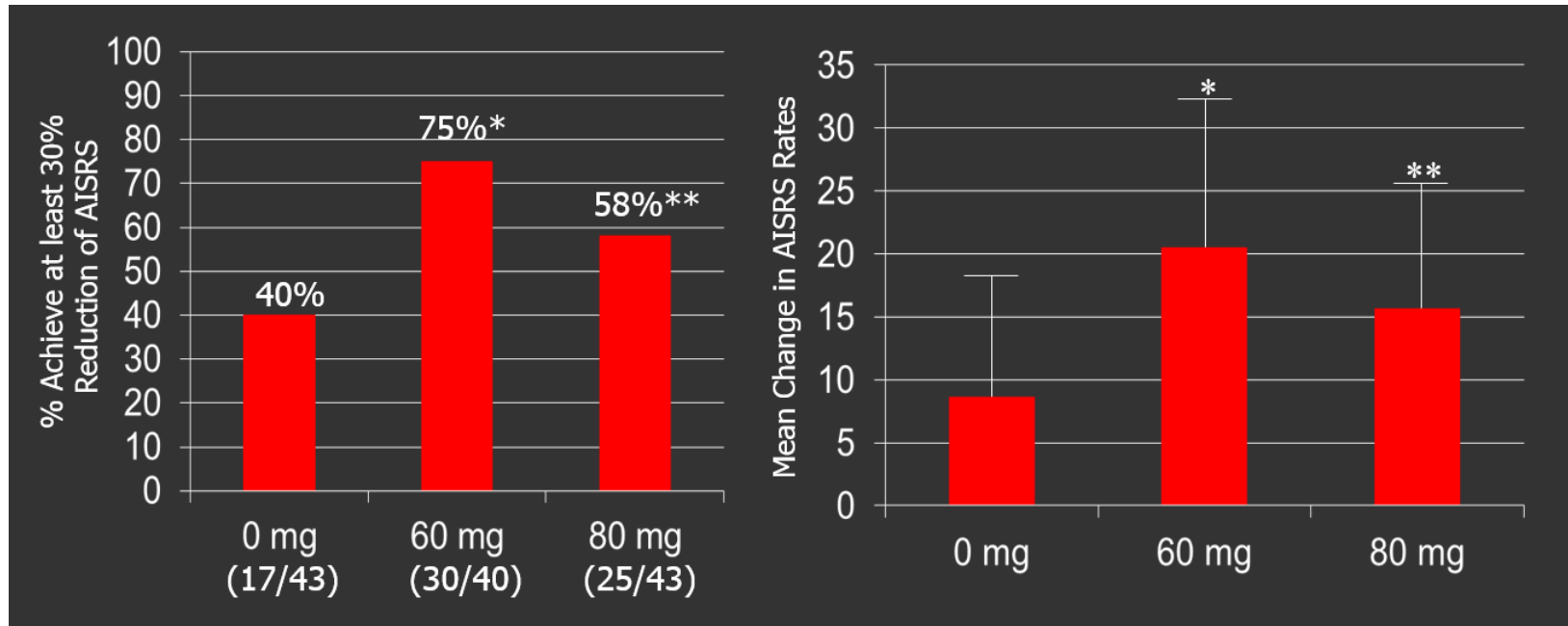
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PRIMARY ADHD OUTCOMES

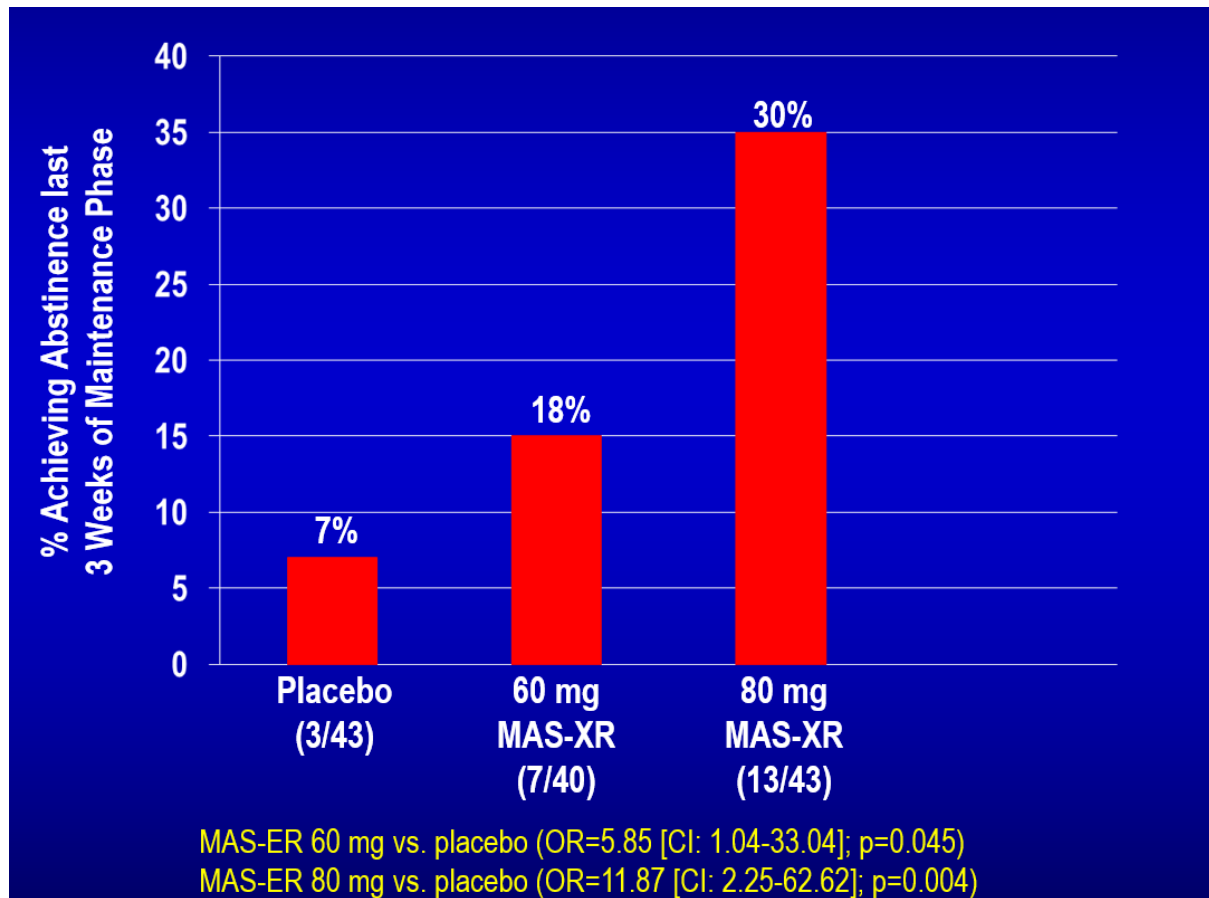
N: 163; Placebo (43), 60 mg (40), 80 mg (43)



* p= 0.0009
** p= 0.069

* p<0.0001
** p= 0.014

COCAINE USE OUTCOME



ADHD & SUD: MPH

Addiction



RESEARCH REPORT

doi:10.1111/add.12369

Methylphenidate for attention deficit hyperactivity disorder and drug relapse in criminal offenders with substance dependence: a 24-week randomized placebo-controlled trial

Maija Konstenius¹, Nitya Jayaram-Lindström¹, Joar Guterstam¹, Olof Beck², Björn Philips³ & Johan Franck¹

Division of Psychiatry, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden,¹ Division of Clinical Pharmacology, Department of Medicine, Karolinska Institutet, Stockholm, Sweden² and Department of Psychology, Linköping University, Linköping, Sweden³

Methylphenidate OROS®

Adult male prison inmates with ADHD and amphetamine dependence

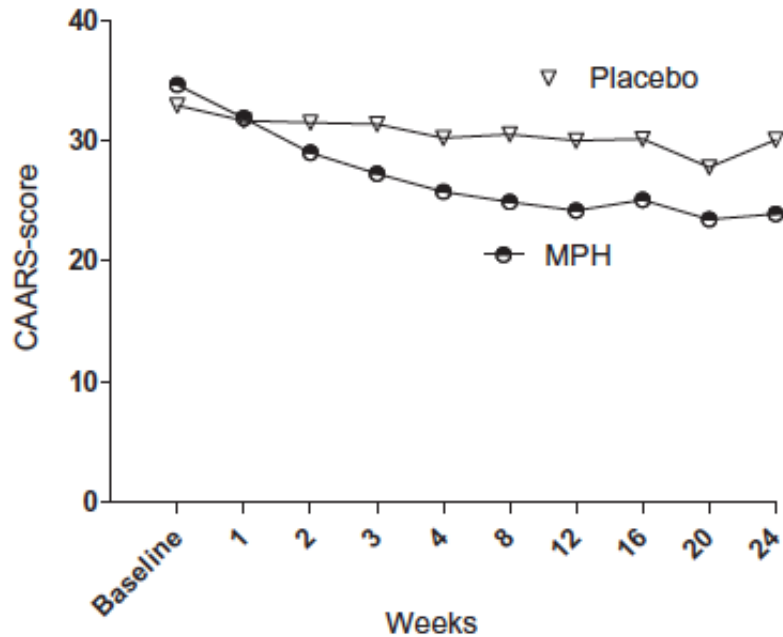


Figure 2 Change in self-rated attention deficit hyperactivity disorder (ADHD) symptoms (95% confidence interval = -13.78 to -1.91, $P=0.011$)

- $n = 54$
- 24 weeks
- MPH-OROS: 96-180 mg/d

Konstenius et al 2014. *Addiction* 109(3):440-449

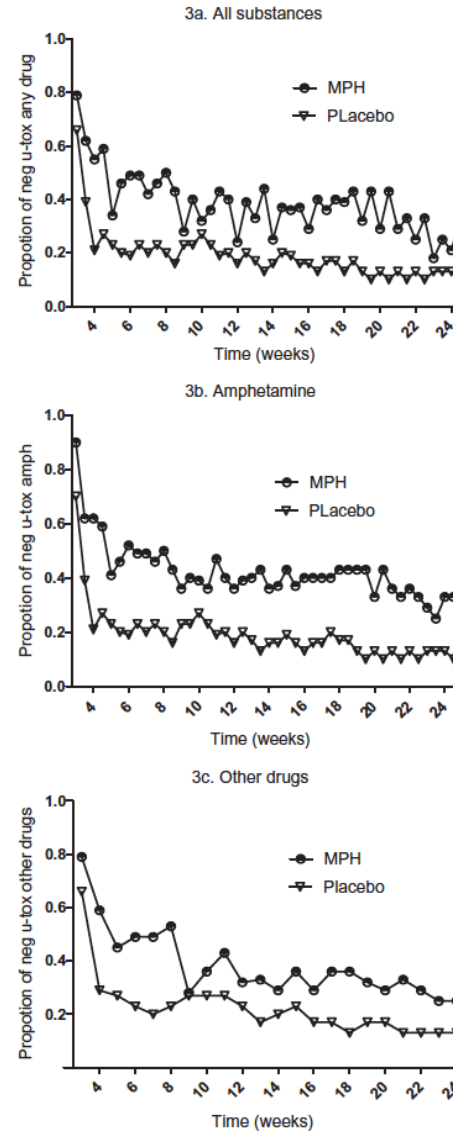


Figure 3 Proportion of negative urine-toxicology after release from prison (weeks 3–24) for the two treatment groups; methylphenidate (MPH) and placebo over 24 weeks of treatment: (a) any drugs amphetamine+other drugs, mean difference 95% confidence interval (CI)=0.05–0.32; (b) amphetamines only, mean difference 95% CI=0.07–0.36; and (c) other drugs, mean difference 95% CI=0.02–0.25

Diminished efficacy of ADHD medication in patients with comorbid SUD

- ❑ Neurobiological and neurocognitive differences are present between ADHD patients with and without SUD:
 - > Smaller striatal grey matter volume with fewer available dopamine transporters
 - > Reduced binding of MPH to brain dopamine transporters
 - > Higher measures of motor- and cognitive impulsivity

- ❑ Together, they may partially explain the reduced effectiveness of methylphenidate in adult

Crunelle et al., 2013

Diminished efficacy of ADHD medication in patients with comorbid SUD

- ❑ Methylphenidate doses in ADHD and comorbid SUD
 - > Patients with SUD use 40% higher methylphenidate doses than those with ADHD only
 - > Patients with SUD show high long-term adherence to methylphenidate treatment
 - > Patients with SUD are treated with methylphenidate without signs of tolerance

Skoglund et al., 2017

EXPLANATIONS OF DIMINISHED MEDICATION EFFICACY

- Incorrect ADHD Diagnosis
- Participant characteristics
- Is ADHD different in SUD Adults
- ADHD severity
- Psychiatric comorbidity
- Type of Substance use
- Influence of previous druguse
- Influence of persistent druguse
- Medication Selection and suboptimal dosing
- Placebo effect and concurrent treatment

Carpentier, 2017

Integrated CBT for patients with SUD and Comorbid ADHD

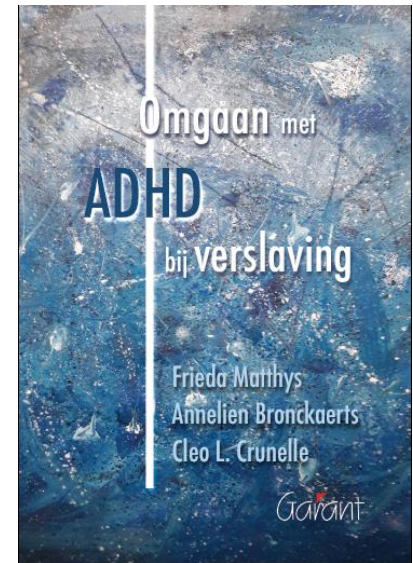
- integrated treatment for substance use disorders and ADHD is a promising new treatment option
- drop-out remains a major challenge in this dual diagnosis patient population.

Van Emmerik, 2017

van Emmerik-van Oortmerssen, 2015

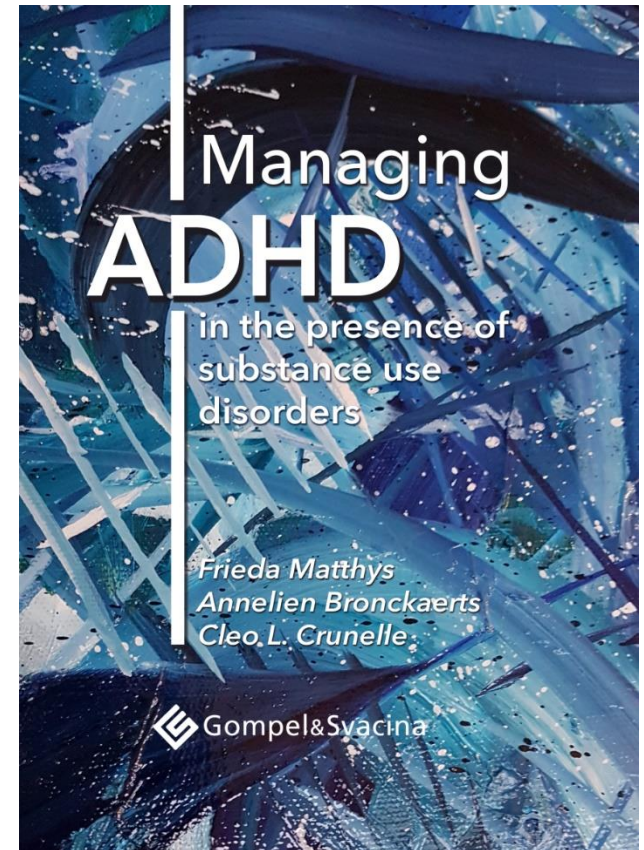
A manual for the treatment of ADHD and SUD

1. Adapting the addiction treatment to the ADHD symptoms
2. Accepting the diagnosis
3. Multidisciplinary approach
4. Personalized treatment (tailored)
5. Skills training



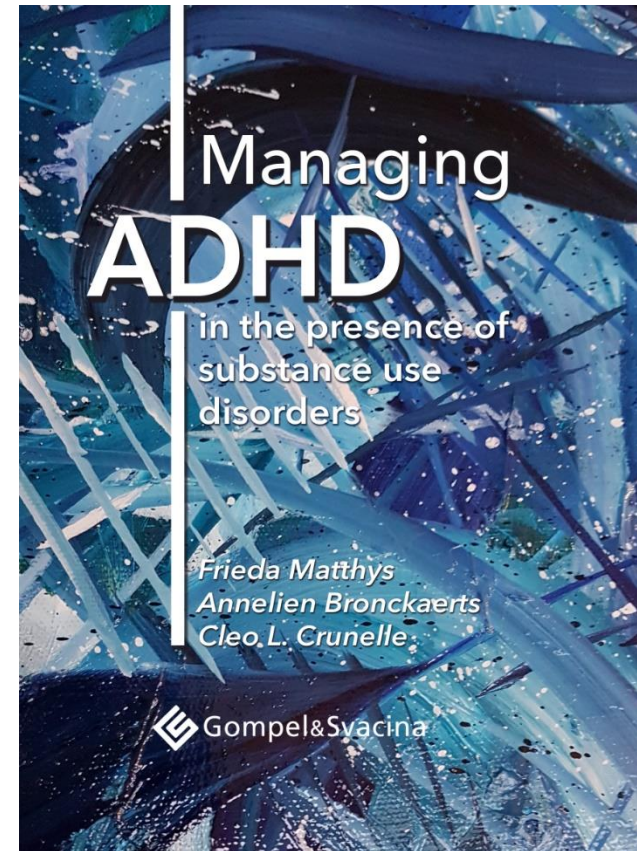
Adapting the addiction treatment to the ADHD symptoms

- 1) Duration of the sessions
- 2) Therapeutical attitude
- 3) Agreements starting the treatment
- 4) Providing a rigorous structure
- 5) Variation and repetition



Skills training

- Learning to plan and organize
- Enlarging time awareness
- Reducing distractibility
- Dealing with addictive substances
- Improving emotion regulation
- Managing cognitions
- Reducing impulsivity
- Improving social skills
- Relapse prevention



Managing ADHD in the presence of substance use disorders

Frieda Matthys, Annelien Bronckaerts & Cleo L. Crunelle

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Managing ADHD

in the presence of substance use disorders

Frieda Matthys
Annelien Bronckaerts
Cleo L. Crunelle

Innovative research is warranted!!!

For reaching two goals:

- Improvement of diagnostic and treatment procedures for patients suffering from both ADHD and SUD
- Prevention of the development of Substance Use Disorders in children/adolescents/adults with ADHD

Coming soon:

INCAS

International Naturalistic Cohort Study of ADHD and Substance Use Disorders (INCAS): clinical characteristics, treatment, and outcome

