

# COMORBIDITY PREVALENCE AND TREATMENT OUTCOME IN CHILDREN AND ADOLESCENTS WITH ADHD

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# program

1. Comorbidity of mental disorders – why is it so common?
2. Implications of comorbidity
3. Prevalence of comorbidities in ADHD
4. Treatment outcome in clinical studies
5. Evidence based guidelines for medical treatment in ADHD with comorbid mental disorders
6. Take home messages

WHY IS COMORBIDITY SO  
COMMON?

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# Comorbidity of mental disorders in child and adolescent psychiatric disorders

Angold et al. 1999

- Meta-analysis of representative general population studies
  - Significant elevated OR for comorbidity between specific diagnoses, compared to the prevalence of each diagnosis alone

Diagnoses	OR	95% CI
ADHD – ODD/CD	10.7	7.7-14.8
ADHD - Dep	5.5	3.5-8.4
ADHD - Anx	3.0	2.1-4.3
CD/ODD – Anx	3.1	2.2-4.6
CD/ODD – Dep	6.6	4.4-11.0
Dep – Anx	8.2	5.8-12.0

# Reasons for comorbidity of mental disorders

- Shared genetic riskfactors
  - SNP's and CNV's
    - ADHD, ODD, CD, autism, schizophrenia
- Shared biological riskfactors
  - Prenatal infections and injuries, preterm birth, birth weight, anoxia
- Shared environmental risk factors
  - Parental psychopathology, socio-economic factors, parenting style, trauma
- Psychiatric disorders often have shared symptomatologi
  - Diagnoses are made on the basis of phenomenology

# Comorbidity in ADHD

- Comorbidity in ADHD is extremely common
- But rates of comorbidity depends on sample definition
  - Children
  - Adolescents
  - Adults
  - Sex
  - Clinical samples versus community samples
    - Much more common in clinical samples
  - In- and exclusion criteria of study eligibility
    - RCT studies often hampered by strict criteria
      - Not representative of the real clinical population
      - Autism spectrum disorders, Intellectual disability

# IMPLICATIONS OF COMORBIDITY

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# Why is it important to be aware of comorbidity in ADHD?

- In clinical assessment:
  - ADHD symptoms may mask comorbid disorders
  - Symptoms of comorbid disorders may mask ADHD symptoms
- In treatment:
  - Comorbid disorders have implications for the choice of treatment in ADHD
    - Depression, tic, psychoses
      - Which disorder should be targeted first?
    - which treatment effect can be expected?
- Prognosis:
  - Comorbid disorders are associated with long term outcome

# Comorbidity and long term prognosis

- Danish register studies
  - Danish Civil Registration System
    - Every person registered with a permanent address in Denmark have a unique individual identification number
  - Danish Psychiatric Central Register
    - All psychiatric diagnoses made in inpatient or outpatient clinics can be identified based on the individual identification number
  - Other registers
    - F.ex. Criminal register, Death Register

# Comorbidity and long term prognosis

- ADHD and comorbid ODD/CD in childhood
- Significant increased risk in adulthood for
  - Substance use disorder (SUD) (HR =3,69)
  - Criminal conviction (HR = 3,2)

Dalsgaard et al. 2013

Dalsgaard et al. 2014

- Lifetime diagnoses of ADHD+ comorbid disorders :
- Significant increased Mortality Rates (MR)
  - ADHD + ODD/CD: MR 6,09
  - ADHD + ODD/CD + SUD: MR 45,71
  - ADHD alone: MR 3,40

Dalsgaard et al 2015

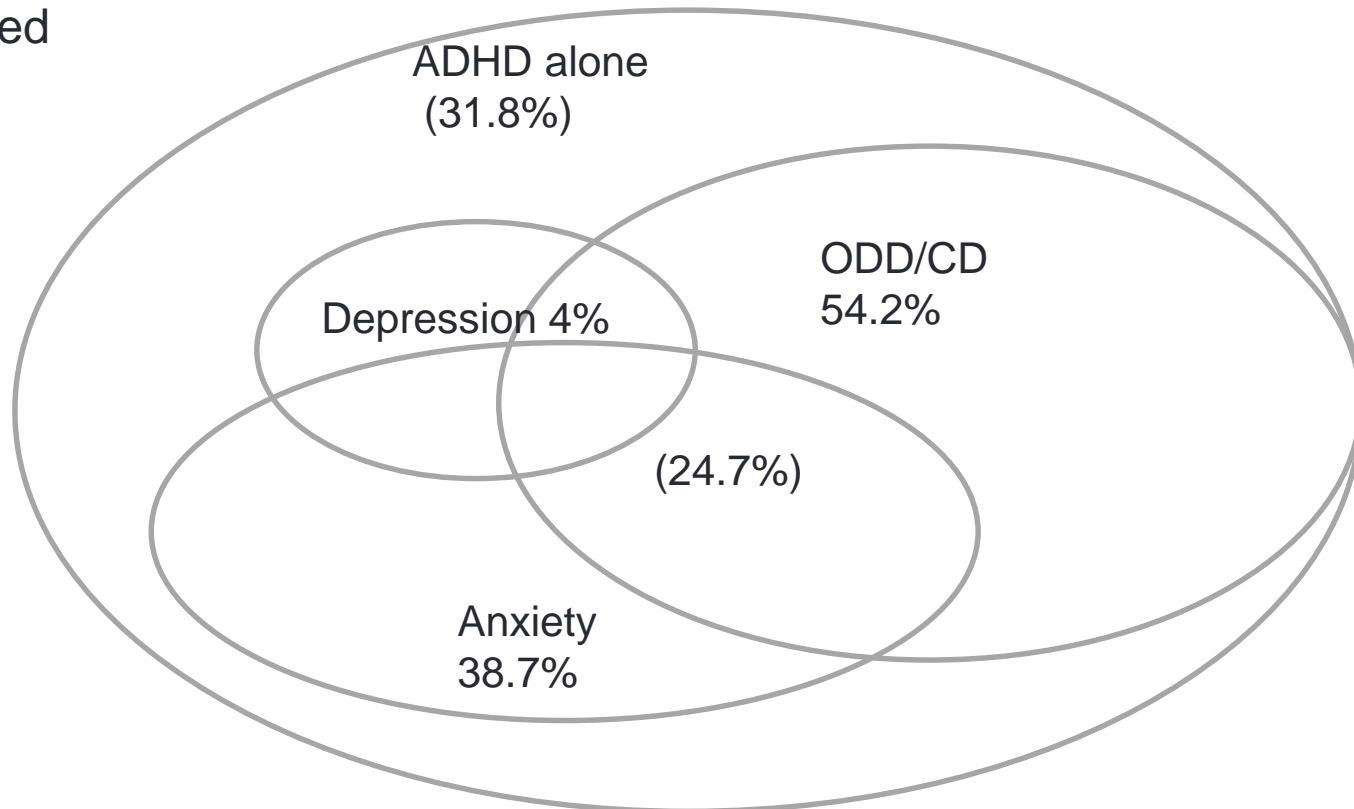
# PREVALENCE OF COMORBIDITY

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# MTA-study – rates of comorbidity

Jensen et al. 1999

- MTA study (N=579 children and adolescents with ADHD)
- 68,2% 1≥ comorbid disorders
- Severe tic disorder, moderate to severe OCD, autism and mental retardation excluded



# ADHD and psychiatric comorbidities - a Danish register study

Jensen C.M, Steinhausen H.C. 2015

- N=14.825 children and adolescents diagnosed with ADHD
  - ICD-10 or ICD-8 between 1995-2010
- Danish register study
  - Danish Civil Registration System
  - Danish Psychiatric Central Register
- Male sex: 79,4%
- All Child and adolescent Mental Health Services in Denmark

# ADHD and psychiatric comorbidities - a Danish register study

Jensen C.M, Steinhausen H.C. 2015

- Diagnoses based on routine clinical practices and diagnostic traditions
- 52,0 % with at least one comorbid disorder
- 26,2 % with two or more comorbid disorders
- Male sex associated with an increased risk for neuropsychiatric disorders
- Female sex associated with an increased risk for internalizing disorders.

# ADHD and psychiatric comorbidities - a Danish register study

Jensen C.M, Steinhausen H.C. 2015

Rates of comorbidities:

- ODD/CD: 16,5%
- Specific developmental disorders: 15,4%
- Autism spectrum disorders: 12,4%
- Intellectual disability: 7,9%
- Tic disorder: 4,8%
- Attachment disorder: 4,1%
  
- Substance use disorder, psychotic disorders, affective disorders, anxiety disorders, OCD, eating disorders, personality disorders: less than 2%



# The Lombardy ADHD registry project - A multicenter, clinical observational study

Reale L. et al. 2017

- N=2861 children and adolescents suspected for ADHD
  - Male sex: 85%
  - Mean age 9,2 (SD2,5)
  - 34 Child- and Adolescent Neuropsych. Services in the Lombardy Region
  - Diagnostic evaluation based on a systematic strict assessment procedure according to international guidelines

# The Lombardy ADHD registry project - A multicenter, clinical observational study

Reale L. et al. 2017

- N=1919 children and adolescents diagnosed with ADHD
  - 34% ADHD only
  - 66% one or more comorbid disorders

Most frequent comorbidity in ADHD sample

Comorbid disorders	rates
Learning disorders	56%
Sleep disorders	23%
ODD	20%
Anxiety disorders	12%

# INDICES-WP6 study – a clinical naturalistic observational cohort study

Kaalund-Brok K. et al  
In preparation

- N=207 drugnaïve children
  - newly diagnosed with ICD-10 hyperkinetic disorder / attention deficit disorder
  - Mean age 9,6 (SD1,5)
  - Child and Adolescent Mental Health Centre, Capital Region of Denmark
  - Clinical diagnostic evaluation based on a systematic strict assessment procedure according to international guidelines
  - Study focus
    - pharmacogenetic
      - Effect of variations in CES1 gene for MPH treatment

# INDICES-WP6 study – a clinical naturalistic observational cohort study

Kaalund-Brok K. et al  
In preparation

- N= 207 children with ADHD
  - ICD-10 Hyperkinetic Disorder: 83,1%
  - ICD-10 Hyperkinetic Conduct Disorder 5,8%
  - ICD-10 ADD without hyperactivity (DF98.8) 11,1%
- 
- 34,8% ADHD only
- 65,2% one or more comorbid disorders

# INDICES-WP6 study – a clinical naturalistic observational cohort study

Kaalund-Brok K. et al  
In preparation

Comorbid disorders	Rates
Cognitive deficits (WISC IQ: 70-85)	27,1%
Specific developmental disorders	22,2
Emotional disorders (mood, anxiety- and adjustment disorders)	13,0%
Autism spectrum disorders	12,6%
Encopresis and enuresis	11,6%
Tic disorders	8,2%
Externalizing disorders (ODD/CD)	6,8%
Attachment disorders	1,4%

# Prevalence of comorbidity- comparison of 2 clinical studies

	Lombardy Region N= 1919	Copenhagen Region N = 207
ADHD only	34%	34,8%
1 ≥ comorbid disorders	66%	65,2%
Disorders of learning and development	56%	49,3
Anxiety / emotional disorders	12%	13%
ODD /CD	20%	6%

Rates of specific disorders influenced by age, sample size, ex- and inclusion criteria and diagnostic traditions

# COMORBIDITY AND IMPLICATIONS FOR TREATMENT

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# The patients we are facing -

## Clinical cases

- Michael 7 years old
- Preterm birth in GA week 34. Lives with both his parents and an older brother. Both parents have good jobs. No history of mental disorder in the family.
- Delayed development of speech and fine motor functions. Normal cognitive functions. He has always been curious, on the move, rapidly shifting from one activity to the other. Very happy for outdoor play activities. Always good peer relations.
- Just started in first grade. Now he is often irritable and in a bad mood in the afternoon. Teachers report that he is unable to sit down when expected, and to follow instructions and pay attention. He is disturbing and does not benefit sufficient from the teaching.
- Child- and adolescent psychiatric assessment confirms a diagnosis of ADHD
- MPH treatment and psychosocial interventions of low intensity have good effect on daily functions and ADHD core symptoms



# The patients we are facing - Clinical cases

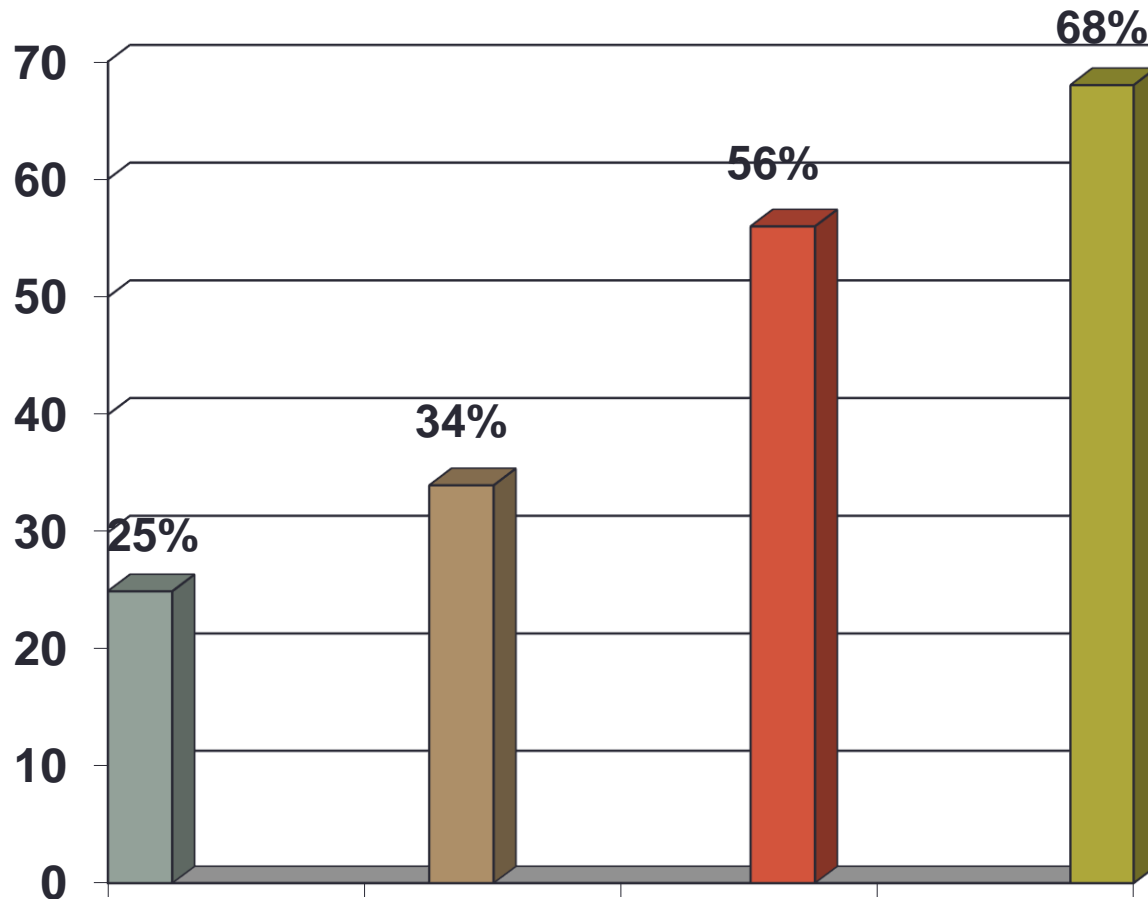
- Samuel 10 years old. Lives with his mother and a younger brother who has a chronic immune defect. The father is described as a drug addict and is at present in prison.
- The mother has a history of depression and is distressed.
- Samuel has always had sleep problems and temper tantrums.
- Kindergarten described problems with attention, excessive motor activity and impulsive, aggressive behavior. The other children were afraid of him. The problems have worsened since he started school, from which he is suspended at present.
- It has been difficult for the mother to comply with the support and guidance offered from the community
- Treatment with stimulants had side effect of severe irritability
- At the moment treatment with atomoxetine is being tested

# MTA study - treatment effect

Jensen et al. 1999

N=579 children and adolescents with ADHD

68,2% 1≥ comorbid disorders



No sign. diff. between CS treatment and comb. treatment  
Except for anxiety disorders

- treatment as usual
- behaviour therapy
- Central stimulants
- CS + beh. Therapy

# The Lombardy ADHD registry project - A multicenter, clinical observational study

Treatment effect:

Reale L. et al. 2017

- N=724
- Follow up period:  $9 \pm 3$  months
- Treatment effect measured with CGI-I and CGI-S( $\Delta$  mean)
- Treatments evaluated
  - MPH monotherapy
  - MPH + psychological treatment (combined treatment)
  - Psychological treatment alone
  - No treatment

# The Lombardy ADHD registry project - Comorbidity and treatment effect

Reale L. et al. 2017

- Lombardy study, 9 ± 3 months follow-up
- Outcome measure: CGI-S
  - Higher ES in cases with comorbidity
  - In general MPH-only not superior to combined treatment
  - Combined treatment superior in cases with comorbid ODD/CD or learning disorder

ES (95% CI)	ADHD only	ADHD + comor.	ADHD + ODD/CD	ADHD + sleep	ADHD + learning	ADHD + anxiety
Psycholog. treatment	0,10 (-0,23 -0,43)	0,40 (0,11-0,69)	0,09 (-0,79-0,97)	0,27 (-0,34-0,89)	<b>0,50*</b> <b>(0,14-0,86)</b>	0,51 (-0,45-1,47)
MPH only	0,63 (-0,03-1,30)	<b>0,89*</b> <b>(0,44-1,34)</b>	0,58 (-0,01-1,16)	<b>1,02*</b> <b>(0,17-1,87)</b>	1,06 (-0,54-2,67)	<b>1,61*</b> <b>(0,34-2,89)</b>
Comb. treatment	0,41 (-0,14-0,97)	<b>0,75*</b> <b>(0,43-1,07)</b>	<b>0,98*</b> <b>(0,08-1,88)</b>	0,57 (-0,08-1,21)	<b>0,66*</b> <b>(0,25-1,06)</b>	0,69 (-0,31-1,68)

# Short term effect and predictors for outcome

Kaalund-Brok K. et al  
In preparation

INDICES-WP6 (Copenhagen study)

- N=207
- Follow-up period 12 weeks
- Treatment: MPH + standard psychosocial treatment in community
- Primary effect measures:
  - DSM-IV- ADHD-RS clinician rated
    - normalisation or borderline normalisation on any DSM-IV-ADHD-RS subscale (clinician rated)
  - CGI-S clinician rated
    - A score of 1 or 2 (normal to mildly ill) on CGI-S

# Short term treatment effect

## INDICES-WP6

Kaalund-Brok K. et al  
In preparation

**Significant short term treatment effect on any outcome measures**

DSM-IV-ADHD rating scale	Week 0 M [SD]	Week 12 M [SD]	Week 0 vs. week 12		
			M dif. [SD]	[95% CI]	p-value
Inattention scale	19.9 [3.7]	9.6 [3.7]	10.3 [4.0]	9.7 - 10.9	<0.001
Hyperactivity-Impulsivity scale	18.0 [5.8]	7.9 [4.0]	10.1 [5.1]	9.4 - 10.8	<0.001
Inattention + Hyp/ Imp. scales	37.9 [7.8]	17.5 [6.8]	20.4 [7.7]	19.3- 21.5	<0.001
CGI-S	5,3 [0,9]	3.0 [1.1]	2.3 [1.0]	2.2 to 2.5	<0.001

# Predictors for outcome

INDICES-WP6

Kaalund-Brok K. et al  
In preparation

- Baseline predictors for time to first normalisation/borderline norm. on DSM-IV-ADHD-RS:
- Predictor for good outcome: Comorbidity
- Predictors for poorer outcome: Female sex, cognitive deficits and young age

Inattention scale	HR	CI 95%	p-value
Sex (girls)	0.64 (neg.)	0.54 to 0.75	<0.001
Cognitive deficits	0.74 (neg.)	0.63 to 0.86	<0.001
Hyperactivity-Impul. scale	HR	CI 95%	p-value
Age (7-9yrs)	0.88 (neg.)	0.71 to 0.96	0.031
Cognitive deficits	0.82 (neg.)	0.78 to 0.99	0.011
Comorbidity	1.17 (pos.)	1.02 to 1.35	0.030

# EVIDENCE BASED GUIDELINES FOR MEDICAL TREATMENT IN ADHD AND COMORBID DISORDERS

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Evidence evaluated on the GRADE system  
Danish Medicines Council 2016



# Evidence based guidelines for medical treatment

Danish Medicines Council 2016

- ADHD and comorbid anxiety disorders
  - Both Methylphenidate (MPH) and Atomoxetine (ATX) have significant effect on ADHD core symptoms (moderate evidence)
- ADHD and comorbid depressive disorder
  - Significant effect of ATX on ADHD core symptoms (mod. evidence)
    - No effect on depressive symptoms
- ADHD and comorbid ODD/CD
  - Significant effect of ATX on both ADHD core symptoms (high evidence) and ODD sympt. (mod. evidence)
  - Guanfacine have slightly better effect on ODD symptoms compared to ATX (low evidence)

# Evidence based guidelines for medical treatment

Danish Medicines Council 2016

- ADHD and comorbid autismspectrum disorders
  - MPH (high evidence) have sign. effect on all ADHD core symptoms
  - ATX (high evidence) have sign. effect on hyp/imp. symptoms
  - Guanfacine (mod. evidence) have sign. effect on hyp/imp. Symptoms
  - No effect of any of the drugs on ASD symptoms
- ADHD and comorbid tic disorder (incl. Tourettes Disorder)
  - MPH, ATX and Guanfacine have sign. effect on ADHD core symptoms (high evidence)
  - Treatment with MPH (high evidence) or ATX- and Guanfacine (mod. evidence) does not worsen tics

# Evidence based guidelines for medical treatment

Danish Medicines Council 2016

- ADHD and comorbid intellectual disability
  - MPH have effect on ADHD core symptoms (low evidence)
    - Smaller effect than in typically developing children
  - Guanfacine have effect on hyperactivity (very low evidence)
    - Effect on inattention not tested
- ADHD and comorbid substance use disorder
  - MPH have a possible effect on ADHD core symptoms (very low evidence)
  - Neither MPH (mod. evidence) nor ATX (low evidence) does improve or worsen abuse of cannabis, cocaine or alcohol

# Take home messages

- Comorbid mental disorders are extremely common in ADHD
- Comorbid ODD/CD have a very high prevalence followed by other neuropsychiatric disorders
- Short term effect (up to 1 year) of medical treatment is not influenced by comorbidity
- Usual first- and second line treatments can be used in most comorbid conditions
- Long term outcome is highly affected of comorbid ODD/CD, including increased risk of criminality, substance use disorder and preterm death



....there's a strong need for improved interventions