

# ADHD and Treatment Considerations

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## Content

- What is ADHD
- Epidemiology of ADHD
- Guidelines on ADHD
- ADHD Treatments
  - Stimulant Treatments
  - Non-Stimulant Treatments

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## Disclaimer

- Advisory work:
  - Holmusk

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What is the DSM-5 criteria for ADHD?

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# DSM-5 Criteria

- 6 or more symptoms for children or 5 or more in those >/= 17 years of age
- Prior to age 12\*
- Present in 2 or more settings
- Symptoms interfere with or reduce quality of social, academic, **or** occupational function.
- Not better explained by an alternate disorder

APA, 2013. DSM-5

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# Inattention

- Often fails to give close attention to details or makes careless mistakes in school work
- Often has difficulty sustaining attention in tasks or play activities
- Often does not seem to listen when spoken to directly
- Often does not follow through on instructions and fails to finish school work
- Often has difficulty organizing tasks and activities
- Often avoids, dislikes, or reluctantly engages in tasks requiring sustained mental effort
- Often loses things necessary for activities (e.g. school assignments, pencils, or books)
- Often is distracted by extraneous stimuli
- Often is forgetful in daily activities

APA, 2013. DSM-5  
CADDRA, 2018. Canadian ADHD Practice Guidelines

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## Inattention

- Organizing
- Initiating
- Staying on Task
  - Distractibility
  - Sustained attention
  - Attention to detail
- Completing Tasks
- Forgetful
- Lose items
- Difficulty listening

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## Hyperactivity/Impulsivity

Often fidgets with hands or feet or squirms in seat

Often leaves seat in classroom when remaining seated is expected

Often runs about or climbs excessively in situations where it is inappropriate

Often has difficulty playing or engaging in leisure activities quietly

Often is "on the go" or often acts as if "driven by a motor"

Often talks excessively

Often blurts out answers to questions before the questions have been completed

Often has difficulty awaiting turn

Often interrupts or intrudes on others (e.g. butts into conversations/games)

Runs, climbs or restless

Uninhibited in conversation

Not able to play quietly

Fidgets or squirms in seat

Interrupts or intrudes on others

Difficulty waiting his or her turn

Get going or acting as if driven by a motor

Evacuates seat unexpectedly

Talks excessively

APA, 2013. DSM-5

CADDRA, 2018. Canadian ADHD Practice Guidelines

Kadiyala, 2020. *General Psychiatry*

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## Specifiers

- Combined
- Predominantly inattentive
- Predominately hyperactive/impulsive
- In partial remission

### Severity:

- Mild
- Moderate
- Severe

APA, 2013. DSM-5

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## Prior to Age 12

- A subset of adults do not recall symptomatology prior to age 12
  - Could be great early life support
  - High IQ to allow compensation
  - Good structure/routine
  - Adult onset

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# CADDRA

**Red Flags for ADHD**

[3, 42-44]

- Organizational skill problems (time management difficulties, missed appointments, frequent late and unfinished projects).
- Erratic work/academic performance.
- Anger control problems.
- Family/marital problems.
- Difficulty in maintaining organized household routines, sleeping patterns and other self-regulating activities.
- Difficulty managing finances.
- Addictions such as substance use, compulsive shopping, sexual addiction, overeating, compulsive exercise, video gaming or gambling.
- Frequent accidents either through recklessness or inattention.
- Problems with driving (speeding tickets, serious accidents, license revoked).
- Having a direct relative who has ADHD.
- Having to reduce their course load, or having difficulty completing assignments in school.
- Low self-esteem or chronic under-achievement.

CADDRA, 2018. Canadian ADHD Practice Guidelines

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# How do you diagnose ADHD?

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# What Do the Guidelines Say?

Table 5. Rating of methodological quality (AGREE scores)

Guideline	AAP (2000)	AAP (2001)	NZ (2001)	AACAP (2002)	DGPPN (2003)	ESCAP (2004)	ESCAP (2006)	BAP (2006)	DGKJP (2007)	AACAP (2007)	NICE (2008)	SIGN (2009)	CADDRA (2011)
Scope and purpose (maximum score 12)	11	8	11	7	5	3	8	8	4	4	12	11	10
Stakeholder involvement (maximum score 16)	8	9	13	4	7	5	7	5	5	4	13	10	9
Rigour of development (maximum score 28)	20	22	19	15	11	14	21	17	9	16	27	23	19
Clarity and presentation (maximum score 16)	15	12	14	12	12	12	12	14	12	16	16	14	16
Applicability (maximum score 12)	3	5	3	3	3	5	5	5	4	3	11	12	6
Editorial independence (maximum score 8)	2	2	2	3	2	5	6	8	2	5	8	8	8
Total score (maximum score 92)	59 (64%)	58 (63%)	62 (67%)	44 (48%)	40 (43%)	44 (48%)	57 (62%)	59 (64%)	36 (39%)	48 (52%)	87 (95%)	78 (85%)	68 (74%)

Seixas et al. 2012 *Journal of Psychopharmacology*

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# Guidelines for the Diagnosis/Treatment

Table 1. Overview of national and international ADHD guidelines

Association	AAP (2000*, 2001*)	NZ (2001)	DGPPN (2003)	ESCAP (2004*, 2006*)	BAP (2006)	DGKJP (2007)	AACAP (2002*, 2007*)	NICE (2008)	SIGN (2009)	CADDRA (2011)
Authors	Perris & Stein et al.	Tuohy et al.	Ebert et al.	Taylor et al. <sup>2</sup> ; Banaschewski et al. <sup>6</sup>	Nutt et al.	Döpfner et al.	Greenhill et al. <sup>7</sup> ; Pliszka et al. <sup>1</sup>	Taylor et al.	Forbes et al.	Weiss et al.
Date of publication	May 2000*; Oct 2001*	Jul 2001	Oct 2003	Jul 2004*; May 2006*	Nov 2006	Nov 2006	Feb 2002*; Jul 2007*	Sep 2008	Oct 2009	Jan 2011
Previous version	-	-	-	Dec 1998	-	1999; 2003	1997	Mar 2006	Jun 2001*	2006; 2008
Origin	USA	New Zealand	Germany	Europe	UK	Germany	USA	UK	UK (Scotland)	Canada
Source	www	www	Journal	Journal	www	www; book	www	www, book	www	www
Target group	Primary care clinicians	Health professionals	Physicians	CAMH, Paeds	GP, Paeds, CAMH, Psych	CAMH	Clinicians, CAMH, Psych	Clinicians	Health professionals	Physicians
Grading of evidence	Yes	No	Yes	Yes	Yes	Yes (inconsistent)	Yes	Yes	Yes	Yes
Funding	Unclear	Unclear	Self-funded; no individual disclosures	Unclear	Pharma	Unclear	Unclear; individual disclosures	Public funding	Public funding	Self-funded; with individual disclosures
Diagnosis	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Treatment	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
C&A	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes
Adult	No	No	Yes (adults only)	Yes (drug treatment only, Banaschewski et al)	Yes	No	Yes (Greenhill et al)	Yes	No	Yes

Seixas et al. 2012 *Journal of Psychopharmacology*

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# How to Diagnose ADHD

- Gold standard: The clinical interview (review of guideline recommendation)
  - Clinical assessment, mental status exam, assessment of impairment, development, comorbidity and family history, physical exam
  - “the use of rating scales has standardized and improved the reliability, breadth and efficiency of assessments”
  - Collateral in children (parent/teacher rating scale)
  - In adults collateral from someone who lives with them

Seixas et al. 2012 *Journal of Psychopharmacology*

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# What Do the Guidelines Say?

Table 2. Recommendations for the assessment and diagnosis of ADHD										
Association	AAP (2000, 2001)	NZ (2001)	DGPPN (2003)	ESCAP (2004, 2006)	BAP (2006)	AACAP (2002, 2007)	DGKJP (2007)	NICE (2008)	SIGN (2009)	CADDRA (2011)
Diagnostic criteria	DSM-IV	DSM-IV	ICD-10; DSM-IV; Wender-Utah criteria	ICD-10; DSM-IV	DSM-IV; ICD-10	DSM-IV; ICD-10	ICD-10; DSM-IV	DSM-IV; ICD-10	DSM-IV; ICD-10	DSM-IV
ADHD specialist	0	+	0	+	+	0	0	+	+	+
Screening	+	+	0	0	+	+	0	+	0	+
Screening for comorbidities	+	+	+	+	+	+	+	+	+	+
Psychiatric interview	Patient, parents, school, informants	Patient, parents, school, informants, observation	Parents, informants	Patient, parents, school	Patient, informants	Patient, parents, school	Patient, parents, school	Patient, informants	Patient, parents, school	Patient, parents, school, informants
Questionnaires and rating scales	Optional (CPRS-R, CTRS-R, SSQ-R); not recommended for diagnosis (CBCL-R, TRF, DSM-IV total scale, CPRS-R Global Problem Index, CTRS-R Global Problem Index)	CPRS-R; CTRS-R; ACTERS; SNAP-IV	DSM-IV symptom checklist; CPRS; WURS; BADOS	C-GAS; axis 6 of the MAS; CBCL; CCC; CPRS-R; CTRS-R; DBD; HSD-R; SSQ-R; IOWA-CTRS; RBPC; Rutter Scales; SNAP-IV; SDQ; TRF; YSR; NIMH DISC-IV; PACS	WURS; ASRS; BADOS; BSOPA-SC; ASRS-V1.1; ADHDRS-IV; Canadian Consensus Screening Checklist	WPRS; WURS; CAARS; not specified; ADHDRS-IV; BADOS; CBCL; CPRS-R; CTRS-R; CASS-I; HSD-R; SSQ-R; IOWA-CTRS; SNAP-IV; SKAMP; VADPRS; VADTRS; CAP		Conners' rating scales, + CAAOID, SDQ, C-GAS		CAAT
Neuropsychological assessment	0	Not routinely; continuous performance tests potentially useful.	0	+	Not for diagnosis; recommended to inform management	—	0	0	0	Psychoeducational assessment and psychological testing
Physical examination	+	+	+	+	+	+	+	+	+	+
Other investigations	Blood lead levels, thyroid function, brain imaging, EEG and continuous performance tests not routinely recommended	EEG, heavy metal tests, thyroid function tests, other blood tests and organ imaging tests not recommended routinely. Personality tests not recommended	EEG; thyroid function tests; CT/MRI	Not routinely	0	Thyroid function tests, serum lead levels, EEG, head MRI, SPECT, PET - all not routinely recommended	Thyroid function tests; EEG	EEG if clinical/historical indications	Blood analysis, EEG and brain imaging may be necessary to exclude underlying medical problem	Polysomnography, EEG and brain imaging may be indicated

Seixas et al. 2012 *Journal of Psychopharmacology*

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# Neuropsychiatric Testing

- Discriminative validity of neuropsychiatric tests in diagnosis ADHD in adults

**Table 3.** Results of Calculations of Sensitivity, Specificity, PPV, NPV, and AUC for Each Instrument in Relation to Clinical ADHD Diagnosis.

	ASRS Screeners	DIVA	QBTtest Act <sup>a</sup>	QBTtest Ina <sup>a</sup>	QBTtest Omi <sup>a</sup>	QBTtest RT Var <sup>a</sup>	PASAT Tot <sup>a</sup>	CPT II Com <sup>a</sup>	CPT II Var <sup>a</sup>
Sensitivity	91.7	90.0	76.7	58.3	73.3	43.3	33.3	33.3	26.7
Specificity	27.1	72.9	43.8	66.7	56.3	75.0	77.1	91.7	85.4
False positives	38.9	19.4	37.0	31.4	32.3	31.6	35.5	16.7	30.4
False negatives	27.8	14.6	40.0	43.9	37.2	48.6	51.9	47.6	51.8
PPV	61.1	80.6	63.0	68.6	67.7	68.4	64.5	83.3	69.6
NPV	72.2	85.4	60.0	56.1	62.8	51.4	48.1	52.4	48.2
Total classification accuracy	63.0	82.4	62.0	62.0	65.7	57.4	52.8	59.3	52.8
AUC	0.759	0.828	0.664	0.673	0.725	0.674	0.663	0.741	0.706

Patterson et al. 2018, *Journal of Attention Disorders*

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# NICE Guidelines

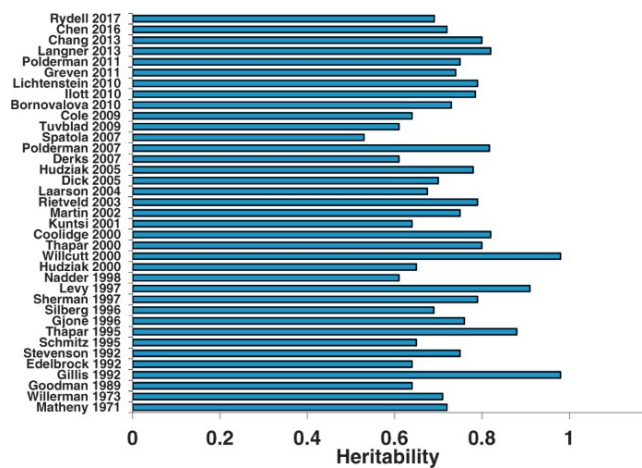
- “rating scales such as the Conners' rating scales and the Strengths and Difficulties Questionnaire are valuable adjuncts, and observations (for example, at school) are useful when there is doubt about symptoms”

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What do you know about the heritability of ADHD?

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# Biological Considerations



Faraone and Larsson, 2019, *Molecular Psychiatry*

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# Biological Consideration

Generally Accepted to be 77-88% heritable

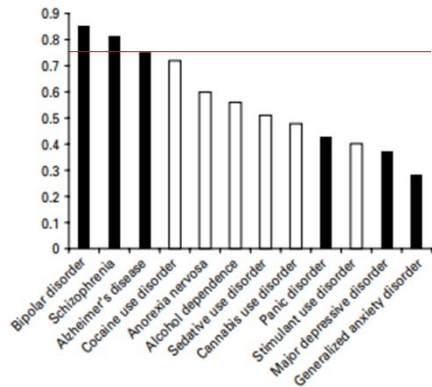
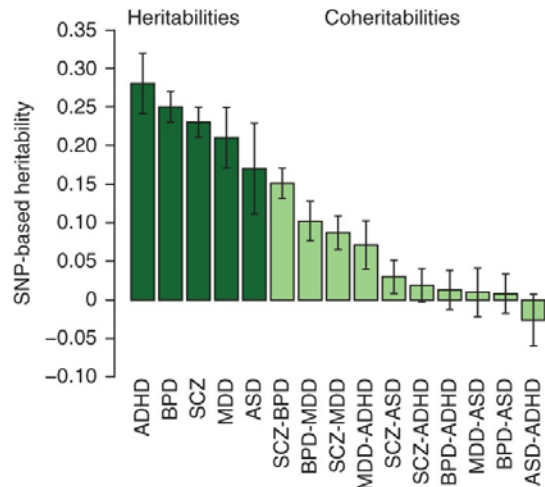


Fig. 1. Heritability summary estimates for psychiatric diseases/disease-like conditions (■) and behavioral disorders (□).

Bienvendu et al. 2010, *Psychological Medicine*

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# Comparison of Common SNP's



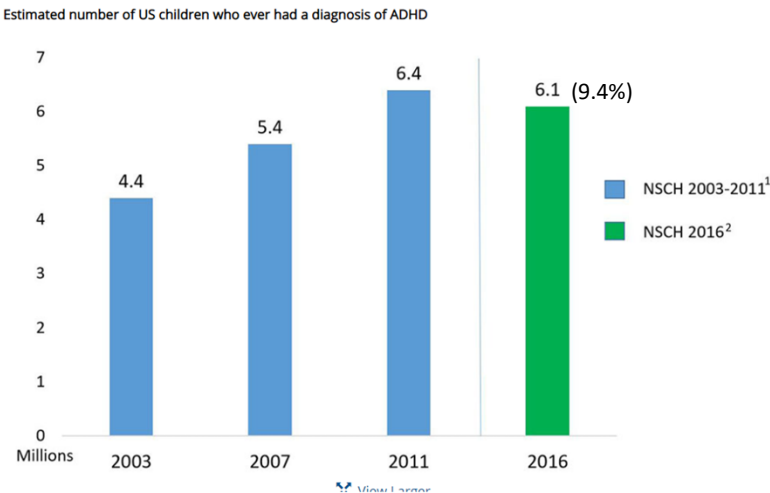
Cross-Disorder Group of the Psychiatric Genomics Consortium  
2013. *Nature Genetics*.

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What are your thoughts about stimulant  
prescribing rates?

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# Epidemiology



[cdc.gov/ncbddd/adhd/data.htm](https://cdc.gov/ncbddd/adhd/data.htm) (accessed:11.16.20)

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## NC Epidemiology

- In 2011 NC: 12.8%
- Treatment in NC: 9.4%

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## Epidemiology: Adults

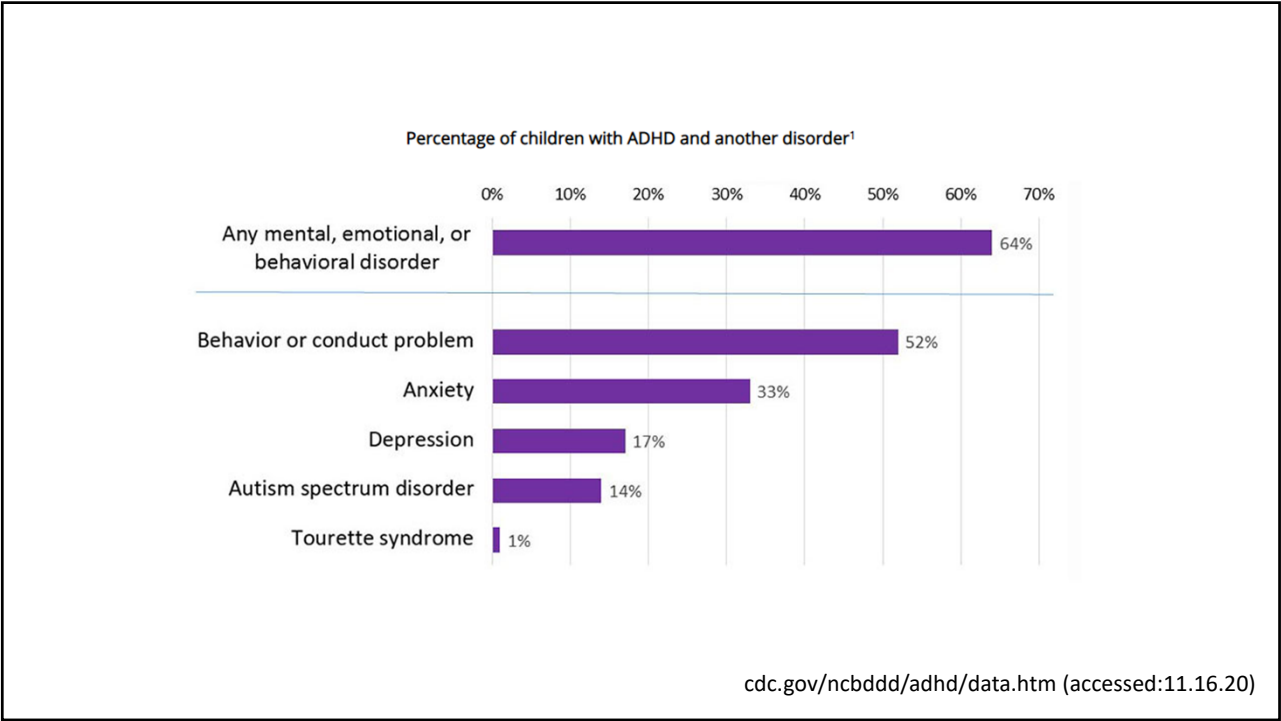
- 4.4%
- 2:1 ratio m:f
- Despite females receiving more mental health care fewer received care specifically for ADHD
- Only 10.9% of respondents with adult ADHD received treatment for ADHD in the 12 months before interview (12.1% of females vs. 10.1% of males,  $z = 0.4$ ,  $p = .657$ ).

Kessler et al. 2006, *American Journal of Psychiatry*

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Table 1 Incidence of comorbidities with ADHD in children		
Comorbidity	Incidence	References
Anxiety	18%	Larson et al <sup>10</sup>
	25%–35%	Geller et al <sup>12</sup>
	25%–50%	Sciberras et al <sup>13</sup>
	27%	Bakken et al <sup>14</sup>
Binge eating	12%	Reinblatt et al <sup>15</sup>
Bipolar disorder	0%–20%	Taurines et al <sup>16</sup>
	7%–22%	Singh et al <sup>17</sup>
	5%	Bakken et al <sup>14</sup>
Conduct disorder/ODD	30%–50%	Dopheide and Pliszka <sup>3</sup>
	40%–60%	Biederman et al <sup>18</sup>
	24%	Bakken et al <sup>14</sup>
Depression	21%	Bakken et al <sup>14</sup>
	16%–26%	Gillberg et al <sup>19</sup>
Learning and language disorders	23%	Bakken et al <sup>14</sup>
	46%	Larson et al <sup>10</sup>
Obsessive compulsive disorder	2%	Jensen and Steinhausen <sup>8</sup>
Pervasive developmental disorders/ASD	12%	Jensen and Steinhausen <sup>8</sup>
	30%–50%	Reichow et al <sup>20</sup>
Substance abuse disorders	22%	Kollins <sup>21</sup>
Tic disorders/Tourette's syndrome	7%	Bakken et al <sup>14</sup>
	20%–30%	Taurines et al <sup>16</sup>
<b>Note:</b> No data were found in the literature for ADHD and antisocial personality disorder in children (ie, <18 years of age).		
<b>Abbreviations:</b> ADHD, attention-deficit hyperactivity disorder; ASD, autism spectrum disorder; ODD, oppositional defiant disorder.		

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# Co-morbidities

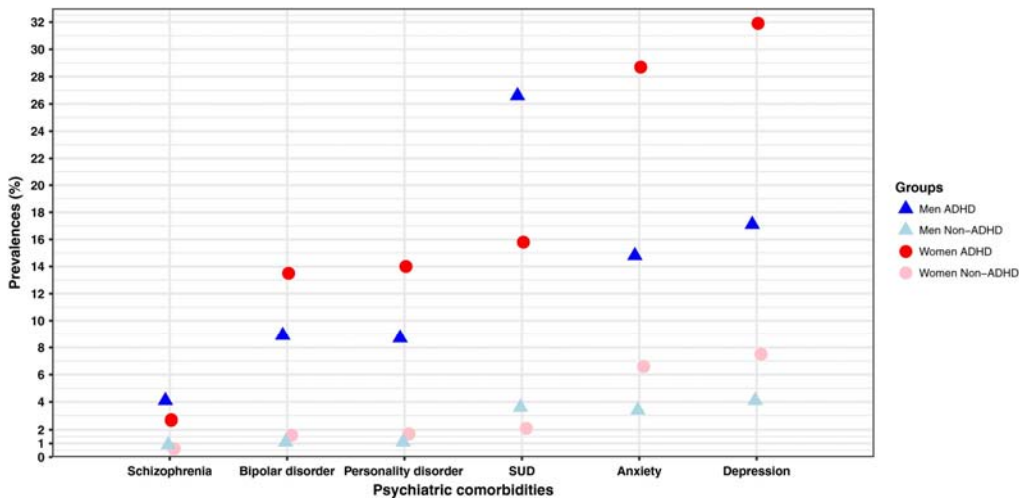
Condition n (%)	Adults with ADHD (n = 89)	Adults without ADHD (n = 94)
Depression	54 (60.7)	18 (19.1)
Insomnia or other sleep disorders	41 (46.1)	7 (7.4)
Anxiety disorder(s)	36 (40.4)	5 (5.3)
Personality disorder	27 (30.3)	1 (1.1)
Bipolar disorder	20 (22.5)	1 (1.1)
Alcohol or drug abuse or dependence	19 (21.3)	6 (6.4)
Oppositional defiant disorder	15 (16.9)	0
Conduct disorder	15 (16.9)	0
Decline to answer	0	4 (4.3)
None of these	0	65 (69.1)

NOTE. ADHD, attention-deficit/hyperactivity disorder.

Pitts et al. 2014, Archives of Psychiatric Nursing

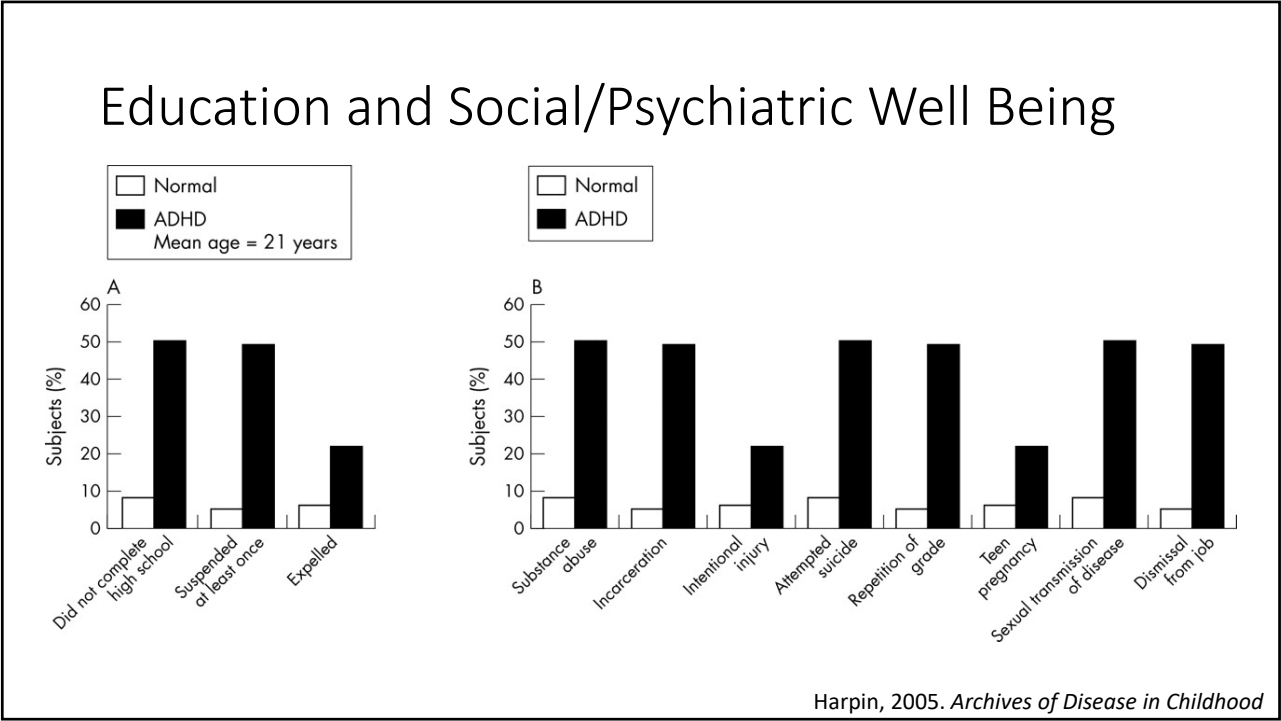
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# Gender Differences in Co-morbidity

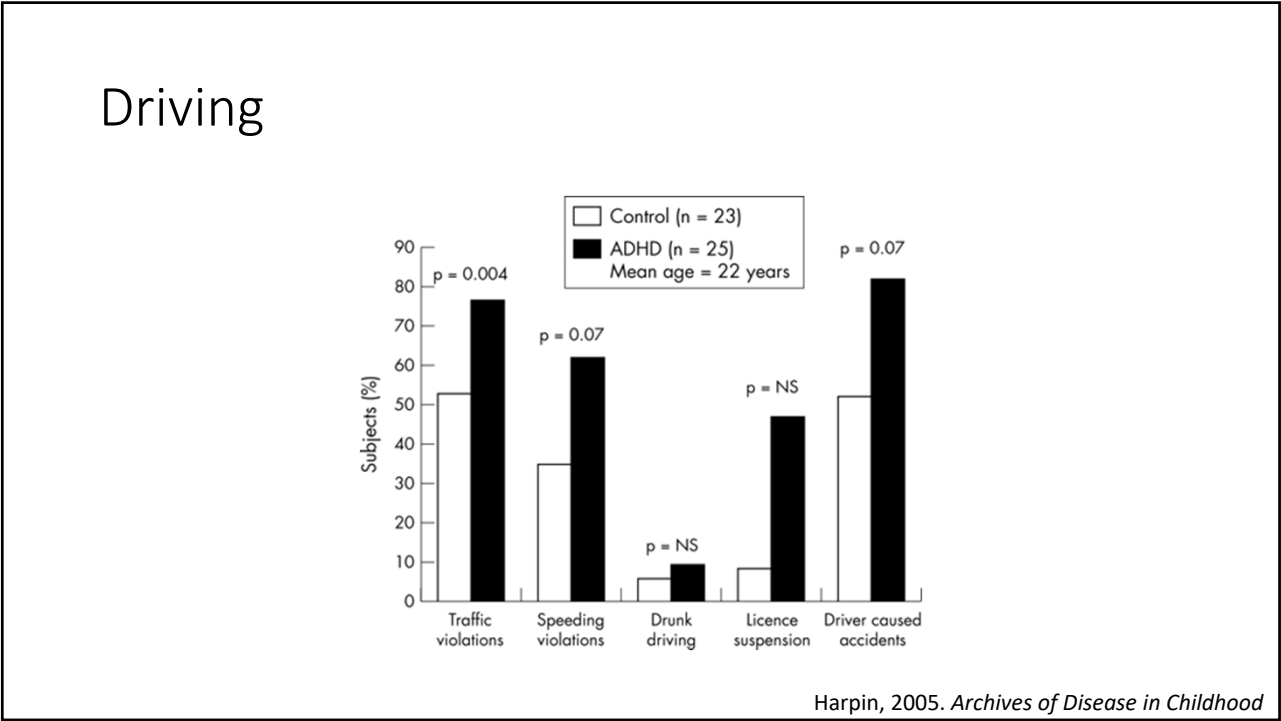


Solberg et al. 2017, Acta Psychiatrica Scandinavica

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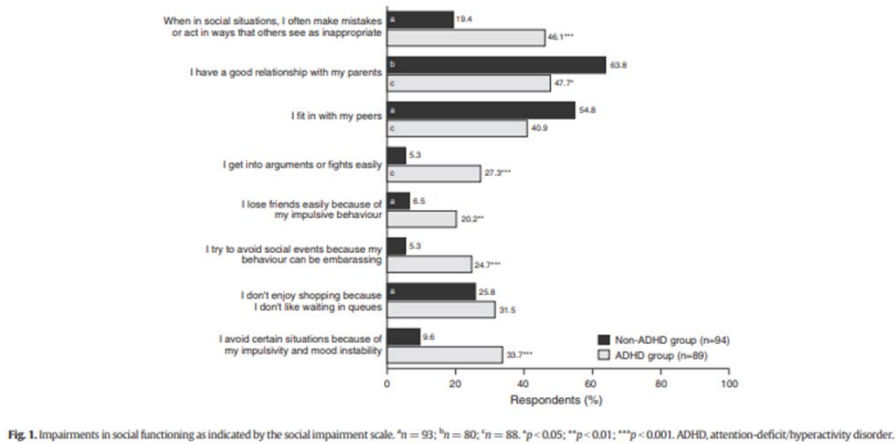
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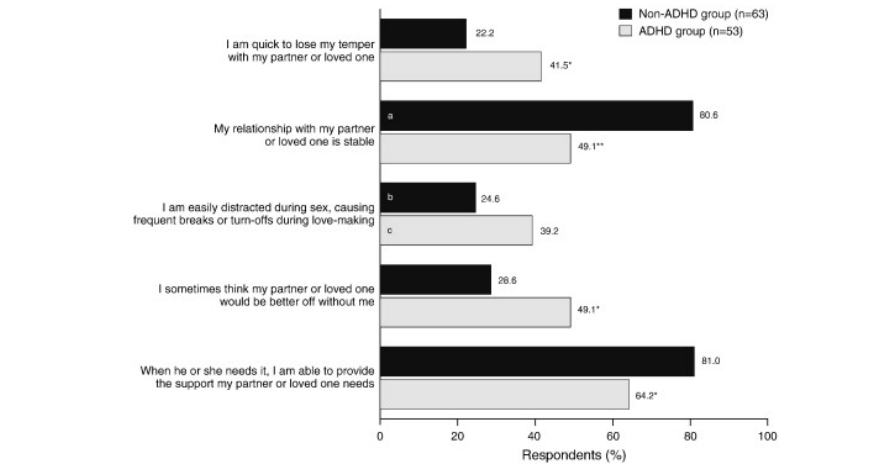
# Social Life



Pitts et al. 2014, Archives of Psychiatric Nursing

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# Romantic Relationships



Pitts et al. 2014, Archives of Psychiatric Nursing

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# Work Function

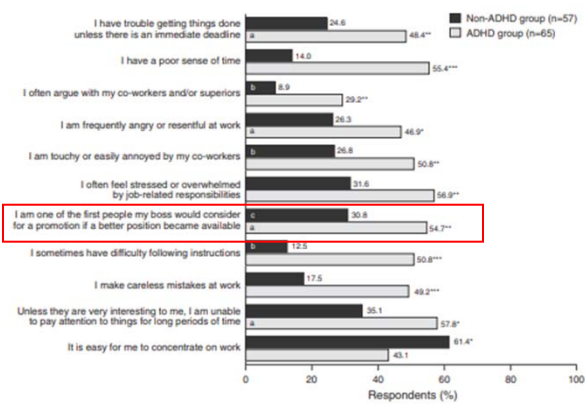


Fig. 3. Impairments in work functioning as indicated by the work impairment scale. \*n = 64; <sup>b</sup>n = 56; <sup>c</sup>n = 52. \*p < 0.05; \*\*p < 0.01; \*\*\*p < 0.001. ADHD, attention-deficit/hyperactivity disorder.

Pitts et al. 2014, Archives of Psychiatric Nursing

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# Financial Life

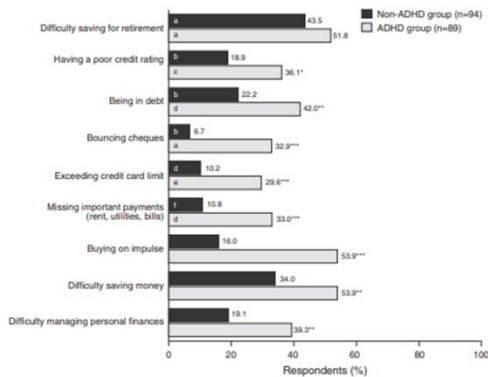
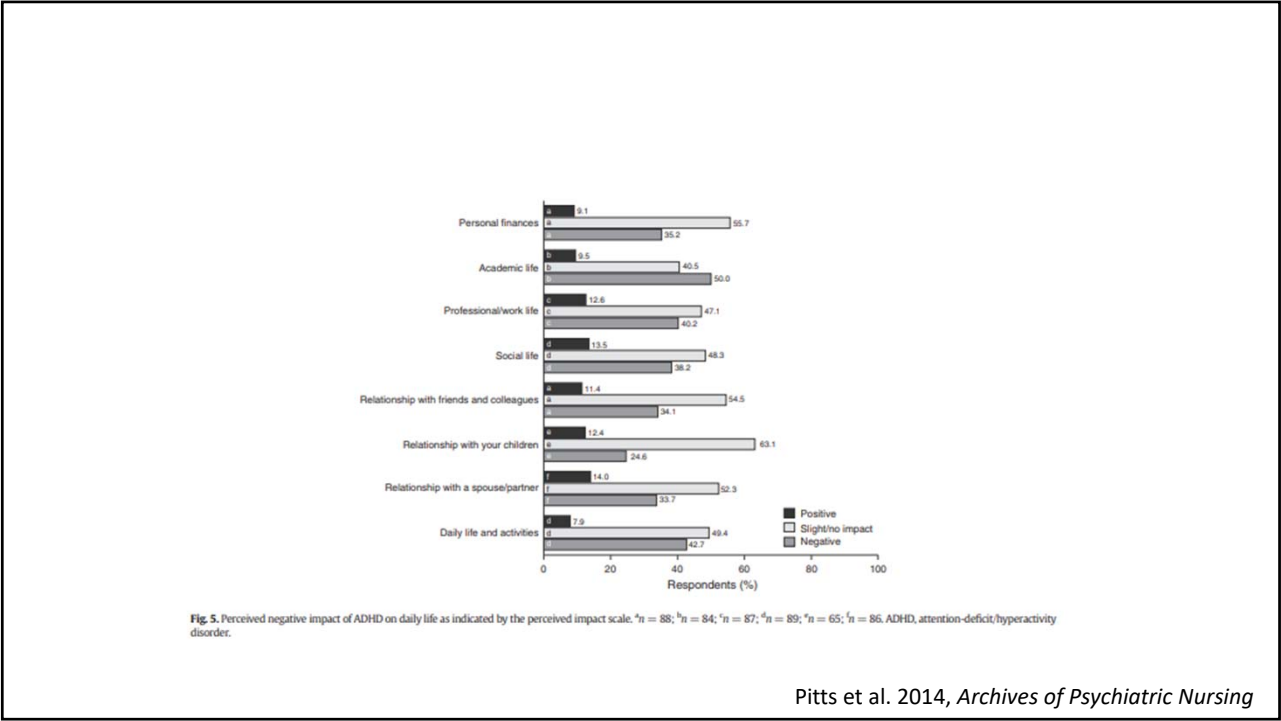


Fig. 4. Financial difficulties as indicated by the financial impairment scale. <sup>a</sup>n = 85; <sup>b</sup>n = 90; <sup>c</sup>n = 83; <sup>d</sup>n = 88; <sup>e</sup>n = 81; <sup>f</sup>n = 93. \*p < 0.05; \*\*p < 0.01; \*\*\*p < 0.001. ADHD, attention-deficit/hyperactivity disorder.

Pitts et al. 2014, Archives of Psychiatric Nursing

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What is the first line treatment for ADHD in children? Adults?

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# Treatment

- Psychosocial intervention
  - Parent training
  - Therapy
  - School intervention
  - Workplace intervention
- Focus on psychopharmacology

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Table 4. Psychosocial treatment recommendations

Association	AAP (2000, 2001)	NZ (2001)	DGPPN (2003)	ESCAP (2004, 2006)	BAP (2006)	AACAP (2002, 2007)	DGKJP (2007)	NICE (2008)	SIGN (2009)	CADDRA (2011)
Individual interventions	0	0	+	+	0	0	+	+	0	+
Group interventions	0	+	+	+	0	0	+	+	0	0
Family-based interventions	0	0	0	+	0	0	+	+	0	+
School-based interventions	+	0	0	+	+	0	+	+	+	+
Occupational interventions	0	0	0	0	+	0	0	0	0	+
Behavioural parent training	+	0	0	+	0	0	+	+	+	+
Behavioural management	0	+	0	+	0	0	+	+	0	+
Psychoeducation	+	0	+	+	+	+	+	+	+	+
Family therapy	0	0	0	0	0	0	+	0	0	+
Social skills training	0	0	0	+	0	-	0	+	0	+
Cognitive therapy	-	0	0	0	0	0	+	0	0	0
CBT	-	0	0	+	0	-	+	+	0	+
Supportive therapy	0	0	0	+	+	0	0	0	0	+
Self-help	0	0	0	+	0	0	+	+	+	+
Counselling	0	0	0	0	0	0	0	0	0	+
Cognitive remediation	0	0	0	Academic skills	0	0	+	0	0	Academic skills
Carer support	+	+	0	+	0	0	0	0	+	+
Other therapies	Play therapy not recommended	Dietary interventions supervised by dietitian and at parents' request. Optometric vision training, sensory integrative training, chiropractic manipulation, tinted lenses, megavitamins, herbal remedies and biofeedback not recommended (-)	0	Elimination and restriction diets not routinely recommended (-)	0	Dietary modification and EEG biofeedback not recommended (-)	Dietary modification, biofeedback recommended (-)	Elimination and restriction diets not recommended; fatty acid supplements not routinely recommended (-)	Avoidance of case-specific food additives (+); omega-3 and omega-6 fatty acid supplements, iron supplements, zinc supplements, antioxidants, Bach flower remedies, homeopathy, massage therapy and neurofeedback (all -)	Anger management; interpersonal therapy; expressive arts therapy; play therapy.
Multimodal interventions	+	0	+	+	0	+	+	+	+	+

Seixas et al. 2012 *Journal of Psychopharmacology*

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# Stimulant Therapy First Line

- Unanimous agreement about stimulant therapy.

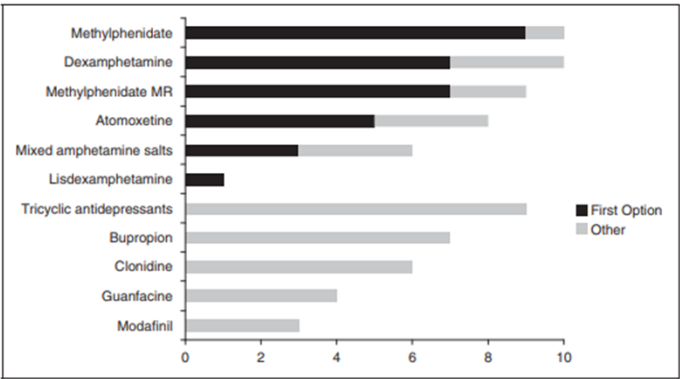


Figure 2. First-option and other recommendations for individual pharmacological agents.

Seixas et al. 2012 *Journal of Psychopharmacology*

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# Stimulant Therapy First Line

- Mixed amphetamines not suggested by 4 groups.

Table 3. Recommendations for pharmacological treatment of ADHD

Association	AAP (2000,2001)	NZ (2001)	DGPPN (2003)	ESCAP (2004,2006)	BAP (2006)	AACAP (2002,2007)	DGKJP (2007)	NICE (2008)	SIGN (2009)	CADDRA (2011)
MPH	1st	1st	1st	1st	1st	1st	1st	1st	1st	+
MPH MR	1st	+	0	+	1st	1st	1st	1st	1st	1st
Dexamphetamine	1st	1st	+	+	1st	1st	+	+, 1st in C&A	1st	1st
Mixed amphetamine salts	1st	0	+	+	0	1st	+	0	0	1st
Lisdexamphetamine	0	0	0	0	0	0	0	0	0	1st
Atomoxetine	0	+	+	+	1st	1st	1st	+, 1st in C&A	+	1st
Bupropion	0	0	+	0	+	+	+	+	+	+
Clonidine	Outside scope	0	0	+	+	+	+	+	+	0
Guanfacine	0	0	0	+	+	+	+	0	0	0
Modafinil	0	0	0	0	+	0	0	+	+	+
Pemoline	-	0	0	+	-	-	0	0	0	0
TCA	Outside scope	+	+	+	+	+	+	+	+	+
Pre-treatment safety measures	0	+	0	0	0	+	+	+	+	+
Explicit dose	+	+	0	+	0	+	+	+	For some agents only	+
Titration	Outside scope	+	0	+	0	+	+	+	+	+
Monitoring	+	+	+	+	+	+	+	+	+	+
Adverse effects	+	+	0	+	+	+	+	+	+	+
Contra-indications	+	0	0	+	0	+	+	+	0	+
Cost considerations	0	0	0	+	+	0	+	+	+	+
Drug holidays	0	0	0	Only if growth retardation	0	+	+	+, exceptions permitted	0	+, exceptions permitted

Seixas et al. 2012 *Journal of Psychopharmacology*

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What do you know about stimulant medication?

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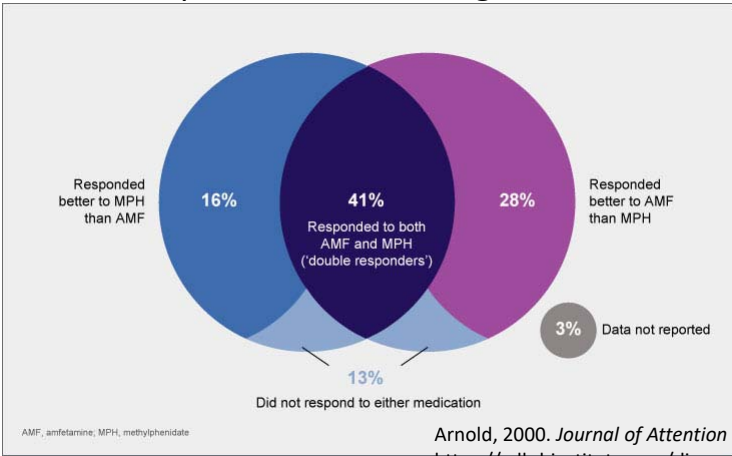
## Pharmacologic Treatments

- Stimulants:
  - Methylphenidate
  - Amphetamine Salts
- Non-stimulant:
  - Atomoxetine
  - Alpha-agonists
  - Bupropion
  - Modafinil
  - Venlafaxine
  - Desipramine/Nortriptyline

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# Stimulants

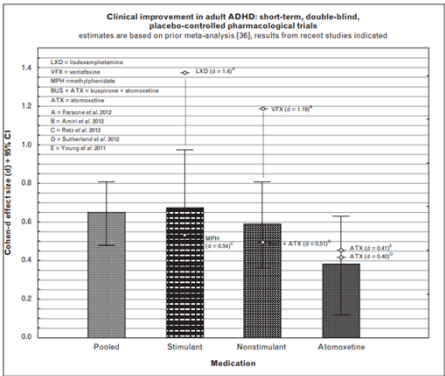
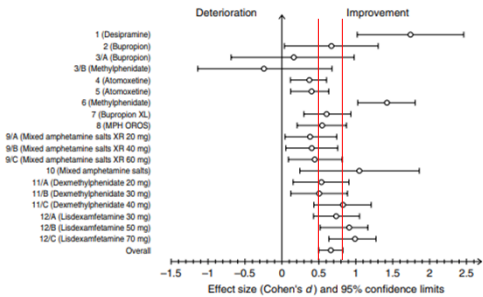
- 87% response rate to one agent or the other.



Arnold, 2000. *Journal of Attention Disorders*  
<https://adhd-institute.com/disease-management/pharmacological-therapy/differential-response-to-treatment/> (accessed 11.16.20)

45

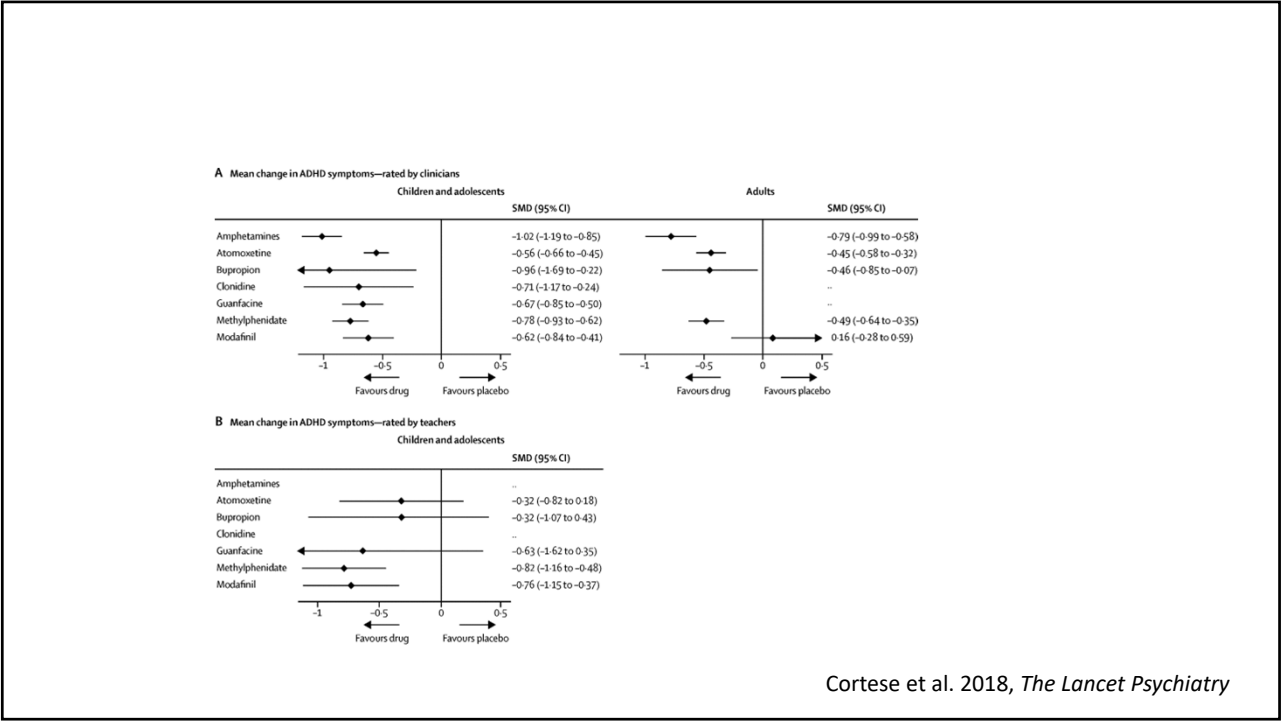
# Comparative Effect Sizes



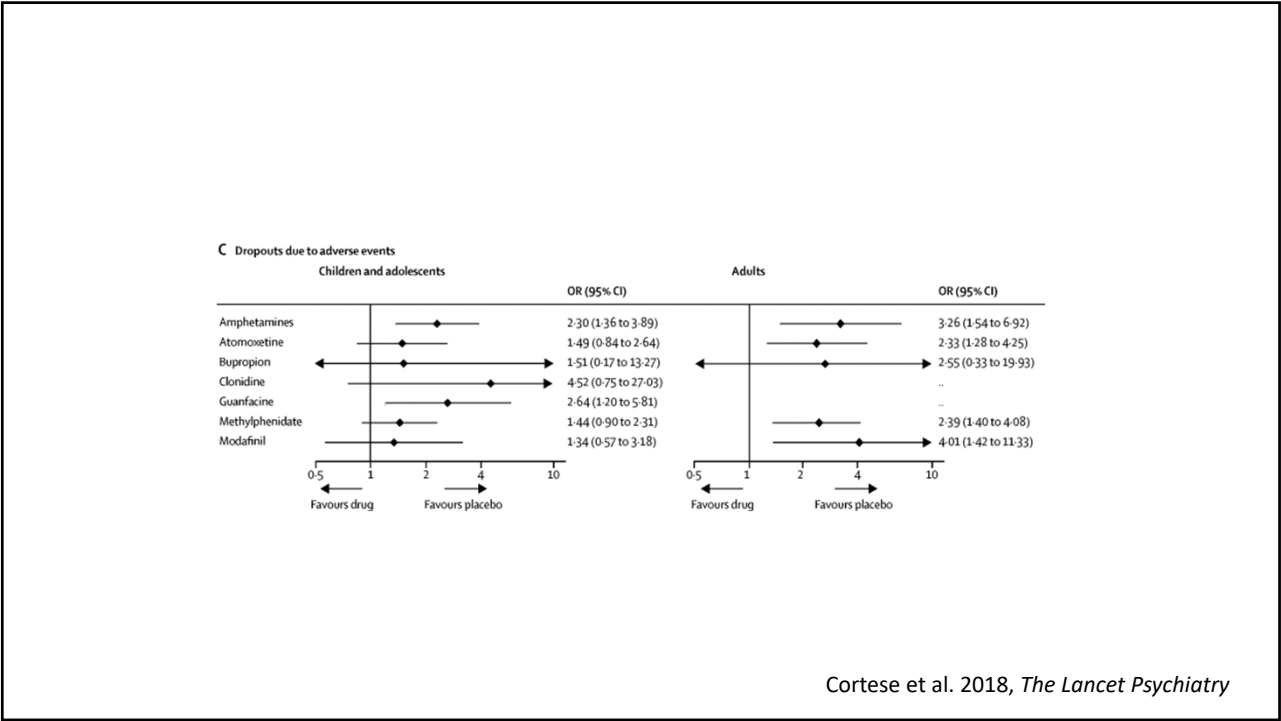
- By comparison bzd has 0.38 +/- 0.15 effect size GAD

Bitter et al. 2012, *Current Opinion in Psychiatry* (Figure to right)  
Meszaros et al. 2009, *International Journal of Neuropsychopharmacology* (Figure to left)  
Hidalgo et al. 2007, *Journal of Psychopharmacology*

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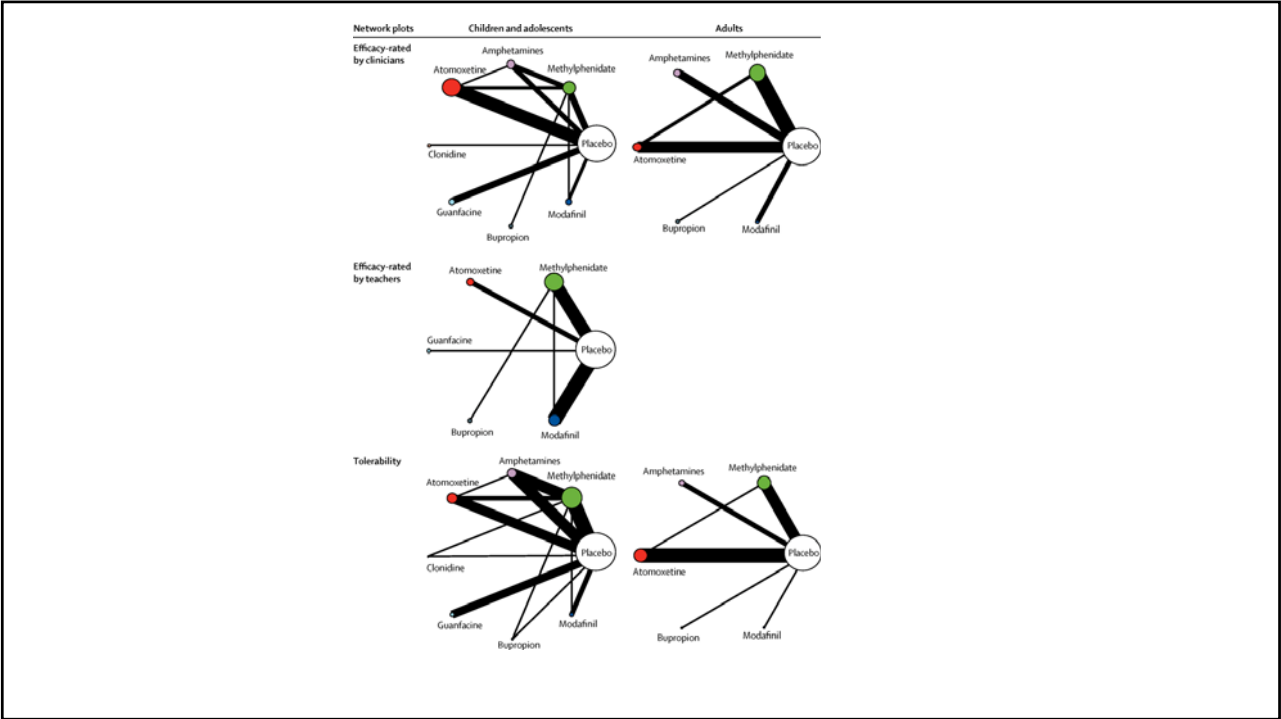


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Response

- Bold is significant
- Negative favors row

	Atomoxetine		Bupropion		Clonidine		Guanfacine		Methylphenidate		Modafinil		Placebo	
	Children	Adults	Children	Adults	Children	Adults	Children	Adults	Children	Adults	Children	Adults	Children	Adults
Amphetamines														
Clinicians	-0.46 (-0.65 to -0.27)*	-0.34 (-0.58 to -0.10)*	-0.06 (-0.81 to 0.68)†	-0.33 (-0.77 to 0.11)*	-0.31 (-0.81 to 0.18)*	-	-0.35 (-0.59 to -0.10)*	-	-0.24 (-0.44 to -0.05)*	-0.29 (-0.54 to -0.05)*	-0.39 (-0.67 to -0.12)*	-0.94 (-1.43 to -0.46)‡	-1.02 (-1.19 to -0.85)‡	-0.79 (-0.99 to -0.58)‡
Teachers	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Atomoxetine	-	-	0.40 (-0.34 to 1.14)*	0.01 (-0.41 to 0.42)*	0.15 (-0.33 to 0.63)*	-	0.11 (-0.09 to 0.30)*	-	0.22 (0.05 to 0.39)*	0.04 (-0.14 to 0.23)†	0.07 (-0.17 to 0.30)*	-0.61 (-1.06 to -0.15)*	-0.56 (-0.66 to -0.45)†	-0.45 (-0.58 to -0.32)*
Teachers	-	-	0.00 (-0.90 to 0.90)†	-	0.31 (-0.79 to 1.42)†	-	0.50 (-0.11 to 1.10)*	-	0.44 (-0.19 to 1.07)*	-	0.44 (-0.19 to 1.07)*	-	0.32 (-0.82 to 0.18)†	-
Bupropion	-	-	-	-	-0.25 (-1.12 to 0.62)†	-	-0.28 (-1.04 to 0.47)†	-	-0.18 (-0.90 to 0.54)†	0.04 (-0.38 to 0.45)*	-0.33 (-1.10 to 0.43)†	-0.62 (-1.20 to -0.03)*	-0.96 (-1.69 to -0.22)†	-0.46 (-0.85 to -0.07)*
Teachers	-	-	-	-	0.31 (-0.92 to 1.55)†	-	0.50 (-0.17 to 1.17)*	-	0.44 (-0.38 to 1.26)*	-	0.44 (-0.38 to 1.26)*	-	0.32 (-1.07 to 0.43)†	-
Clonidine	-	-	-	-	-	-	-0.03 (-0.53 to 0.46)†	-	0.07 (-0.42 to 0.56)†	-	-0.08 (-0.59 to 0.43)†	-	-0.71 (-1.17 to -0.24)†	-
Guanfacine	-	-	-	-	-	-	-	-	0.11 (-0.13 to 0.34)†	-	-0.05 (-0.32 to 0.23)†	-	-0.67 (-0.85 to -0.50)†	-
Teachers	-	-	-	-	-	-	-	-	0.18 (-0.86 to 1.22)†	-	0.12 (-0.93 to 1.15)†	-	-0.63 (-1.62 to 0.35)†	-
Methylphenidate	-	-	-	-	-	-	-	-	-	-	-0.15 (-0.41 to 0.10)†	-0.65 (-1.11 to -0.19)*	-0.78 (-0.93 to -0.62)†	-0.49 (-0.64 to -0.35)†
Teachers	-	-	-	-	-	-	-	-	-	-	-0.06 (-0.53 to 0.42)†	-	-0.82 (-1.16 to -0.48)*	-
Modafinil	-	-	-	-	-	-	-	-	-	-	-	-	-0.62 (-0.84 to -0.40)†	0.16 (-0.28 to 0.59)†
Teachers	-	-	-	-	-	-	-	-	-	-	-	-	-0.76 (-1.15 to -0.37)†	-

Data are standardized mean difference (95% CI) between treatments. Results in bold are significant. Negative values favour the treatment in the row and positive values favour the treatment in the column. Drugs are reported in alphabetical order. Results are based on network estimates. No data for clonidine and guanfacine in adults are reported because no studies identified by our search tested these two drugs in adults. No teacher ratings were available for clonidine. ADHD=attention-deficit hyperactivity disorder. †Low quality of evidence. ‡Very low quality of evidence. ‡Moderate quality of evidence.

Table 1: Effect of ADHD drugs in children and adults at timepoints closest to 12 weeks in terms of efficacy, as rated by clinicians and teachers

Cortese et al. 2018, *The Lancet Psychiatry*

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Tolerability

	Atomoxetine		Bupropion		Clonidine		Guanfacine		Methylphenidate		Modafinil		Placebo	
	Children	Adults	Children	Adults	Children	Adults	Children	Adults	Children	Adults	Children	Adults	Children	Adults
Amphetamines	1.54 (0.79–3.01)*	1.40 (0.54–3.66)†	1.53 (0.17–13.88)†	1.28 (0.14–11.40)†	0.51 (0.08–3.27)†	–	0.87 (0.35–2.16)†	–	1.60 (0.94–2.73)†	1.36 (0.54–3.43)†	1.72 (0.64–4.59)†	0.81 (0.23–2.93)†	<b>2.30</b> <b>(1.36–3.89)†</b>	<b>3.26</b> <b>(1.54–6.92)†</b>
Atomoxetine	–	–	0.99 (0.11–9.15)†	0.91 (0.11–7.77)†	0.33 (0.05–2.14)†	–	0.57 (0.22–1.47)†	–	1.04 (0.55–1.94)†	0.97 (0.47–2.02)*	1.11 (0.40–3.09)†	0.58 (0.19–1.93)†	1.49 (0.84–2.64)*	2.33 (1.28–4.25)*
Bupropion	–	–	–	–	0.33 (0.02–5.51)†	–	0.57 (0.06–5.77)†	–	1.05 (0.12–9.14)†	1.07 (0.13–8.92)†	1.12 (0.11–11.62)†	0.64 (0.06–6.37)†	1.51 (0.17–13.27)†	2.55 (0.33–19.93)†
Clonidine	–	–	–	–	–	–	1.71 (0.24–12.22)†	–	3.14 (0.51–19.33)†	–	3.36 (0.46–24.64)†	–	4.52 (0.75–27.03)†	–
Guanfacine	–	–	–	–	–	–	–	–	1.83 (0.74–4.57)†	1.97 (0.63–6.16)†	–	–	<b>2.64</b> <b>(1.20–5.81)*</b>	–
Methylphenidate	–	–	–	–	–	–	–	–	–	–	1.07 (0.41–2.83)†	0.60 (0.19–1.92)†	1.44 (0.90–2.31)*	<b>2.39</b> <b>(1.40–4.08)‡</b>
Modafinil	–	–	–	–	–	–	–	–	–	–	–	–	1.34 (0.57–3.18)†	<b>4.01</b> <b>(1.42–11.33)†</b>

Data are odds ratio (95% CI). Values above 1 favour the treatment in the column and values below 1 favour the treatment in the row. Results in bold are significant. Drugs are reported in alphabetical order. Results are based on network estimates. No data for clonidine and guanfacine in adults are reported because no studies identified by our search tested these two drugs in adults. ADHD=attention-deficit hyperactivity disorder. \*Low quality of evidence. †Very low quality of evidence. ‡Moderate quality of evidence. §High quality of evidence.

Table 2: Effect of ADHD drugs in children and adults at timepoints closest to 12 weeks in terms of tolerability

Cortese et al. 2018, *The Lancet Psychiatry*

51

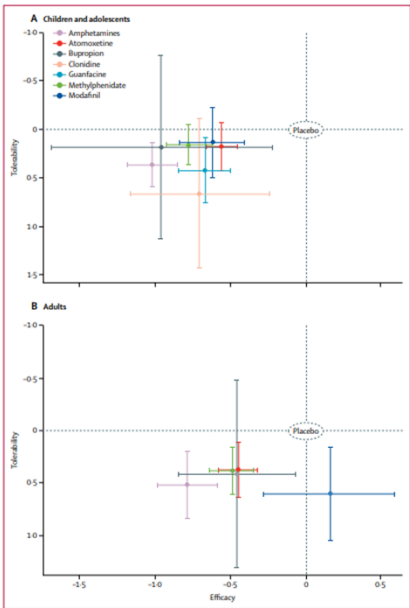


Figure 4: Two-dimensional graphs of efficacy versus tolerability in studies in children and adolescents and adults. Effect sizes for individual drugs are represented by coloured nodes, with bars representing corresponding 95% CI.

Cortese et al. 2018, *The Lancet Psychiatry*

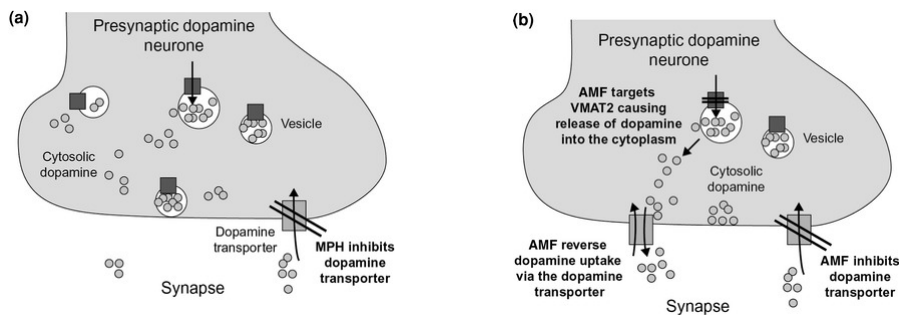
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## Moral of the Story

- Stimulants are first line agents
- Guidelines vary:
  - Children use methylphenidate as first option
  - Adults use amphetamine salt as first option
  - Generally preferable to try long acting agent first
  - Failure: try alternate stimulant class of medication

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## Stimulants



Hodgkins et al. 2012, *European Child and Adolescent Psychiatry*

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## Note to residents.

- I had hoped to take you through the up to date table entitled “Drugs for adult ADHD” at this point. Table can be found in article titled “Treatment of Attention Deficit Hyperactivity Disorder in Adults”

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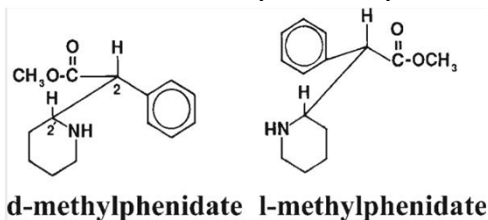
## Methylphenidate

- Dexmethylphenidate
  - Short and long acting formulations
  - Oral (tablet and capsule only)
- Methylphenidate (short and long acting formulations)
  - Oral (tablet, chewable, capsule, suspension, and patch)

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## Methylphenidate

- Usually comes in combination dl-methylphenidate
- Recognized that l-methylphenidate is an inactive isomer
- Animal models demonstrate attenuation of d-mph motor response in rats when l-mph supplied.
- Still l-mph attenuation on d-mph in humans not demonstrated.
- Metabolized by carboxylesterase 1.



Patrick et al. 2008 *Human Psychopharmacology*

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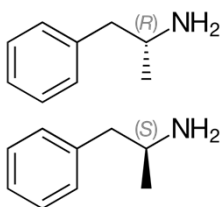
## Amphetamine Salts

- Dextroamphetamine
  - Short and long acting.
  - Tablet and capsule
- Dextroamphetamine and amphetamine (mixed salts)
  - Short and long acting
  - Tablet, ODT, and capsule
- Lisdexamfetamine

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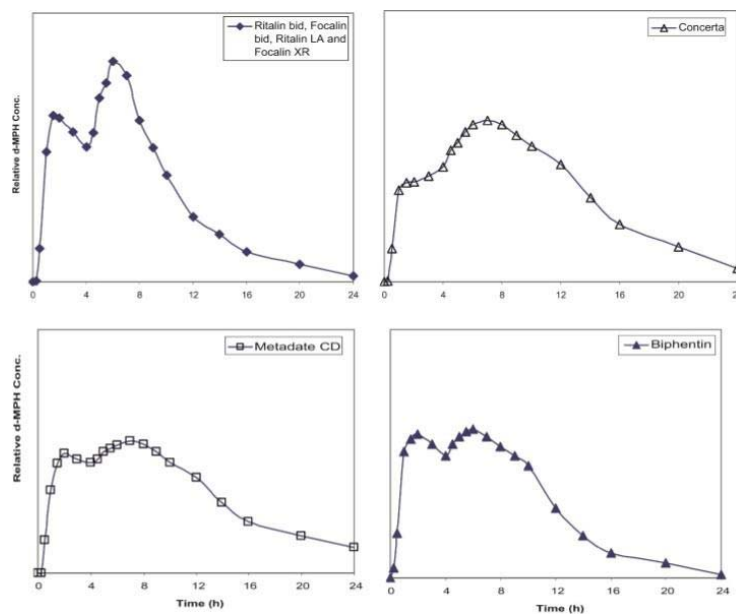
## Amphetamine Salts

- Usually comes in combination dl-amphetamine
- Both are active, though, l isomer less potent
- Metabolized through oxidative deamination (FMO3) to an inactive product.



Patrick et al. 2008 *Human Psychopharmacology*

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Patrick et al. 2008, *Human Psychopharmacology*

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# Amphetamine Salts

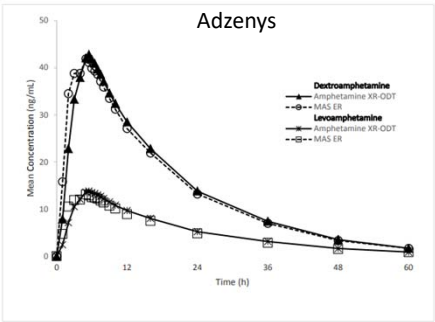
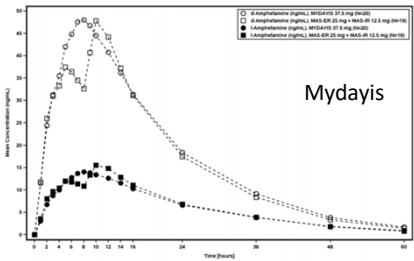


Figure 1 Mean Plasma Concentrations of d- and l-amphetamine Following Oral Administration of MYDAYIS 37.5 mg vs MAS-ER 25 mg Followed by Immediate-Release MAS-IR 12.5 mg 8 Hours Later in Adults



Adzenys [Package Insert]. 2016  
Mydayias [Package Insert]. 2017

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Name	Mode of Delivery	Duration of Action
Ritalin SR, Metadate ER, Methylin ER	Gradual release	4-8 h
Metadate CD	30% IR, 70% 3 h later	7-9 h
Ritalin LA	50% IR, 50% 4 h later	7-9 h
Quillivant XR	20% IR, 80% gradual release	8-10h
Focalin XR	50% IR, 50% 4 h later	Up to 12 h
Concerta	22% IR, pump	Up to 12 h
Daytrana patch	Gradual release	3-5 h after removal
Adderall XR	50% IR, 50% 4 h later	8-12 h
Dexedrine spansule	50% IR, 50% gradual	10 h
Vyvanse	Activated in GI tract	10 h

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# Concerta

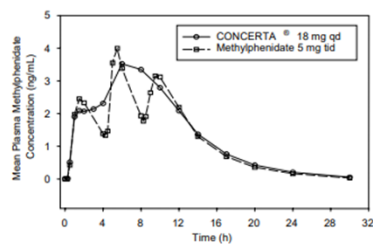
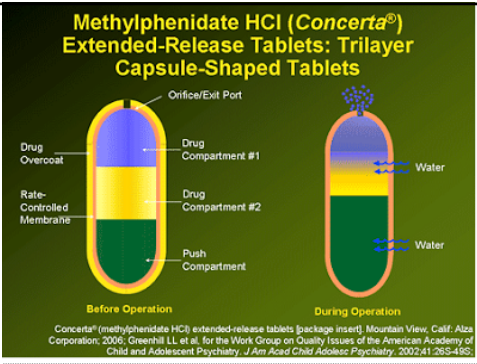
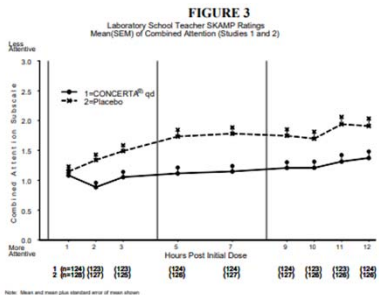


Figure 1. Mean methylphenidate plasma concentrations in 36 adults, following a single dose of CONCERTA® 18 mg qd and immediate-release methylphenidate 5 mg tid administered every 4 hours

Concerta [Package Insert]. 2010.  
Greenhill et al. 2002. *Journal of American Academy of Child and Adolescent Psychiatry*



from [http://www.medscape.org/viewarticle/547415\\_10](http://www.medscape.org/viewarticle/547415_10)



## A Note on Authorized Generic Concerta

- Not all Concerta is made equal.
- Some patients seem to have a less favorable response to generic vs brand Concerta. This may be due to subtle variations in the laser hole and tablet structure.
- In those cases you should have note on the patient script authorized generic only.
- If you have a chance you should read on the difference between authorized generic vs generic medication.



## Stimulant Precautions

- Cardiac disease in patient (family history of sudden death <40 y/o)
- Bipolar disorder/Psychosis
- Substance abuse (particular attention to alcohol/sedative hypnotics and stimulant abuse)
- Pregnancy Category C (new study this year may result in this changed to category D)

### Additional Considerations:

- Anxiety (start SSRI)
- Tic Disorders

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## Stimulant Medications

- Black Box Warning:
  - High abuse potential and dependence: All
  - Psychosis/Tolerance: Concerta
  - Sudden Death: Adderall and Dexedrine
- Common Side Effects: Anxiety, decreased appetite and weight loss, insomnia, dry mouth, headache, upset stomach

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## Monitoring

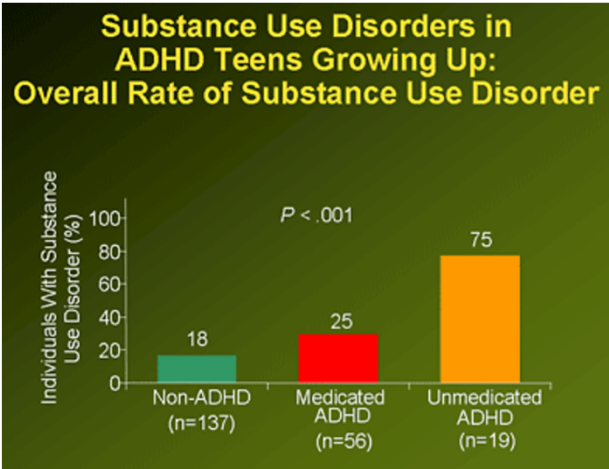
- Blood pressure and heart rate
- Weight
- Height in children
- SUD
- Manic/psychotic symptoms
- Anxiety, sleep, appetite

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Does stimulant treatment influence  
substance abuse risk?

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# SUD and ADHD Treatment



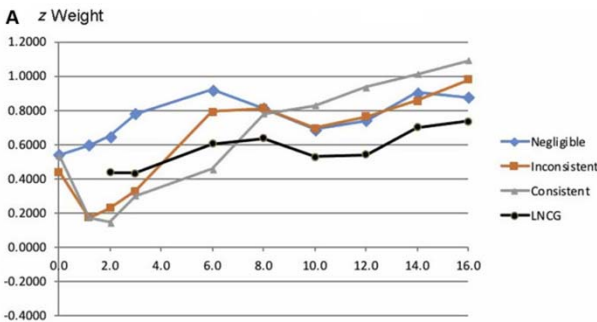
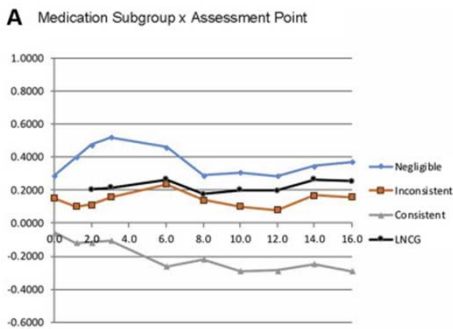
[https://www.medscape.org/viewarticle/547415\\_8](https://www.medscape.org/viewarticle/547415_8) slide (a  
11.16.2020)  
Biederman et al. 1999. *Pediatrics*

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Thoughts on stimulant treatment and growth?

70

# Growth and Stimulant Treatment



*We have previously believed that kids on long term treatment eventually “catch-up” this does not appear to be the case for consistent treatment. None the less the symptomatic benefits of treatment may outweigh this finding and parents should be advised of the finding.*

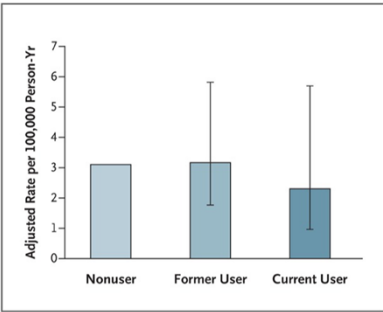
Greenhill et al. 2020, *Journal of the American Academy of Child and Adolescent Psychiatry*

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# Severe Cardiovascular Event (Children/Young Adults)

**Table 3. Adjusted Hazard Ratios for Individual Cardiovascular End Points, According to the Use of ADHD Drugs.<sup>a</sup>**

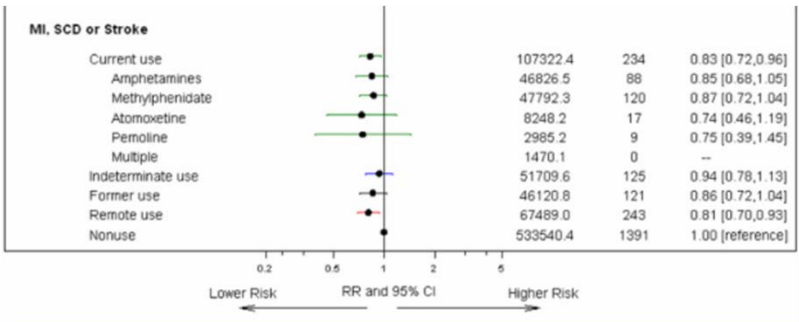
End Point	Person-Yr number	Events	Rate per 100,000 Person-Yr	Hazard Ratio (95% CI) <sup>†</sup>
<b>Sudden cardiac death</b>				
Nonuser	1,597,962	17	1.06	1.00
Former user	607,475	13	2.14	1.52 (0.65–3.56)
Current user	373,667	3	0.80	0.88 (0.23–3.35)
<b>Acute myocardial infarction</b>				
Nonuser	1,597,962	6	0.38	1.00
Former user	607,475	3	0.49	0.88 (0.16–4.71)
Current user	373,667	0	0	NA
<b>Stroke</b>				
Nonuser	1,597,962	26	1.63	1.00
Former user	607,475	9	1.48	0.80 (0.33–1.96)
Current user	373,667	4	1.07	0.93 (0.29–2.97)



Cooper et al, 2011. *New England Journal of Medicine*

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# Severe Cardiovascular Event (Adult)



Habel et al. 2011, *The Journal of the American Medical Association*

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# Stimulants and Pregnancy

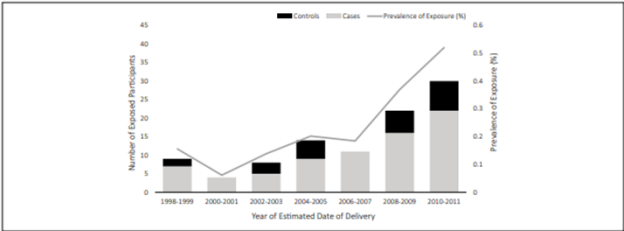


Figure 2. Distributions of any ADHD medication use in the 3 months before conception through the end of pregnancy by the year of their estimated date of delivery, National Birth Defects Prevention Study, 1998-2011.

Anderson et al. 2020, *Journal of Attention Disorders*

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# Stimulants and Pregnancy

**Table 1.** Characteristics of Control Mothers Exposed and Unexposed to ADHD Medications<sup>a</sup> From 3 Months Before Conception Through the End of Pregnancy, National Birth Defects Prevention Study, 1998-2011.

	Exposed to ADHD medications before or anytime during pregnancy (n = 24)	Unexposed to ADHD medications before or anytime during pregnancy (n = 11,430)	p <sup>b</sup>
Age (years)			
<20	3 (12.5%)	1,105 (9.7%)	.25
20-34	15 (62.5%)	8,705 (76.2%)	
≥35	6 (25.0%)	1,620 (14.2%)	
Race/ethnicity			
Non-Hispanic White	18 (78.3%)	6,635 (58.1%)	.05
Not non-Hispanic White	5 (21.7%)	4,790 (41.9%)	
Education (years)			
≤12	4 (17.4%)	4,537 (40.1%)	.03
>12	19 (82.6%)	6,764 (59.9%)	
Income			.49
<US\$40,000	10 (47.6%)	5,770 (55.1%)	
≥US\$40,000	11 (52.4%)	4,707 (44.9%)	
Any early pregnancy smoking <sup>c</sup>			.56
Yes	3 (13.0%)	2,011 (17.7%)	
No	20 (87.0%)	9,330 (82.3%)	
Any early pregnancy alcohol use <sup>d</sup>			.13
Yes	12 (52.2%)	4,178 (37.0%)	
No	11 (47.8%)	7,127 (63.0%)	
Any early pregnancy folic acid use <sup>e</sup>			.91
Yes	13 (54.2%)	6,055 (53.0%)	
No	11 (45.8%)	5,375 (47.0%)	
Pregnancy intention			.12
Wanted to be pregnant then	8 (42.1%)	5,532 (59.5%)	
Wanted to wait until later	3 (15.8%)	1,885 (20.3%)	
Did not want to be pregnant at all	4 (21.1%)	1,063 (11.4%)	
Did not care	4 (21.1%)	822 (8.8%)	

**Table 2.** Associations Between ADHD Medication<sup>a</sup> Use From One Month Before Conception Through the Third Month of Pregnancy and Selected Birth Defects, National Birth Defects Prevention Study, 1998-2011.

Defect	ADHD medication exposed <sup>a</sup> (N)	ADHD medication unexposed <sup>a</sup> (N)	cOR (95% CI)	aOR <sup>a</sup> (95% CI)
Controls <sup>a</sup>	20	11,362		
Tetralogy of Fallot	3	1,157	1.5 [0.4, 5.0]	
Coarctation of the aorta	4	1,120	2.0 [0.7, 6.0]	
Pulmonary valve stenosis	3	1,506	1.1 [0.3, 3.7]	
Atrial septal defect (secundum or NOS)	6	2,915	1.2 [0.5, 2.9]	
Neural tube defects <sup>d</sup>	3	2,084	0.8 [0.2, 2.8]	
Craniosynostosis	3	1,574	1.1 [0.3, 3.7]	
Cleft palate	4	1,536	1.5 [0.5, 4.3]	
Cleft lip with or without cleft palate	3	3,012	0.6 [0.2, 1.9]	
Gastroschisis	7	1,374	2.9 [1.2, 6.9] <sup>g</sup>	3.0 [1.2, 7.4] <sup>g</sup>
Omphalocele	3	424	4.0 [1.2, 13.6] <sup>g</sup>	
Hypospadias, 2nd/3rd degree	5	2,505	1.3 [0.4, 3.8]	
Transverse limb deficiency	4	695	3.3 [1.1, 9.6] <sup>g</sup>	

Anderson et al. 2020, Journal of Attention Disorders

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# Stimulant Failure

**Table 5.10 Facts to Consider Prior to Making Medication Changes**

<b>D</b>	<b>Dosage</b> – Has the medication been tried on a high enough dose, is the duration of effect adequate? Side effects: Is the dosage too low or too high?
<b>A</b>	<b>All</b> – Have all medications within the higher line(s) of treatment (when clinically indicated and reasonable) been attempted? If not, explore why.
<b>T</b>	<b>Time</b> – Has enough time been given to examine patient response and for side effects to resolve?
<b>E</b>	<b>Examine</b> – Has the patient-doctor team determined specific targets for treatment and means to measure changes? Select standardized measures to examine response and plan examination of response from many perspectives (e.g., teacher, parent, spouse and self-report).
<b>R</b>	<b>Review</b> – Has the diagnostic process reviewed potential comorbidity, psychosocial complications and lifestyle issues?

CADDRA, 2018. Canadian ADHD Practice Guidelines

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## Non-stimulants

- Atomoxetine
- Bupropion
- Guanfacine/Clonidine
- Modafinil
- Venlafaxine
- Desipramine/Nortriptyline

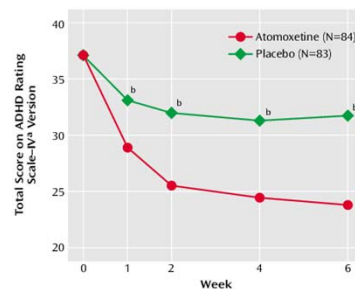
cover bupropion, venlafaxine,  
line/nortriptyline as I figure you will hear about them  
e

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## Atomoxetine

When to Use:

- High substance abuse risk
- As adjunct or solo agent for those who have partial response/failure to stimulants



Michelson et al. 2002, *American Journal of Psychiatry*

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# Atomoxetine

- SNRI
- DAT inhibition in the prefrontal cortex
- Metabolism: CYP2D6
- Inhibit: CYP2D6
- ½ life of 5 hours, can be dosed once or twice a day
- Adults: start 40mg and titrate to max dose 100mg
- Children: weight based

	Atomoxetine		Bupropion		Clonidine		Guanfacine		Methylphenidate		Modafinil		Placebo	
	Children	Adults	Children	Adults	Children	Adults	Children	Adults	Children	Adults	Children	Adults	Children	Adults
<b>Amphetamines</b>														
Clinicians	-0.46 (-0.65 to -0.27)*	-0.34 (-0.58 to -0.10)*	-0.06 (-0.81 to 0.68)†	-0.33 (-0.77 to 0.11)*	-0.31 (-0.81 to 0.18)*	-	-0.35 (-0.59 to -0.10)*	-	-0.24 (-0.44 to -0.05)*	-0.29 (-0.54 to -0.05)*	-0.39 (-0.67 to -0.12)*	-0.94 (-1.43 to -0.46)†	-1.02 (-1.19 to -0.85)†	-0.79 (-0.99 to -0.58)†
Teachers	-	-	-	-	-	-	-	-	-	-	-	-	-	-
<b>Atomoxetine</b>														
Clinicians	-	-	0.40 (-0.34 to 1.14)*	0.01 (-0.41 to 0.42)*	0.15 (-0.33 to 0.63)*	-	0.11 (-0.09 to 0.32)*	-	0.22 (0.05 to 0.39)*	0.04 (-0.14 to 0.23)†	0.07 (-0.17 to 0.31)*	-0.61 (-1.06 to -0.15)*	-0.56 (-0.66 to -0.45)*	-0.45 (-0.58 to -0.32)*
Teachers	-	-	0.00 (-0.90 to 0.90)†	-	-	-	0.31 (-0.79 to 1.42)†	-	0.50 (-0.11 to 1.10)*	-	0.44 (-0.19 to 1.07)*	-	-0.32 (-0.82 to 0.18)†	-

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# Atomoxetine

- Black Box Warning: Increased suicidal ideation

Table 2: Common Treatment-Emergent Adverse Reactions Associated with the Use of STRATTERA in Acute (up to 18 weeks) Child and Adolescent Trials

Adverse Reaction	Percentage of Patients Reporting Reaction from BID Trials		Percentage of Patients Reporting Reaction from QD Trials	
	STRATTERA (N=715)	Placebo (N=434)	STRATTERA (N=882)	Placebo (N=500)
<b>Gastrointestinal Disorders</b>				
Abdominal pain <sup>a</sup>	17	13	18	7
Vomiting	11	8	11	4
Nausea	7	6	13	4
Constipation <sup>b</sup>	2	1	1	0
<b>General Disorders</b>				
Fatigue	6	4	9	2
<b>Psychiatric Disorders</b>				
Mood swings <sup>c</sup>	2	0	1	1

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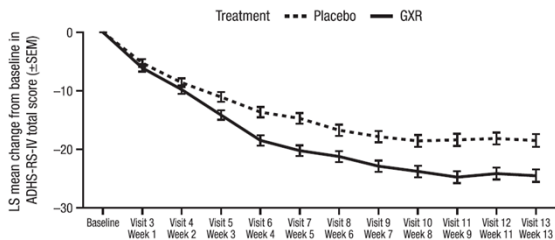
# Atomoxetine

- Concern for hepatotoxicity (avoid in those with liver injury)
- Concern for cardiovascular events (consult cardiology)

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# Guanfacine

- When to Use:
  - Reserve for second/third line or augmentation
  - Good adjunct for hyperactivity, impulsivity, sleep disturbance
  - Co-morbid tic disorder, ODD



Wilens, 2015. *Journal of the American Academy of Child and Adolescent Psychiatry*.

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# Guanfacine

Atomoxetine		Bupropion		Clonidine		Guanfacine		Methylphenidate		Modafinil		Placebo	
Children	Adults	Children	Adults	Children	Adults	Children	Adults	Children	Adults	Children	Adults	Children	Adults
<b>Amphetamines</b>													
Clinicians	-0.46 (-0.65 to -0.27)*	-0.34 (-0.58 to -0.10)*	-0.06 (-0.81 to 0.68)†	-0.33 (-0.77 to 0.11)*	-0.31 (-0.81 to 0.18)*	-0.35 (-0.59 to -0.10)*	-	-0.24 (-0.44 to -0.05)*	-0.29 (-0.54 to -0.05)*	-0.39 (-0.67 to -0.12)*	-0.94 (-1.43 to -0.46)†	-1.02 (-1.19 to -0.85)†	-0.79 (-0.99 to -0.58)†
Teachers	-	-	-	-	-	-	-	-	-	-	-	-	-
<b>Atomoxetine</b>													
Clinicians	-	-	0.40 (-0.34 to 1.14)*	0.01 (-0.41 to 0.42)*	0.15 (-0.33 to 0.63)*	0.11 (-0.09 to 0.32)*	-	0.22 (0.05 to 0.39)*	0.04 (-0.14 to 0.23)†	0.07 (-0.17 to 0.31)*	-0.61 (-1.06 to -0.15)*	-0.56 (-0.66 to -0.45)*	-0.45 (-0.58 to -0.32)*
Teachers	-	-	-	-	-	0.31 (-0.79 to 1.42)†	-	0.50 (-0.11 to 1.10)*	-	0.44 (-0.19 to 1.07)*	-	-0.32 (-0.82 to 0.18)†	-
<b>Bupropion</b>													
Clinicians	-	-	-	-	-0.25 (-1.12 to 0.62)†	-0.28 (-1.04 to 0.47)†	-	-0.18 (-0.90 to 0.54)†	0.04 (-0.38 to 0.45)*	-0.33 (-1.10 to 0.43)†	-0.62 (-1.20 to -0.03)*	-0.96 (-1.69 to -0.46)†	-0.46 (-0.85 to -0.07)*
Teachers	-	-	-	-	-	0.31 (-0.92 to 1.55)†	-	0.50 (-0.17 to 1.17)*	-	0.44 (-0.38 to 1.26)*	-	-0.32 (-1.07 to 0.43)†	-
<b>Clonidine</b>													
Clinicians	-	-	-	-	-	-0.03 (-0.53 to 0.46)†	-	0.07 (-0.42 to 0.56)†	-	-0.08 (-0.59 to 0.43)†	-	-0.71 (-1.17 to -0.24)†	-
<b>Guanfacine</b>													
Clinicians	-	-	-	-	-	-	-	0.11 (-0.13 to 0.34)*	-	-0.05 (-0.32 to 0.23)*	-	-0.67 (-0.85 to -0.50)†	-
Teachers	-	-	-	-	-	-	-	0.18 (-0.86 to 1.22)†	-	0.12 (-0.93 to 1.18)†	-	-0.63 (-1.62 to 0.35)†	-
<b>Methylphenidate</b>													
Clinicians	-	-	-	-	-	-	-	-	-	-0.15 (-0.41 to 0.10)*	-0.65 (-1.11 to -0.19)*	-0.78 (-0.93 to -0.62)†	-0.49 (-0.64 to -0.35)†
Teachers	-	-	-	-	-	-	-	-	-	-0.06 (-0.53 to 0.42)†	-	-0.82 (-1.16 to -0.48)†	-
<b>Modafinil</b>													
Clinicians	-	-	-	-	-	-	-	-	-	-	-	-0.62 (-0.84 to -0.41)*	0.16 (-0.28 to 0.59)*
Teachers	-	-	-	-	-	-	-	-	-	-	-	-0.76 (-1.15 to -0.37)†	-
Data are standardized mean difference (95% CI) between treatments. Results in bold are significant. Negative values favour the treatment in the row and positive values favour the treatment in the column. Drugs are reported in alphabetical order. Results are based on network estimates. No data for clonidine and guanfacine in adults are reported because no studies tested these two drugs in adults. No teacher ratings were available for clonidine. ADHD=attention deficit hyperactivity disorder. *Low quality of evidence. †Very low quality of evidence. (Moderate quality of evidence).													
Table 1. Effect of ADHD drugs in children and adults at timepoints closest to 12 weeks in terms of efficacy, as rated by clinicians and teachers													

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# Guanfacine

- MOA:
  - Alpha2a agonist, presynaptic in brainstem resulting in reduced peripheral sympathetic tone (low systolic/diastolic bp)
  - Postsynaptic agonism of alpha2a (prefrontal cortex)
- SE's: sleepiness, tiredness, headache, and stomachache
- IR and XR formulation
- Dosing: Start at 1mg and titrate in 1mg increments
- Taper at 1mg every 3 to 7 days
- Metabolism: Renal excretion of ~50% and Remainder CYP3A4
- Pregnancy category B

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# Clonidine

Atomoxetine		Bupropion		Clonidine		Guanfacine		Methylphenidate		Modafinil		Placebo	
Children	Adults	Children	Adults	Children	Adults	Children	Adults	Children	Adults	Children	Adults	Children	Adults
<b>Amphetamines</b>													
Clinicians	-0.46 (-0.65 to -0.27)*	-0.34 (-0.58 to -0.10)*	-0.06 (-0.81 to 0.68)†	-0.33 (-0.7 to 0.11)*	-0.31 (-0.81 to 0.18)†	-0.35 (-0.59 to -0.10)*	-	-0.24 (-0.44 to -0.05)*	-0.29 (-0.54 to -0.05)*	-0.39 (-0.67 to -0.12)*	-	-0.94 (-1.43 to -0.46)‡	-1.02 (-1.19 to -0.79) (-0.99 to -0.58)‡
Teachers	-	-	-	-	-	-	-	-	-	-	-	-	-
<b>Atomoxetine</b>													
Clinicians	-	-	0.40 (-0.34 to 1.14)*	0.01 (-0.44 to 0.42)*	0.15 (-0.33 to 0.63)*	0.11 (-0.09 to 0.32)*	-	0.22 (0.05 to 0.39)*	0.04 (-0.14 to 0.23)‡	0.07 (-0.17 to 0.31)*	-	-0.61 (-1.06 to -0.15)*	-0.56 (-0.66 to -0.45)* (-0.45 to -0.32)*
Teachers	-	-	0.00 (-0.90 to 0.90)†	-	-	0.31 (-0.79 to 1.42)†	-	0.50 (-0.11 to 1.10)*	-	0.44 (-0.19 to 1.07)*	-	-	-0.32 (-0.82 to 0.18)†
<b>Bupropion</b>													
Clinicians	-	-	-	-	-0.25 (-1.12 to 0.62)†	-0.28 (-1.04 to 0.47)†	-	-0.18 (-0.90 to 0.54)†	0.04 (-0.38 to 0.45)*	-0.32 (-1.10 to 0.43)†	-	-0.62 (-1.20 to -0.03)*	-0.96 (-1.69 to -0.22)‡ (-0.46 to -0.85 to -0.07)*
Teachers	-	-	-	-	-	0.31 (-0.92 to 1.55)†	-	0.50 (-0.17 to 1.17)*	-	0.44 (-0.38 to 1.26)*	-	-	-0.32 (-1.07 to 0.43)†
<b>Clonidine</b>													
Clinicians	-	-	-	-	-	-0.03 (-0.53 to 0.46)†	-	0.07 (-0.42 to 0.56)†	-	-0.08 (-0.59 to 0.43)†	-	-	-0.71 (-1.47 to -0.24)‡
<b>Guanfacine</b>													
Clinicians	-	-	-	-	-	-	-	0.11 (-0.13 to 0.34)*	-	-0.05 (-0.32 to 0.23)*	-	-	-0.67 (-0.85 to -0.50)‡
Teachers	-	-	-	-	-	-	-	0.18 (-0.86 to 1.22)†	-	0.12 (-0.93 to 1.18)†	-	-	-0.63 (-1.62 to 0.35)†
<b>Methylphenidate</b>													
Clinicians	-	-	-	-	-	-	-	-	-	-0.15 (-0.41 to 0.10)*	-	-0.65 (-1.11 to -0.19)*	-0.78 (-0.93 to -0.62)‡ (-0.49 to -0.35)‡
Teachers	-	-	-	-	-	-	-	-	-	-0.06 (-0.53 to 0.47)†	-	-	-0.82 (-1.16 to -0.48)*
<b>Modafinil</b>													
Clinicians	-	-	-	-	-	-	-	-	-	-	-	-	-0.62 (-0.84 to -0.41)* 0.16 (-0.28 to 0.59)*
Teachers	-	-	-	-	-	-	-	-	-	-	-	-	-0.76 (-1.15 to -0.37)†

Data are standardized mean difference (95% CI) between treatments. Results in bold are significant. Negative values favour the treatment in the row and positive values favour the treatment in the column. Drugs are reported in alphabetical order. Results are based on network estimates. No data for clonidine and guanfacine in adults are reported because no studies identified by our search tested these two drugs in adults. No teacher ratings were available for clonidine. ADHD=attention-deficit hyperactivity disorder. \*Low quality of evidence. †Very low quality of evidence. ‡Moderate quality of evidence.

Table 1: Effect of ADHD drugs in children and adults at timepoints closest to 12 weeks in terms of efficacy, as rated by clinicians and teachers

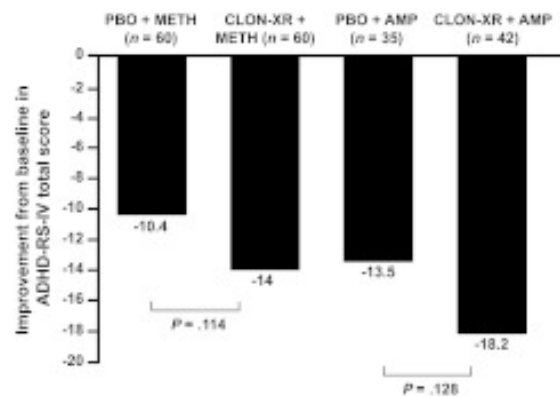
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# Clonidine

- MOA:
  - Alpha2a agonist, presynaptic in brainstem resulting in reduced peripheral sympathetic tone (low systolic/diastolic bp)
  - Postsynaptic agonism of alpha2a (prefrontal cortex)
  - Less selective than Guanfacine (binds 2a, 2b, 2c) may be why more sedative
- SE's: sleepiness, tiredness, headache, and stomachache
- IR, XR, and patch formulation
- Dosing: Start at 0.1mg and titrate in 0.1mg increments (max 0.4mg)
- Taper at 0.1mg every 3 to 7 days
- Metabolism: Renal excretion/Some liver metabolism
- Pregnancy category C

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# Combo Stimulant Treatment and Alpha2 Agonist



Kollins et al. 2011, *Pediatrics*

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# Modafinil

	Atomoxetine		Bupropion		Clonidine		Guanfacine		Methylphenidate		Modafinil		Yacebo	
	Children	Adults	Children	Adults	Children	Adults	Children	Adults	Children	Adults	Children	Adults	Children	Adults
<b>Amphetamines</b>														
Clinicians	-0.46 (-0.65 to -0.27)*	-0.34 (-0.58 to -0.10)*	-0.06 (-0.81 to 0.68)†	-0.33 (-0.77 to 0.11)*	-0.31 (-0.81 to 0.18)*	-	-0.35 (-0.59 to -0.10)*	-	-0.24 (-0.44 to -0.05)*	-0.29 (-0.54 to -0.05)*	-0.39 (-0.67 to -0.12)*	-0.94 (-1.43 to -0.45)‡	-1.02 (-1.19 to -0.85)‡	-0.79 (-0.99 to -0.58)‡
Teachers	-	-	-	-	-	-	-	-	-	-	-	-	-	-
<b>Atomoxetine</b>														
Clinicians	-	-	0.40 (-0.34 to 1.14)*	0.01 (-0.41 to 0.42)*	0.15 (-0.33 to 0.63)*	-	0.11 (-0.09 to 0.32)*	-	0.22 (0.05 to 0.39)*	0.04 (-0.14 to 0.23)†	0.07 (-0.17 to 0.31)*	-0.61 (-1.06 to -0.15)*	-0.56 (-0.66 to -0.45)*	-0.45 (-0.58 to -0.32)*
Teachers	-	-	0.00 (-0.90 to 0.90)†	-	-	-	0.31 (-0.79 to 1.42)†	-	0.50 (-0.11 to 1.10)*	-	0.44 (-0.19 to 1.07)*	-	-0.32 (-0.82 to 0.18)†	-
<b>Bupropion</b>														
Clinicians	-	-	-	-	-0.25 (-1.12 to 0.62)†	-	-0.28 (-1.04 to 0.47)†	-	-0.18 (-0.90 to 0.54)†	0.04 (-0.38 to 0.45)*	-0.33 (-1.10 to 0.43)†	-0.62 (-1.20 to -0.03)*	-0.96 (-1.49 to -0.42)‡	-0.46 (-0.85 to -0.07)*
Teachers	-	-	-	-	-	-	0.31 (-0.92 to 1.55)†	-	0.50 (-0.17 to 1.17)*	-	0.44 (-0.38 to 1.26)*	-	-0.32 (-1.07 to 0.43)†	-
<b>Clonidine</b>														
Clinicians	-	-	-	-	-	-	-0.03 (-0.53 to 0.46)†	-	0.07 (-0.42 to 0.56)†	-	-0.08 (-0.59 to 0.43)†	-	-0.71 (-1.27 to -0.14)‡	-
<b>Guanfacine</b>														
Clinicians	-	-	-	-	-	-	-	-	0.11 (-0.13 to 0.34)*	-	-0.05 (-0.32 to 0.23)*	-	-0.67 (-0.85 to -0.50)‡	-
Teachers	-	-	-	-	-	-	-	-	0.18 (-0.86 to 1.22)†	-	0.12 (-0.93 to 1.18)†	-	-0.63 (-1.62 to 0.35)†	-
<b>Methylphenidate</b>														
Clinicians	-	-	-	-	-	-	-	-	-	-	-0.15 (-0.41 to 0.10)*	-0.65 (-1.11 to -0.19)*	-0.78 (-0.93 to -0.62)‡	-0.49 (-0.64 to -0.35)‡
Teachers	-	-	-	-	-	-	-	-	-	-	-0.06 (-0.53 to 0.41)†	-	-0.82 (-1.16 to -0.48)‡	-
<b>Modafinil</b>														
Clinicians	-	-	-	-	-	-	-	-	-	-	-	-	-0.62 (-0.84 to -0.41)*	0.16 (-0.28 to 0.59)*
Teachers	-	-	-	-	-	-	-	-	-	-	-	-	-0.76 (-1.15 to -0.37)†	-

†Low quality of evidence; ‡Moderate quality of evidence; \*High quality of evidence. Results are based on network estimates. No data for clonidine and guanfacine in adults are reported because no studies identified by our search tested these two drugs in adults. No teacher ratings were available for clonidine. ADHD=attention deficit hyperactivity disorder. \*Low quality of evidence. †Very low quality of evidence. ‡Moderate quality of evidence.

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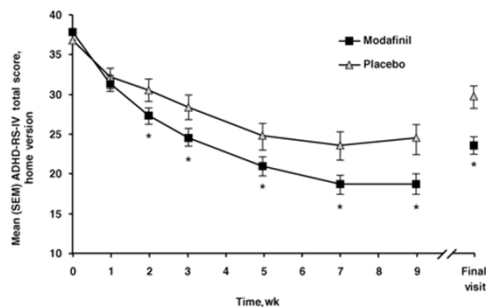
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# How does modafinil work?

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## Modafinil

- Uses:
  - Reserve as 2<sup>nd</sup> or 3<sup>rd</sup> line
  - Evidence does not show efficacious as adjunct



Biederman et al. 2005, *Pediatrics*  
Schmitz et al. 2012, *Frontiers in Psychiatry*

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## Modafinil

- MOA:
  - DAT blockade, partial alpha-1-b blockade, demonstrated to increase 5-HT2 receptor activity
- SE's: sleepiness, tiredness, headache, and stomachache
- Dosing: 200-425mg once daily (depending on weight)
- Metabolism: CYP3A4
  - Inhibits 2C19
  - Induces 3A4
- Pregnancy category C
- SE/Adverse Events: SJS, headache, nausea, anxiety, insomnia

Provigil [Package Insert], 2015

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## Questions

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