Bijlage bewijstabellen bij de Richtlijn oppositioneel-opstandige stoornis (ODD) en gedragsstoornis (CD) bij kinderen en jongeren
Inhoud

Bewijstabellen bij hoofdstuk 4, Beloop

Bewijstabellen bij hoofdstuk 6.2, Psychologische behandelingen

Bewijstabellen bij hoofdstuk 6.3, Farmacologische behandeling
Bewijstabellen bij hoofdstuk 4, Beloop

Voor de volledige literatuurbeschrijvingen van de onderzoeken, zie hoofdstuk 3, literatuur.

<table>
<thead>
<tr>
<th>Study aim</th>
<th>Follow-up of adolescents who as children were treated as in-patient or in an outpatient or both because they are severely disturbed behavior exhibited</th>
</tr>
</thead>
</table>
| Study design | Cohort study (follow-up)  
Setting: hospital and home situations  
Location: The Netherlands |
| Number of patients | N = 47 |
| Patient characteristics | Age: mean age 10.1 years  
Sex: 42 boys, 5 girls |
| Inclusion | DSM-IV diagnosis or DBD diagnosis  
IQ of 80 and less  
Observed by teachers.  
Psychiatric and psychological testing. |
| Intervention(s) | Intervention:  
– in-patient treatment setting.  
Control:  
– day treatment setting.  
The final results were compared between these two groups (and also compared with other studies).  
Both groups received:  
– cognitive behavioral therapy;  
– social skills training;  
– contingency management;  
– parent training;  
– special classes at school about treatment;  
in combination with pharmacotherapy for the treatment of ADHD, aggressive behavior and depression.  
Follow-up time: follow-up after 6 years.  
Treatment period: 0.7 to 2.8 years (mean 1.7 year) |
Outcome

Primary:
- behavior of adolescents with DBD after treatment (internal or days).

Secondary:
- rating views of parents (using CBCL, Child Behavior Checklist, DISC-IV) and adolescents (YSR: Youth Self Report, SSS: sensation seeking scale, BDI: Beck Depression Inventory, interview) itself.

Other outcomes:
- smoking, drug use, depression, police contact

Results

87% of adolescents (N = 45) and 90% (N = 47) of their caretakers participated in follow-up. No difference between the outpatient setting and patients, so therefore taken as a group (and compared to other studies).

53% of the adolescents was again diagnosed as DBD, using DISC-IV (parent version). 47% no ODD or CD diagnosis.

Parents and adolescents evaluate behavior differently. Parents: 70% of adolescents fall within the clinical setting (CBCL). 20% of adolescents indicated that about themselves (YSR).

In the follow-up, no differences between adolescents with in-patient or day treatment (CBCL and YSR). All adolescents compared with two other studies.*

Smoking: 71% vs. 34% HBSC sample.
Marijuana: 64% vs. 39% SSO-I sample.
Hard drugs-use: 18% vs. 19% SSO-I.
Police contact:
- alternative sanction: 22% vs. 27% SSO-I.
- in-cell: 17% vs. 7% SSO-I.

Overall: 38% positive outcome and 34% poor outcome (in terms of living situation, delinquency, school dropout, smoking)

Quality assessment

In the study, there is no comparable control group.

The manual of the questionnaires contained normative scores in a few representative samples. With regard to other data, similar samples were available, but differed with respect to age, gender or education level.

Therefore view with claims handling.

Half of the participants had another DBD diagnosis, more adolescents used cannabis, smoked, had been in jail, quit school.

Quality of evidence

B

BDI: Beck Depression Inventory, interview; CBCL: Child Behavior Checklist; DBD: disruptive behavior disorder; DISC-IV: Diagnostic Interview Schedule for Children, versie IV; HBSC: Health Behaviour in School-aged Children; SSO: Standard Survey Offenders; SSS: sensation seeking scale; YSR: Youth Self Report
**Boylan e.a. (2007). Comorbidity of internalizing disorders in children with oppositional defiant disorder**

<table>
<thead>
<tr>
<th>Study aim</th>
<th>Presents evidence on the association of internalizing disorders with ODD across childhood and adolescence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>Systematic Review</td>
</tr>
<tr>
<td>Number of studies</td>
<td>28 articles included</td>
</tr>
<tr>
<td>Number of patients</td>
<td>Between 79 and 10,438 patients in 1 study</td>
</tr>
<tr>
<td>Patient characteristics</td>
<td>Age: Children and adolescents up to 18 years old. Sex: ?</td>
</tr>
<tr>
<td>Inclusion</td>
<td>Inclusion: articles found in PubMed, CINAHL, Psych Info, Medline.</td>
</tr>
<tr>
<td></td>
<td>– English studies</td>
</tr>
<tr>
<td></td>
<td>– ODD key term</td>
</tr>
<tr>
<td></td>
<td>– Studies had to use: DSM-III, DSM-IIIR, DSM-IV, DSM-IV-TR</td>
</tr>
<tr>
<td></td>
<td>– Age: under 18.</td>
</tr>
<tr>
<td></td>
<td>Exclusion: ?</td>
</tr>
<tr>
<td>Intervention(s)</td>
<td>Select articles with information about ODD and internalizing comorbidity</td>
</tr>
<tr>
<td>Outcome</td>
<td>Primary:</td>
</tr>
<tr>
<td></td>
<td>– Prevalence of ODD in clinical and epidemiologic samples?</td>
</tr>
<tr>
<td></td>
<td>– Degree of comorbidity between ODD and internalizing disorders?</td>
</tr>
<tr>
<td>Results</td>
<td>ODD prevalence estimates vary between 2% and 14% in epidemiological samples, and 28-50% in clinical samples. The best estimate of comorbidity, presented here as an unweighted average of the OR study: 17.2 for depression with ODD and 5.4 for any anxiety disorder with ODD in epidemiological studies. In clinical studies, the ORs for depression more similar 6.0 and 8.9 for each anxiety disorder.</td>
</tr>
<tr>
<td>Quality assessment</td>
<td>Study question: +</td>
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<tr>
<td></td>
<td>Search: +</td>
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<tr>
<td></td>
<td>Selection: +</td>
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<tr>
<td></td>
<td>Quality assessment: +</td>
</tr>
<tr>
<td></td>
<td>Data extraction: +</td>
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<tr>
<td></td>
<td>Description of original studies: +</td>
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<td></td>
<td>Handling heterogeneity: +</td>
</tr>
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<td></td>
<td>Statistical pooling: +</td>
</tr>
<tr>
<td></td>
<td>Funding/conflicts of interest: -</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>A2.</td>
</tr>
<tr>
<td></td>
<td>Tables of original articles describing.</td>
</tr>
<tr>
<td></td>
<td>– Different results are well described.</td>
</tr>
<tr>
<td></td>
<td>– The limitation of the majority of the surveyed studies is that they do not specifically distinguish between the nature of the anxiety of the child, or difference between dysthymia and major depression. This allows the natures of conclusions (about comorbidity effects) are limited.</td>
</tr>
</tbody>
</table>
Frick & White (2008) The importance of callous unemotional traits for developmental models of aggressive and antisocial behavior

Study aim: CU traits and the severity of conduct problems, aggression, delinquency and antisocial behavior

Study design: Narrative literature review

Location: University of New Orleans, USA

Number of studies: 30 (described in a table, with some information)

Number of patients: N between 37 and 1443

Patient characteristics:
- Age: 5-18 years
- Sex: mostly men

Inclusion:
- Psychopathic traits or callous unemotional (CU) traits specifically

Measures:
- APSD = Antisocial Process Screening Device (Frick & Hare, 2001);
- CPS = Childhood Psychopathy Scale (Lynam, 1997);
- PCL-YV = Psychopathy Checklist: Youth Version (Forth, Kosson, & Hare, 2003);
- SRP-II = Self-Report of Psychopathy-II (Harpur & Hare, unpublished instrument).

Outcome:
- Primary: presence of a callous and unemotional interpersonal style at antisocial and aggressive youth

Results:
There appears to be a rather substantial and growing body of research supporting the use of CU traits to designate a distinct subgroup of antisocial youth. These traits seem to be relatively stable across childhood and adolescence and they seem to designate a group of antisocial youth who show a more severe, aggressive, and stable pattern of antisocial behavior. Further, this subgroup of youth show a number of distinct cognitive, emotional, and personality characteristics such as showing abnormalities in their responsiveness to punishment cues, showing a diminished responsiveness to distress cues in others, and showing less trait anxiety when controlling for their level of antisocial behavior.

There is some optimism that this research on CU traits could guide more effective interventions for a subgroup of youth who operate at a high cost to society because of their chronic and serious delinquent and aggressive acts.
Quality assessment

Study question: +
Search: -
Selection: -
Quality assessment: -
Data extraction: -
Description of original studies: ?
Handling heterogeneity: -
Statistical pooling: -
Conflict of interest statement: Paul J. Frick is the author of the Antisocial Process Screening Device, in which he has a significant financial interest

Quality of evidence
C
– Narrative review.
– Researchers looked at 30 articles and have drawn conclusions from it. The articles are not obtained through a good search strategy.
– There is little done with the results, no pool, no quality, no data extraction, no clarity on heterogeneity, et cetera


Study aim
With a longitudinal study the following is researched: if most adults with mental disorders are found to have a juvenile psychiatric history, this would shift etiologic research and prevention policy to focus more on childhood mental disorders

Study design
Prospective study

Number of patients
1037

Patient characteristics
Children were followed from birth until their 26th and received a psychiatric diagnosis according to DSM criteria, when they were 11, 13, 15, 18, 21 and 26 years old.

Inclusion
Participants were taken from a New Zealand birth cohort: The Dunedin Multidisciplinary Health and Development Study.

Intervention(s)
At different ages one is assessed by interview using the DSM criteria.
– 11.13 and 15 years: DSM-III
– 18 and 21 years: DSM-III R
– 26 years: DSM-IV
– 11 to 15 years: Diagnostic Interview Schedule for Children
– Older: Diagnostic Interview Schedule

Reporting period of 12 months at any age

Outcome
% Of young people who were defined diagnoses on the DSM criteria
Results

Adult cases that defined the Diagnostic Interview Schedule:
- 73.9% diagnosis before 18 year;
- 50.0% before 15 year.
Among treatment-using cases:
- 76.5% diagnosis before 18 year;
- 57.5% before 15 year.
Among cases receiving intensive mental health services:
- 77.9% diagnosis before 18 year;
- 60.3% before 15 year.
Adult disorders were generally preceded by their juvenile counterparts (e.g., adult anxiety was preceded by juvenile anxiety), but also by different disorders. Specifically, adult anxiety, schizophrenia disorders were preceded by a broad array of juvenile disorders.
For all adult disorders, 25% to 60% of cases had a history of conduct and/or oppositional defiant disorder.

Quality assessment

96% of all living cohort members were at follow-up when they were 26. N = 980.
Failure of participants is not described.
The study suggests that juvenile conduct disorder cases constitute a vital prevention opportunity for reducing the burden associated with many major adult psychiatric disorders.

Quality of evidence

- Follow-up study without a comparable group

Moffitt & Caspi (2001). Childhood predictors differentiate life-course persistent and adolescence-limited antisocial pathways among males and females

Study aim

Comparison on childhood risk factors of males and females exhibiting childhood-onset and adolescent-onset antisocial behavior, using data from the Dunedin longitudinal study

Number of patients

N = 993 when the patients are 18.
At start: N=1037 when the patients were 3 years old.

Patient characteristics

Data from the: Dunedin Multidisciplinary Health and development Study.
Started with 3 year of age 91% births between April 1972 and March 1973.

Intervention(s)

Participants were designated on the life-course-persistent path (LCP) of the adolescence-limited path (AL).
The interventions were assessments at different ages.
Researches present data for 26 measures, selected to represent the 3 domains of childhood risk specified by the theory; family adversity and inadequate parenting
Outcome
- LCP versus AL
- females in AL and LCP paths

Results
- Delinquency:
  LCP: childhood-onset delinquents had childhoods of inadequate parenting, neurocognitive problems and temperament and behavior problems.
  For the AL path; adolescent-onset delinquents did not have these pathological backgrounds.
- Gender:
  LCP path: Sex-comparisons showed a male-female ratio of 10:1 (for childhood-onset delinquency). (Moffit e.a., 1996: 6 females (1%) and 47 males (10%).)
  For the AL path, this ratio is 1.5:1 (for adolescence-onset delinquency). (Moffit e.a., 1996: 122 males (26%) and 78 females (18%).)
  LCP: childhood-onset females had high-risk backgrounds, bur adolescent-onset females did not (showing the same pattern as males)

Quality assessment
The effect sizes reports for the LCP-AL differences in cognitive risk, increased with age, form small effects for neurological abnormalities, motor skills, and the Peabody vocabulary test at age 3 years, to medium effects for verbal IQ and reading at age 7,9 and 11 years.
LCP-AP behavioral risk; increased with age, from a small effect for difficult-to-manage at age 2 years, to a medium effect for under control observed at age 3 years, to a large effect for hyperactivity at ages 5-11 years.
The LCP group can be distinguished in the early years of life.

Quality of evidence
C
Follow-up study without a comparable group
### Pajer e.a. (2007) Female conduct disorder: Health status in young adulthood

<table>
<thead>
<tr>
<th>Study aim</th>
<th>Relationship between poor health in adults and antisocial behavior of girls in their adolescence, and whether this is related to demographic factors and pre-existing health problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>Longitudinal study</td>
</tr>
<tr>
<td>Number of patients</td>
<td>N = 93 girls</td>
</tr>
<tr>
<td>Patient characteristics</td>
<td>Age: girls between 15 and 17 years</td>
</tr>
<tr>
<td>Ethnicity: Caucasian or African American</td>
<td></td>
</tr>
<tr>
<td>Inclusion</td>
<td>- normal controls: experimented with drugs and at least five cigarettes a day.</td>
</tr>
<tr>
<td>Exclusion</td>
<td>- other age;   - pubertal stage &lt; Tanner Stage V;   - Head trauma in history where one more is lost consciousness 15 min;   - IQ &lt; 65;   - Psychosis or medical illness that can affect the HPA axis;   - Normal control group: had or has a psychiatric illness.</td>
</tr>
<tr>
<td>Baseline characteristic</td>
<td>- characteristics are similar, looking at age, socio-econ. status, ethnicity, smoking, alcohol use, marijuana use</td>
</tr>
<tr>
<td>Intervention(s)</td>
<td>Intervention group:   - 52 girls with conduct disorders (CD).</td>
</tr>
<tr>
<td>Control group</td>
<td>- 41 girls with normal control (NC).</td>
</tr>
<tr>
<td>Intervention for both girls with and without a CD diagnosis</td>
<td>- Psychiatric diagnosis: DISC;   - DSM-IV (CD criteria changed slightly because CD in girls is controversial);   - Semi-structured interviews, lifetime histories of illness, surgery, injury to girls and their parents;   - Self-reported instrument (CHIP-AE) on health last 12 months;   - BMI calculated.</td>
</tr>
<tr>
<td>Follow-up</td>
<td>- follow-up of 3 years. 3 times a follow-up occurred (1, 2 and 3 years);   - 85% of all girls (CD and NC) complemented follow-up 3.</td>
</tr>
</tbody>
</table>
| Outcome | Association between CD and health. With health and illness variables.
Results:
- No significant group differences around: injuries, medical illnesses, or episodes initiating or stopping medication, emergency room visits, hospitalizations, visit physicians.
- BMI: no significance difference;
- Gynaecology: girls with CD started sexual intercourse earlier (Wald = 9.98: Expt (β) = .218; df = 1; p = .002);
- and had their first pregnancy at significantly younger ages (Wald = 5.05: Expt (β) = .349; df = 1; p = .025).

Conclusion:
- adolescent girls with CD as young adults have poorer overall health, more discomfort, more health risk behaviors, and earlier onset of adult reproductive behaviors. Even when controlling for demographic factors and pre-existing health history.

Quality assessment
- Only self-reported data. Self-reported data combined with data from e.g. laboratory, registered health information and so probably had a different outcome data.
- Recruitment with advertisements within the community of western Pennsylvania city, advantage is that different cultures/training and economic status achieved only drawback is that the girls come from those communities.

Quality of evidence B

**Rowe e.a. (2010) Developmental pathways in oppositional defiant disorder and conduct disorder**

<table>
<thead>
<tr>
<th>Study aim</th>
<th>The relationship between DSM-IV CD and DSM-IV ODD capitalizing on longitudinal follow-ups that now cover the years from late childhood to early adulthood</th>
</tr>
</thead>
</table>
| Study design | Cohort study  
| Blind: | +  
| Duration of the study: | 12 years.  
| Setting: | predominantly rural area of the southern United States |
| Number of patients | N = 1.420 individuals |
| Patient characteristics | Age: between 9 and 13 years old.  
| Sex: | 56% male |
| Inclusion |  
| – first a representative sample who had to complete the CBCL;  
| – all children scoring above a predefined CBCL score (designed to identify the highest scoring 25% of the population) and a 10% random sample of the remainder were included. |
| Exclusion |  
| – children and parents who scored under the predefined CBCL score. |
| Intervention(s) |  
| – The child and primary caretaker (mostly the mother) were interviewed separately every year, using the CAPA (Child and Adolescent Psychiatric Assessment).  
| – The YAPA (Young Adult Psychiatric Assessment) was used for the participants at ages 19 and 21. |
| Follow-up |  
| – more than 10 years, till all included children became 21 years old (1993-2005). |
| Outcome | Primary outcome: relationship between DSM-IV CD and DSM-IV ODD |
Results

ODD was independently associated with increased risk of later CD (especially for boys).

There was no evidence that ODD → CD was a particularly common pathway:
- % ODD → CD in all participants: .8, (n = 21);
- % CD → ODD .9 (n=26).

CD → ODD was more common than ODD → CD (this was unexpected).

CD largely predicted behavioral outcomes, whereas ODD showed stronger prediction to emotional disorders in early adult life.

The researchers want to show that ODD and CD are two separate disorders in children. If anyone has ODD, this can later on develop into CD, but it can also be the other way.

Quality assessment

Research group: +
Selection bias: ?
Exposure: +
Outcome: +
Blinded outcome measurement: +
Follow-up: +
Selective loss-to-follow up: ?
Confounders/prognostic factors: +
Overall assessment: +

Finance: The Great Smoky Mountains Study was supported by National Institute of Mental Health Grants National Institute on Drug Abuse and the William T. Grant Foundation

Quality of evidence

Overall quality of evidence: A2

Well conducted study with enough respondents, but there is no information about confounding.

CBCL: Child Behavior Checklist
Waschbusch (2002) A meta-analytic examination of comorbid hyperactive-impulsive-attention problems and conduct problems

Study aim
Quantitatively reviewed prevalence rates, defining features, associated features, developmental trajectory, and etiology to examine taxonomic questions about comorbid hyperactive-impulsive–attention problems (HIA) and conduct problems (CP)

Number of studies
13 relevant studies were identified

Number of patients
24,487 participants included

Patient characteristics
Age: ranged from 4 to 20

Inclusion
Inclusion:
– children with hyperactive-impulsive-attention problems (HIA) and conduct problems (CP) or with any of these problems;
– disruptive behavior problems in children.

Exclusion:
– studies that did not clearly differentiate HIA from CP;
– studies that used a sample that was identified because of serious problems other than HIA or CP (e.g., depression, mania, mental retardation, psychosis);
– studies that examined a primarily adult sample (defined as over 19);
– studies that reported results that did not allow for treatment effects to be separated out (e.g., medication or behavioral treatment studies without a placebo condition);
– studies that were not empirical (i.e., a review article or theoretical paper).

Intervention(s)
Intervention was to answer 3 questions about comorbid hyperactive-impulsive attention problems (HIA) and conduct problems (CP):
– do HIA and CP co-occur randomly?
– does comorbid HIA-CP differ from HIA-only and CP-only?
– do HIA and CP combine synergistically?

Outcome
Outcome measure:
six effect sizes were computed from these studies.
– HIA-CP vs. controls, (b) HIA-only vs. controls;
– CP only vs. controls;
– HIA-CP vs. HIA-only, (e) HIA-CP vs. CP-only;
  HIA-only vs. CP-only.

Standardized mean difference ($SMD$) effect sizes (Cohen’s $d$) were used for continuous data and odds ratio effect sizes were used for categorical data.
Results:  - HIA and CP co-occur at a greater than random rate, that comorbid HIA-CP differs from HIA-only and CP-only in multiple ways, and that there is little evidence that HIA and CP combine synergistically.

Conclusion:  - HIA and CP co-occur at a rate greater than chance;  - the comorbid condition (HIA-CP) differs in meaningful ways as compared with the individual disorders of which it is composed (HIA-only and CP-only);  - available evidence indicates that HIA-CP consists of an additive, rather than synergistic, combination of HIA and CP.

Quality assessment  
- Study question: +  
- Search: +  
- Selection: ?  
- Quality assessment: +  
- Data extraction: +  
- Description of original studies: +  
- Handling heterogeneity: +  
- Statistical pooling: +  
- Funding / conflicts of interest: -

Quality of evidence  
A2  - It is not described whether the articles were independently assessed.  - The article was not about interventions, but more about prevalence of comorbid problems.

CP: conduct problems; HIA: hyperactive-impulsive-attention problems
Bewijstabellen bij hoofdstuk 6.2, Psychologische behandelingen

Voor de volledige literatuurbeschrijvingen van de onderzoeken, zie hoofdstuk 6.2, literatuur.


<table>
<thead>
<tr>
<th>Study aim</th>
<th>How effective are child-based CBT interventions compared to no-treatment, attention, and wait-list controls?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>Randomized controlled trials (RCT’s)</td>
</tr>
<tr>
<td>Blindness</td>
<td>?</td>
</tr>
<tr>
<td>Location</td>
<td>?</td>
</tr>
<tr>
<td>Authors are from:</td>
<td>Medical College of Pennsylvania, Hahnemann University;</td>
</tr>
<tr>
<td></td>
<td>Wordsworth Academy, Fort Washington.</td>
</tr>
<tr>
<td>Number of studies</td>
<td>N = 30 studies</td>
</tr>
<tr>
<td>Number of patients</td>
<td>Between 12 and 563 children in a study</td>
</tr>
<tr>
<td>Patient characteristics</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>mean age between 5.0 and 16.1 years.</td>
</tr>
<tr>
<td>Sex</td>
<td>boys mean 42.73 (SD 51.2)</td>
</tr>
<tr>
<td></td>
<td>Girls: 25.30 (SD 53.6)</td>
</tr>
<tr>
<td>Inclusion</td>
<td>Inclusion:</td>
</tr>
<tr>
<td></td>
<td>Studies using</td>
</tr>
<tr>
<td></td>
<td>– a child-based CBT intervention for antisocial behavior;</td>
</tr>
<tr>
<td></td>
<td>– subjects age 18 and younger;</td>
</tr>
<tr>
<td></td>
<td>– a no-treatment, attention, or wait-list control group; (d) a measure of antisocial behavior and (e) the English language (between 1974 and 19980 were identified through literature.</td>
</tr>
<tr>
<td>Exclusion</td>
<td>studies using assessments of aggressive responses to hypothetical vignettes, or aggression scores based on projective measures, were excluded</td>
</tr>
<tr>
<td>Intervention(s)</td>
<td>Intervention:</td>
</tr>
<tr>
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</tr>
<tr>
<td></td>
<td>– Cognitive-behavioral therapy (CBT).</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Control:</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>– no-treatment;</td>
</tr>
<tr>
<td></td>
<td>– attention groups;</td>
</tr>
<tr>
<td></td>
<td>– wait-list groups.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Follow-up:</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>· follow-up period (months) 4.81 (SD 4.44) 1 to 12.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Primary:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>– Efficacy of Child-Based CBT for Antisocial Behavior</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Secondary:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>– Predictors of CBT Efficacy</td>
</tr>
<tr>
<td></td>
<td>– (Several variables were examined as potential predictors of post treatment effect size).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Results</th>
<th>Mean effect size d of CBT interventions was 0.48 (median = 0.26; range from -1.60 to 4.29; SD = 1.14) unweighted and 0.23 weighted at post-treatment, which were significantly greater than zero based on 95% confidence intervals. The weighted effect size indicates that the average score of the treated group post-treatment was higher than the average score for 59% of the control group. Mean effect size at follow-up was 0.66 (median = 0.32; range from -0.53 to 4.01; SD = 1.18) unweighted, and 0.51 weighted, which were also significantly greater than zero based upon 95% confidence interval estimates. The weighted effect size indicates that the average score of the treated group at follow-up was higher than the average score for 69% of the control group. Treatment components, number of treatment sessions, session length, sessions per week, use of a clinical vs. nonclinical sample, type of control group, source of outcome ratings and publication year were unrelated to treatment efficacy.</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Quality assessment: +</td>
</tr>
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<td></td>
<td>Search: ?</td>
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<td>Selection: ?</td>
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<td>Data extraction: +</td>
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<td></td>
<td>Description of original studies: +</td>
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<td>Handling heterogeneity: +</td>
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<tr>
<td></td>
<td>Statistical pooling: +</td>
</tr>
<tr>
<td></td>
<td>Funding/conflicts of interest: ?</td>
</tr>
</tbody>
</table>
Quality of evidence B
- Searches only in one database for articles.
- It’s not clear how many articles researchers found before inclusion.
- It’s not clear whether the articles were assessed by two independent reviewers.
- So it isn’t a very strong article.

Overall information:
it appears that child-based CBT interventions may be an effective part of a multimodal treatment for children, particularly older children, who exhibit antisocial behavior. Although the present review did not compare CBT to other child treatments, existent studies suggest that CBT is at least as, and possibly more, effective than alternative child-based interventions in reducing antisocial behavior.
The sample was significantly homogeneous (Q27 = 17.87, p >.10), indicating that included studies share a common population effect size.


**Study aim**
To assess the effectiveness of Triple P Level 4 interventions in the management of behavioral problems in children by pooling the evidence from relevant literature that included Level 4 Triple P interventions.

**Patient characteristics**
Children 2-12 years old with behavior problems.

**Inclusion**
Studies had to meet the following inclusion criteria.
- The study examined the effects of a Level 4 Triple P intervention, an intensive parent training program for children with more severe behavioral difficulties or who are at risk of developing such problems.
- Effectively of Triple P was assessed using a questionnaire for the parents to evaluate disruptive behavior in their children aged 2 to 11.
- Sufficient empirical data were reported for the calculation of standardized effect sizes.

**Exclusion:**
- Studies with samples of children older than 11 were excluded because Triple P has a separate program for teens.

**Intervention(s)**
- Intervention: Level 4 of the Triple P program. (Level 4 is an intensive 8- to 10-part parenting training for children with more severe behavioral problems or at risk of developing such problems).
- Control: no intervention.
- Follow-up: 6 to 12 months.
Outcome

For each study, the researchers calculated an effect size: the standardized difference between the means of two groups (Cohen’s d).

Results

Results:
- Level 4 of Triple P has moderate to large effects on behavior problems of children that last in follow-up measurements of 6 to 12 months. A large effect size was found at both post intervention (d = 0.88) and long-term follow-up assessment of the child behavior (d = 1.00). At 6 and 12 months follow-up, overall mean effect sizes of d = 1.07 and d = 0.84.

Conclusion:
- Interventions using level 4 Triple P to improve the behavior of the child to demonstrate, as observed by the parents. Improvements in children’s behavior have long been visible and seem even slightly better in the long run.

Quality assessment

Study question: +
Search: +
Selection: +
Quality assessment: +
Data extraction: +
Description of original studies: +
Handling heterogeneity: +
Statistical pooling: +
Funding/conflicts of interest: +

Quality of evidence

A1
- The researchers are very clear in how they have proceeded and what to do with heterogeneity.
- The original studies were compared with overall results and statistically pooled from there.
- Triple P is the therapy for behavioral problems in children 2 to 12, so not only for children with ODD or CD.
- The results of the (different) trials were positive.
Eyberg e.a. (2008). Evidence-based psychosocial treatments for children and adolescents with disruptive behavior

Study aim
- Focus on the psychosocial treatment literature to make a report for child and adolescent disruptive behavior, including oppositional defiant disorder and conduct
- Identify evidence-based psychological treatments for child and adolescent disruptive behavior.

Study design
Literature review

Number of studies
N = 16

Number of patients
?

Patient characteristics
Age: 3-17 years old.
Sex: between 52% and 100% boys

Inclusion
Well-conducted group-design studies include prospective study design, clear inclusion/exclusion criteria for the sample in question, appropriate control or comparison conditions, random assignment to conditions, reliable measures of disruptive behavior, clearly specified sample characteristics (child sex, age, race = ethnicity, and targeted behavior problems), and clearly described statistical procedures

Intervention(s)
Intervention:
- evidence-based psychosocial treatments.

Treatment was defined as a specific procedure or set of procedures with therapeutic intent:
- Anger Control Training;
- Group Assertive Training;
- Helping the Noncompliant Child;
- Incredible Years (parent and child);
- Multidimensional Treatment Foster Care;
- Multi-systemic Therapy;
- Parent-Child Interaction Therapy;
- Parent Management Training Oregon Model;
- Positive Parenting Program;
- PSST Practice/PMT;
- Rational-Emotive Mental Health Program.

Control:
- waitlist;
- no treatment.

Outcome
Primary:
- moderators and mediators of treatment outcome;
- clinical representativeness and generalizability of the studies.
**Results**

Most of the EBTs identified in this review have demonstrated maintenance of treatment gains for at least 1 year after treatment completion.

In general, medications tend to produce highly variable treatment response among youth with disruptive behavior disorders.

Most of the studies in their review examined predictors of treatment outcome rather than moderators and/or mediators of change. Across all studies, identified predictors of treatment response have been highly inconsistent.

Once an EBT is selected, it is important to maintain treatment integrity by following treatment manual guidelines.

The review provides support for both parent-training and child-training EBTs for youth with disruptive behavior.

### Quality assessment

- **Study question:** 
  - Search: +
  - Selection: +
  - Quality assessment: +
  - Data extraction: +
  - Description of original studies: +
  - Handling heterogeneity: +
  - Statistical pooling: +
  - Funding/conflicts of interest: +

### Quality of evidence

- A2
  - Whole search procedure is described.
  - It describes the EBTs and their evidence base and covers research on moderators and mediators of treatment outcome, as well as the clinical representativeness and generalizability of the studies.
Feinfield & Baker (2004). *Empirical support for a treatment program for families of young children with externalizing problems*

<table>
<thead>
<tr>
<th>Study aim</th>
<th>To evaluate the efficacy of a multimodal treatment for young children with behavioral (external normalize behaviors). Not specifically ODD and/or CD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>Randomized controlled trial (RCT). Blinding: single for randomisation allocation, blinding no further. Analysis: ITT. Study: 12 week course, after 5 months follow-up. Setting: Child Study Center. Location: Department of Psychology, University of California, Los Angeles.</td>
</tr>
<tr>
<td>Number of patients</td>
<td>N = 24 in treatment group</td>
</tr>
<tr>
<td>Number of patients</td>
<td>N = 23 in control</td>
</tr>
<tr>
<td>Patient characteristics</td>
<td>Age:</td>
</tr>
<tr>
<td>Patient characteristics</td>
<td>– 4 to 8 years;</td>
</tr>
<tr>
<td>Patient characteristics</td>
<td>– 6.6 years on average.</td>
</tr>
<tr>
<td>Patient characteristics</td>
<td>Sex:</td>
</tr>
<tr>
<td>Patient characteristics</td>
<td>– girls in treatment group: 21%;</td>
</tr>
<tr>
<td>Patient characteristics</td>
<td>– in control group 8.7%;</td>
</tr>
<tr>
<td>Patient characteristics</td>
<td>– (not a good division!).</td>
</tr>
<tr>
<td>Inclusion</td>
<td>Inclusion:</td>
</tr>
<tr>
<td>Inclusion</td>
<td>– child was 4 to 8 years;</td>
</tr>
<tr>
<td>Inclusion</td>
<td>– primary problem was a persistent and significantly disrupted behavioral (eg aggression, not listening, oppositional behavior);</td>
</tr>
<tr>
<td>Inclusion</td>
<td>– the child had undergone CBCL and there was reckoned that there were behavioral problems. (T score of 60 or higher) or the Eyberg Child Behavior Inventory (ECBI; score of 12 or more);</td>
</tr>
<tr>
<td>Inclusion</td>
<td>– 83% of the target was a T-score of 60 or higher on the Teacher Report Form (TRF).</td>
</tr>
<tr>
<td>Exclusion</td>
<td>Exclusion:</td>
</tr>
<tr>
<td>Exclusion</td>
<td>– developmental delay in children.</td>
</tr>
<tr>
<td>Baseline characteristics</td>
<td>Baseline characteristics:</td>
</tr>
<tr>
<td>Baseline characteristics</td>
<td>– 44.7% white and 55.3% were minority or had a mixed identity;</td>
</tr>
<tr>
<td>Baseline characteristics</td>
<td>– the average age of primary caregivers was 38.4 years (SD = 8.0). Twenty-three (49%) of parents were married. In 41 families (88.2%), the mother was the primary caregiver;</td>
</tr>
<tr>
<td>Baseline characteristics</td>
<td>– 43% percent of primary caregivers had graduated, 56% had an annual income of at least $ 31,000.</td>
</tr>
</tbody>
</table>
**Intervention(s)**

Intervention:
- parent and child group 30 minutes;
- than one parent group session of 1.5 hours (including exercises and role plays) (9×) and a 3× individual sessions of 40 minutes;
- homework for them between sessions;
- children were then given a children's groups and meetings in just three sessions with two children;
- before and after testing.

**Control:**
- wait list group.

**Follow-up:**
- after five months both groups had a telephone interview and a paper questionnaire for parent and teacher follow-up.

**Outcome Primary:**

Outcome measures are divided into four categories.

- the child’s behavior, given by the parent (report);
- Child’s behavior by the teacher (report);
- custody in practice;
- attitude of parents and stress.

**Secondary:**

- Results were evaluated using various tests and questionnaires: CBCL, ECBI, TRF, PCRQ, APQ, PSOC, PSI.
Results

- Effect sizes:
  - standardized effect sizes based on treatment (Cohen's d, bias adjusted) were at an average range (CBCL Aggression: 0.47; ECBI: 0.41; HSQ: 0.69);
  - effect sizes for: power assertion was high (.86).

Parents: CBCL Externalizing.
- Pre: 66.1;
- after treatment: 59.2 after 5 months follow up: 55.9.

CBCL aggression:
- pre: 68.2;
- after treatment: 60.2;
- after 5 months follow up: 57.4.

Teacher: TRF Externalizing.
- Pre: 65.3;
- after treatment: 64.7;
- after 5 months follow up: 59.3.

TRF aggression:
- pre: 66.5;
- after treatment: 66.2;
- after 5 months follow up: 59.9.

Parenting stress: PSI child domain.
- Pre: 129.3;
- after treatment: 118;
- after 5 months follow up: 115.7.

PSI total score:
- pre: 258.7;
- after treatment: 241.7;
- after 5 months follow up: 234.5.

Quality assessment

- Randomisation: +
- Allocation concealed: -
- Patient and clinician blinded: -
- Assessor blinded: -
- Intervention and control groups were similar: +
- Follow-up: +
- Intention-to-treat analyze: +
- Finance: +

Quality of evidence

- B.

No blindness

APQ: Alabama Parenting Questionnaire; CBCL: Child Behavior Checklist; ECBI: Eyberg Child Behavior Inventory; PCRQ: Parent-Child Relationship Questionnaire; PSI: Psychological Screening Inventory; PSOC: Parenting Sense of Competence Scale; TRF: Teacher’s Report Form

Study aim
The effects of psychotherapy in reducing aggressive behaviour in children and adolescents using meta-analysis were estimated.

Study design
Meta-analysis
Blind: +
Duration of the study: ?
Setting: day-care and school settings
Location: ?

Number of studies
65 studies (33 studies with untreated control and 32 studies with no untreated control)

Number of patients
Between 10 and 350 participants. Covering 4971 cases

Patient characteristics
Age: 4 to 16 years old
Sex: described for every study (mostly girls were included)

Inclusion
- the children were in clinical range when their disruptive or aggressive behaviour were evaluated;
- reports were published or written in the period covering January 1987 until January 2008;
- mean age was below 18;
- the study reported at least one quantitative measure (rating scale or method of observation) of change in disruptive and aggressive behaviour.

Exclusion
- studies with participants in non-clinical range;
- studies of psychosocial interventions not identified or described by the authors;
- single-case studies;
- studies not maintaining psycho-pharmacological treatment throughout the study period;
- studies only reporting follow-up data;
- inpatient or residential treatments

Intervention(s)
Intervention:
- studies in with an untreated control group.
Control:
- studies involving no untreated control group.

Treatments:
- behavioural therapy [BT], cognitive behavioural therapy [CBT],
- BT and CBT in combination,
- family therapy [FT],
- Psychodynamic Therapy [dyn].

Follow-up time:?
Outcome

Primary:
- teacher reported change in aggression, change in social functioning, and changes in parental distress were calculated

Results

The mean effect size (ES) of change in aggression in studies with untreated controls was 0.62 and in studies without untreated controls the ES was 0.95. In studies with or without untreated controls, the ESs in teacher reported aggression was 0.41 and 0.63, the ESs in changes in social functioning was 0.42 and 0.49, and the ESs in changes in parental distress was 0.39 and 0.47, respectively.

From these studies, 32 independent ESS were calculated. The overall design a mean ES was 0.41 and the average overall design ES-2 was 0.63, Both effects were significantly different from 0.

Quality assessment

Question: +
Search: -
Selection: +
Quality assessment:+

Quality of evidence

A2
Conclusion:
- Researchers only searched in PsycINFO.
- There are two anonymous reviewers of the ECAP who have contributed to the quality of the study (through recommendations).

Psychosocial treatments aimed at reducing aggressive behaviour have positive effects and additional treatment effects are moderate. In the moderator analysis, studies with untreated controls obtained significantly larger ESs if the sample size was small. In studies without untreated controls, studies presenting diagnostic information, and studies with younger children resulted in significantly larger ESs, and studies applying behavioural interventions obtained significantly larger ESs as compared to studies applying family therapeutic interventions.

ECAP: European Child and Adolescent Psychiatry; ES: effect size
Hogue e.a. (2008) Treatment adherence, competence, and outcome in individual and family therapy for adolescent behavior problems

<table>
<thead>
<tr>
<th>Study aim</th>
<th>The impact of treatment adherence and therapist competence on treatment outcome in a controlled trial of individual cognitive-behavioral therapy (CBT) and multidimensional family therapy (MDFT) for adolescent substance use and related behavior problems (marijuana use, personal problems related to drug use) up to 6 months after treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>Trial</td>
</tr>
<tr>
<td></td>
<td>Blindness: -</td>
</tr>
<tr>
<td></td>
<td>Analysis: these dependent variables were selected specifically because they had already demonstrated significant outcome effects in the clinical trial from which study cases were drawn.</td>
</tr>
<tr>
<td>Study duration</td>
<td>6 months.</td>
</tr>
<tr>
<td>Setting</td>
<td>Out patients.</td>
</tr>
<tr>
<td>Location</td>
<td>New York?</td>
</tr>
<tr>
<td>Number of patients</td>
<td>N = 136 adolescents (62 CBT, 74 MDFT)</td>
</tr>
<tr>
<td>Patient characteristics</td>
<td>Age: 13-17 years, average age 15.5 years</td>
</tr>
<tr>
<td>Sex</td>
<td>81% male</td>
</tr>
<tr>
<td>Inclusion</td>
<td>Inclusion:</td>
</tr>
<tr>
<td></td>
<td>- cases from an earlier randomized trial were included in the current study if they completed a baseline and post treatment assessment (discharge and/or 6-month follow-up) and at least one videotaped therapy session.</td>
</tr>
<tr>
<td>Baseline characteristics:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- all used drugs;</td>
</tr>
<tr>
<td></td>
<td>- 79% met criteria for ODD and/or CD and 49% for mood and/or anxiety disorder;</td>
</tr>
<tr>
<td></td>
<td>- all youths in the trial were drug users:</td>
</tr>
<tr>
<td></td>
<td>- 75% meeting DSM-IV criteria for cannabis dependence;</td>
</tr>
<tr>
<td></td>
<td>- 13% meeting DSM-IV criteria for cannabis abuse;</td>
</tr>
<tr>
<td></td>
<td>- 20% meeting DSM-IV criteria for alcohol dependence;</td>
</tr>
<tr>
<td></td>
<td>- 4% meeting DSM-IV criteria for alcohol abuse;</td>
</tr>
<tr>
<td></td>
<td>- 13% meeting DSM-IV criteria for other drug dependence;</td>
</tr>
<tr>
<td></td>
<td>- 2% meeting DSM-IV criteria for other drug abuse.</td>
</tr>
<tr>
<td></td>
<td>- some clients met diagnostic criteria for more than one substance use disorder.</td>
</tr>
<tr>
<td></td>
<td>- 79% met criteria for oppositional defiant and/or conduct disorder.</td>
</tr>
<tr>
<td></td>
<td>- 49% met criteria for a mood and/or anxiety disorder</td>
</tr>
</tbody>
</table>
Intervention(s) Intervention:
- cognitive-behavioral therapy (CBT).

Control:
- multidimensional family therapy (MDFT).

Follow-up:
- 6-month follow up.

Therapists were supervised weekly by model experts via live individual supervision, videotape feedback, and group supervision. Both treatments prescribed office-based, weekly sessions conducted over 16-24 weeks.

Participants included an ethnically diverse group of adolescents and families from a large urban area. Parallel fidelity measures were used for both CBT and MDFT, which permitted us to combine all participants into a single analysis to increase power and generalizability.

Outcome Primairy:
- marijuana use frequency: Timeline follow-back. The timeline follow-back measures quantity and frequency of daily consumption of substances by using a calendar and other memory aids to gather retrospective estimates;
- drug use problems: Personal Experience Inventory (PEI);
- externalizing and internalizing symptoms: Child Behavior Checklist (CBCL) and Youth Self-Report (YSR).

Secondary:
- therapist main effects for process and outcome variables.
Results

In CBT, greater levels of adherence predicted greater declines in marijuana use. In CBT and MDFT, stronger adherence predicted greater reductions in parent reports of externalizing behaviors. Also in both conditions, intermediate levels of adherence predicted the largest declines in parent reports of internalizing behaviors, with high and low adherence predicting smaller improvements – a curvilinear (or quadratic) effect on internalizing.

Adherence-outcome effects were small-to-medium in size. Therapist competence was not related to any outcome in either condition, nor did it moderate the impact of adherence on outcome.

Results:
- number of days in past 30 during which the adolescent smoked marijuana, the primary drug of use in this sample. Both conditions, mean number of marijuana use days was 11.9 (SD = 12.5) at baseline, 6.8 (11.9) at post, and 5.2 (8.6) at follow-up;
- both conditions, the mean problem severity score was 28.9 (SD = 17.9) at baseline, 23.6 (19.2) at post, and 19.5 (18.9) at follow-up;
- both conditions, the mean score for CBCL externalizing was 25.5 (SD = 11.9) at baseline, 20.9 (12.7) at post, and 18.6 (12.2) at follow-up;
  - for YSR externalizing, 19.1 (SD= 9.2) at baseline, 17.1 (8.5) at post, and 15.9 (8.9) at follow-up;
  - for CBCL internalizing, 11.5 (SD= 8.0) at baseline, 9.4 (7.9) at post, and 8.1 (8.0) at follow-up.
- Therapist main effects for process and outcome variables. A significant effect was found only for adherence in CBT, F(5, 58) = 4.58, p < .01.
  - Post hoc Scheffe tests identified a mean difference between Therapist 2 (M = 2.51, SD = 0.38) and Therapist 4 (M = 2.03, SD = 0.28).

Quality assessment
Randomisation: +
Allocation concealed: +
Patient and clinician blinded: ?
Assessor blinded: ?
Intervention and control groups were similar: ?
Follow-up: +
Intention-to-treat analysis: ?
Finance: preparation of this article was supported by Grants from the National Institute on Drug Abuse
Quality of evidence B.

- The study found that treatment adherence predicted treatment outcome in manualized behavioral interventions for substance abuse and related behavior problems in urban adolescents. Treatment adherence was linked to improvement in multiple outcomes up to 6 months after discharge.

CBT: cognitive-behavioral therapy; MDFT: multidimensional family therapy; PEI: Personal Experience Inventory

**Kaminski e.a. (2008) A meta-analytic review of components associated with parent training program effectiveness**

<table>
<thead>
<tr>
<th>Study aim</th>
<th>Evaluate parent training programs to enhance behavior and adjustment in children aged 0-7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of studies</td>
<td>77 published evaluations of parent training programs (i.e., programs that included the active acquisition of parenting skills)</td>
</tr>
</tbody>
</table>
| Patient characteristics | Age: 0-7 years old children with early problem behaviors  
Sex: described in table for all studies if there was information about is (more than 50% were boys) |
| Inclusion |  
- programs that were conducted in English and published as an article, book, or book chapter. |
| Exclusion |  
- programs targeted solely to literacy outcomes or intended only to increase parent-child shared reading times and sensorimotor stimulation therapies;  
- programs targeted to parents with developmental disabilities or parents of children with developmental disabilities. |
| Intervention(s) | Prevention or treatment of child behavior problems |
| Outcome | Primary: effect sizes on measures of parenting behaviors and children’s externalizing behavior |
Results

There was a significant, positive overall effect size, supporting the use of such programs in changing parenting behavior and in preventing or ameliorating early child behavior problems. The mean effect size for parenting outcomes appeared larger than the mean effect size for child outcomes; the effect size for parenting behaviors and skills were smaller than the effect sizes for parenting knowledge, attitudes, or self efficacy. Similar patterns have been observed in other meta analyses.

The overall weighted effect size of the final set of 77 studies across all coded outcomes was 0.34 (95% CI=0.29–0.39), reflecting a significant mean difference between treatment and comparison groups at immediate post-test of just larger than a third of a standard deviation.

The Q test of homogeneity of effect sizes was significant (Q [76] = 330.91, p < 0.001)

Quality assessment

Randomisation: +
Allocation concealed: +
patient and clinician Blinded:+
Assessor blinded: +
Intervention and control groups were similar: +
Follow-up: +
Intention-to-treat analysis: +

Quality of evidence

A1

Conclusion: there was a significant, positive overall effect size, supporting the use of parent training programs in changing parenting behavior and in preventing or ameliorating early child behavior problems
<table>
<thead>
<tr>
<th>Study aim</th>
<th>The present study identifies and summarizes treatment effects for children and adolescent conduct problems based on accrued meta-analytic studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>Meta-analyses</td>
</tr>
<tr>
<td>Blindness: blind</td>
<td>Location: Saint Louis University</td>
</tr>
<tr>
<td>Number of studies</td>
<td>$N = 26$ meta-analyses with in total more than 2000 studies</td>
</tr>
<tr>
<td>Number of patients</td>
<td>not described</td>
</tr>
<tr>
<td>Patient characteristics</td>
<td>Age: described in 8 meta-analyses (between 9.7 and &lt; 19 years)</td>
</tr>
<tr>
<td></td>
<td>Sex: described in 3 studies: 85-90% male</td>
</tr>
<tr>
<td>Inclusion</td>
<td>Inclusion of meta-analytic studies of treatments for children and youth antisocial behavior according to the following eligibility criteria:</td>
</tr>
<tr>
<td></td>
<td>– investigations whereby the population, sample, or outcomes are focused on antisocial children and youth;</td>
</tr>
<tr>
<td></td>
<td>– review or synthesis quantitative (i.e., meta-analysis) in nature as opposed to a qualitative review of studies;</td>
</tr>
<tr>
<td></td>
<td>– peer-reviewed investigations;</td>
</tr>
<tr>
<td></td>
<td>– studies targeting adults only if the studies used mixed groups of adults and youth by which we could easily decipher the effects for the children and youth;</td>
</tr>
<tr>
<td></td>
<td>– studies reporting an effect size;</td>
</tr>
<tr>
<td></td>
<td>– studies published in English.</td>
</tr>
<tr>
<td>Exclusion:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– studies that focused specifically on prevention-based treatments for children and youth with conduct problems;</td>
</tr>
<tr>
<td></td>
<td>– meta-analyses that assessed whether one type of treatment component worked better than another without reporting effect sizes or listed a statistically significant coefficient in lieu of an effect size are not included;</td>
</tr>
<tr>
<td></td>
<td>– studies that involved youth with symptoms of attention-deficit/hyperactivity disorder (ADHD) but did not include modulation of any antisocial outcomes are excluded.</td>
</tr>
<tr>
<td>Intervention(s)</td>
<td>Intervention</td>
</tr>
<tr>
<td></td>
<td>Treatments were placed in four types:</td>
</tr>
<tr>
<td></td>
<td>– behavioral or cognitive-behavioral therapy (CBT);</td>
</tr>
<tr>
<td></td>
<td>– family;</td>
</tr>
<tr>
<td></td>
<td>– multimodal;</td>
</tr>
<tr>
<td></td>
<td>– group based, and miscellaneous (e.g., pharmacotherapy).</td>
</tr>
<tr>
<td>Control:</td>
<td>-</td>
</tr>
<tr>
<td>Outcome</td>
<td>Primary: effect sizes for the interventions</td>
</tr>
<tr>
<td>---------</td>
<td>--------------------------------------------</td>
</tr>
<tr>
<td>Results</td>
<td>The majority (45%) of effect sizes was small to medium in magnitude ($d &lt; .36$). In terms of the distribution of effect sizes ($n = 125$), the mean is $d = 0.43$ (SD = 0.32). Although there is considerable variation in effect sizes, the results seem to demonstrate evidence for equifinality. Many treatments are likely capable of working for the same problem. Furthermore, these effects are sturdy across a number of interrelated outcomes. A few summative points are worth noting:</td>
</tr>
<tr>
<td>–</td>
<td>interventions that aggregate negative peers are probably less effective for reducing conduct problems (e.g., recidivism) than those where individuals have access to positive peers;</td>
</tr>
<tr>
<td>–</td>
<td>skills training is important;</td>
</tr>
<tr>
<td>–</td>
<td>politically popular treatments among both policy makers and practitioners are not necessarily effective;</td>
</tr>
<tr>
<td>–</td>
<td>there is a continuum of behavior severity not necessarily captured in these studies that needs to be accounted for in terms of treatment matching</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Quality assessment: +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Search</td>
<td>+</td>
</tr>
<tr>
<td>Selection</td>
<td>+</td>
</tr>
<tr>
<td>Data extraction</td>
<td>+</td>
</tr>
<tr>
<td>Description of original studies</td>
<td>+</td>
</tr>
<tr>
<td>Handling heterogeneity</td>
<td>?</td>
</tr>
<tr>
<td>Statistical pooling</td>
<td>+</td>
</tr>
</tbody>
</table>

Funding/conflicts of interest: this research was conducted thanks to generous support by a grant from the Donald D. Hammill Foundation (a non-profit foundation)

<table>
<thead>
<tr>
<th>Quality of evidence</th>
<th>A1</th>
</tr>
</thead>
</table>
**Lundahl e.a. (2006) A meta-analysis of parent training: moderators and follow-up effects**

<table>
<thead>
<tr>
<th>Study aim</th>
<th>To evaluate the studies about potential of parenting courses to demonstrate that the disturbed behavior of the child changes, but also the behavior of the parents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>Meta-analysis</td>
</tr>
<tr>
<td>Number of studies</td>
<td>N = 63 peer-reviews studies</td>
</tr>
<tr>
<td>Number of patients</td>
<td>Between 11 and 221 per study</td>
</tr>
<tr>
<td>Inclusion</td>
<td>Studies were included if they:</td>
</tr>
<tr>
<td></td>
<td>– reported on parent training programs targeting disruptive child behaviors (but not criminal activity);</td>
</tr>
<tr>
<td></td>
<td>– had at least one treatment and one control group which were drawn from the same population;</td>
</tr>
<tr>
<td></td>
<td>– had treatment and control groups composed of at least five participants;</td>
</tr>
<tr>
<td></td>
<td>– treated families in which the target children were not developmentally or cognitively delayed;</td>
</tr>
<tr>
<td></td>
<td>– involved actual parent training rather than analog procedures or one-time interventions done within a laboratory setting;</td>
</tr>
<tr>
<td></td>
<td>– were published in peer-reviewed sources;</td>
</tr>
<tr>
<td></td>
<td>– reported pre-test and post-test means and standard deviations for both the treatment and control groups;</td>
</tr>
<tr>
<td></td>
<td>– evaluated outcomes beyond satisfaction with the particular parent training program;</td>
</tr>
<tr>
<td></td>
<td>– were written in English</td>
</tr>
<tr>
<td>Intervention(s)</td>
<td>Intervention:</td>
</tr>
<tr>
<td></td>
<td>– parenting training programs. These were group sessions or individual sessions;</td>
</tr>
<tr>
<td></td>
<td>– behavior and non-behavior (aimed at improving parent-child communication patterns) training.</td>
</tr>
<tr>
<td>Control</td>
<td>control treatment.</td>
</tr>
<tr>
<td>Follow-up</td>
<td>– Only 4 studies examined the long-term impact of non-behavioral parent training programs.</td>
</tr>
<tr>
<td></td>
<td>– Of these, 3 provided data on child behavior (d = 0.52) and 3 provided data on parental perceptions (d = 0.04), and no study reported on the long-term impact on parenting behavior.</td>
</tr>
<tr>
<td></td>
<td>Among studies which collected data on the long-term effects of parent training, the average length of follow-up was 7.72 months (n = 56, SD = 8.30)</td>
</tr>
</tbody>
</table>
Data files were constructed crossing the three outcome constructs:
- child behavior;
- parent behavior;
- parental perceptions.

With the two time frames (i.e., immediate and follow-up effects).

Cohen's d as the measure of effect size

Among the three outcome constructs, 68 effect sizes were specific to the child behavior construct, 51 to the parent behavior construct, and 48 to the parental perceptions construct with respective composite d's of 0.42, 0.47, and 0.53 Each overall composite effect size contained significant heterogeneity

Quality assessment

Question: +
Search: -
Selection: +
Quality assessment: +
Data extraction: ?
Description of original studies: +
Handling heterogeneity: +
Statistical pooling: +
Funding/conflicts of interest: -

Quality of evidence

A2.

Conclusions:
- the search strategy missed some important databases;
- parenting training, designed to reduce the disturbed behavior in children, is a powerful intervention with effect sizes of a moderate range after treatment;
- up to 1 year after training the effect is present, though it is a small size.

Individual parental therapy is far superior to group therapy for parents (particularly for families from lower social economical class)

<table>
<thead>
<tr>
<th>Study aim</th>
<th>Extended the findings from previous meta-analytic work by comparing the effectiveness of behavioral parent-training (BPT) and cognitive-behavioral therapy (CBT) for youth with antisocial behavior problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>Meta-analysis</td>
</tr>
<tr>
<td>Number of studies</td>
<td>N = 71 studies were included (31 BPT and 40 CBT studies)</td>
</tr>
<tr>
<td>Number of patients</td>
<td>?</td>
</tr>
<tr>
<td>Patient characteristics</td>
<td>Age: ?</td>
</tr>
<tr>
<td></td>
<td>Sex: ?</td>
</tr>
<tr>
<td>Inclusion</td>
<td>Inclusion criteria:</td>
</tr>
<tr>
<td></td>
<td>– treatment for the benefit of antisocial behavior;</td>
</tr>
<tr>
<td></td>
<td>– article about young people under 18 years;</td>
</tr>
<tr>
<td></td>
<td>– BPT treatment or CBT;</td>
</tr>
<tr>
<td></td>
<td>– BPT or CBT versus treatment or placebo control group;</td>
</tr>
<tr>
<td></td>
<td>– a behavioral interventions for antisocial behavior;</td>
</tr>
<tr>
<td></td>
<td>– sufficient data available to calculate the ESS.</td>
</tr>
<tr>
<td>Exclusion</td>
<td>· focused on hyperactivity or developmental disability;</td>
</tr>
<tr>
<td></td>
<td>· studies focusing exclusively on substance abuse;</td>
</tr>
<tr>
<td></td>
<td>· studies with BPT and CBT was compared with another treatment or no control deviant;</td>
</tr>
<tr>
<td></td>
<td>· studies with insufficient data, or as if results were reported as not significant.</td>
</tr>
<tr>
<td>Intervention(s)</td>
<td>Intervention: BPT and CBT</td>
</tr>
<tr>
<td>Control group</td>
<td>no treatment-placebo-control</td>
</tr>
<tr>
<td>Outcome</td>
<td>– The effects of BPT and CBT for aggressive behavior problems in children and adolescents (measured by ES)</td>
</tr>
<tr>
<td></td>
<td>– Effectiveness of BPT and CBT compared several demographic variables.</td>
</tr>
<tr>
<td></td>
<td>Outcome measures were assessed by parental reports, teacher reports and observation.</td>
</tr>
</tbody>
</table>
Results

BPT:
- BPT ES for post-treatment was 0.47 (CI = .34 -. 61);
- significant heterogeneity between the 30 BPT ESS Q (29) = 50.43 p < .01.

CBT:
- post-treatment ES for CBT was 0.35 (CI = .25-.47);
- significant heterogeneity between the 41 CBT ESS Q (40) = 76.58, p < .01.

Indicates that these interventions are effective for treating aggressive behavior in adolescents.

BPT performed in a clinical setting ES highest average (0.44), followed by CBT in clinical (0.29) and non-clinical (0.21) settings.

CBT shows age-dependent. BPT is not.

BPT may be more effective for younger youth because they are cognitive underdeveloped skills or a high degree of impulsivity and/or low verbal IQ.

Ethnicity and gender are difficult to determine from the trials and are not always mentioned.

Quality assessment

Study question:+
Search: -
Selection:+
Quality assessment:? 
Data extraction: +
Description of original studies: -
Handling heterogeneity: +
Statistical pooling: +
Funding / conflicts of interest: +

Quality of evidence B

- There is clear and clearly described what is done to do the research as discretely as possible.
- Study was conducted among all children with a behavior problem, not only ODD and/or CD, but they described the two disorders in detail.
- BPT performed in a clinical setting ES highest average (0.44), followed by CBT in clinical (0.29) and non-clinical (0.21) settings.
- Not searched in Medline, Cochrane and Embase.
Maughan e.a. (2005) Behavioral parent training as a treatment for externalizing behaviors and disruptive behavior disorders: A meta-analysis

<table>
<thead>
<tr>
<th>Study aim</th>
<th>The effectiveness of behavioral Parenting Training for children and adolescents with externalizing behaviors and disruptive behavior disorders.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>Meta-analysis</td>
</tr>
<tr>
<td>Number of studies</td>
<td>79 studies were included</td>
</tr>
</tbody>
</table>
| Number of patients| 2083 participants for between-group study  
                     1088 participants for the within-group study  
                     1482 single-subject studies                                                                                                   |
| Patient characteristics | Age: children between 3 and 16 years old                                                                                           |
| Inclusion        | Inclusion:  
                     – at least one externalizing behavior;  
                     – treatment procedures had to include the training of parents/caregivers in the use of reinforcement and/or time-out and one additional behavioral procedure;  
                     – at least one outcome measure had to address the child's behavior;  
                     – each study needed to fit into one of three design categories:  
                     – a between subject group design (experimental design with no treatment-control group);  
                     – within subjects-group design (participants in a particular subset of the treatment conditions with repeated measurements taken on at least 2 occasions; pre- and post treatment);  
                     – single-subject design (changes in behavior were documented for an individual participant). |
| Exclusion        | Exclusion:  
                     – studies of children treated primarily for autism or developmental disabilities.                                             |
| Intervention(s)  | Intervention:  
                     – behavioral parent training (BPT).                                                                                           |
| Control          |  
                     · no intervention.                                                                                                            |
| Follow up        | Follow up:  
                     – varies by study. Follow-up results are based on observations and parent reports and took place after the sessions |
| Outcome          | Weighted effect of the different studies                                                                                         |
Results:
- weighted overall effects were:
  - $d = .30$ for between-studies;
  - $d = .68$ for the within-subjects studies;
  - $d = .54$ for the single subject studies.

The overall average weighted effect size using the 'no assumption' method was 1.56.

Conclusion:
- despite the limitations, the results showed that BPT is a successful intervention in the reduction of disturbed behavior in children.

Quality assessment:
- Study question: +
- Search: +
- Selection: +
- Quality assessment: ?
- Data extraction: +
- Description of original studies: -
- Handling heterogeneity: +
- Statistical pooling: +
- Funding/conflicts of interest: +

Quality of evidence:
- A2
- There is no information about the original studies.
- No independence reviewers to assess the articles.


<table>
<thead>
<tr>
<th>Study aim</th>
<th>Improve the long-term outcomes of children with ODD by evaluating interventions that target multiple risk and protective factors and systems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>Randomized controlled trial (RCT)</td>
</tr>
<tr>
<td>Setting:</td>
<td>-</td>
</tr>
<tr>
<td>Location:</td>
<td>participants were recruited from families requesting treatment at the University of Washington Parenting Clinic, a clinic widely known in the region for its treatment of young children with conduct problems</td>
</tr>
<tr>
<td>Number of patients</td>
<td>N = 159 children</td>
</tr>
<tr>
<td>Patient characteristics</td>
<td>4 to 8 year old children mean age 70.99 months</td>
</tr>
<tr>
<td>Sex:</td>
<td>90% boys.</td>
</tr>
</tbody>
</table>
Inclusion: the primary referral problem was child misconduct (e.g., noncompliance, aggression, oppositional behaviors) that had been occurring for at least 6 months; parents reported more than 10 child behavior problems, on the ECBI; the child met DSM-IV criteria for ODD; the child was enrolled in preschool or elementary school.

Exclusion: debilitating physical impairment, intellectual deficit, or history of psychosis; receive any form of psychological treatment at the time of referral.

Baseline characteristics: 26% of the sample attended preschool, 29% kindergarten, 27% first grade, 29% second grade; 79% were Euro-American

Intervention(s): parent training (PT); parent plus teacher training (PT + TT); child training (CT); child plus teacher training (CT + TT); parent, child, plus teacher training (PT + CT + TT); Control: waiting list control group.

Follow-up: 6 months

Outcome: treatment effects for each measure were examined using six-group analysis of covariance; ANCOVA, with pretest scores as covariates for corresponding posttest scores.

Secondary: conducted planned comparisons (on post scores adjusted for pretest scores) contrasting each treatment condition with the control condition.
Results

The six-group ANCOVA revealed significant experimental effects for:

- the mother negative parenting composite score: $F(5, 151) = 7.26, p < .001$;
- the father negative parenting composite score: $F(5,108) = 6.65, p < .001$;
- the mother positive parenting composite score: $F(5, 151) = 3.29, p < .01$;
- the father positive parenting composite score, $F(5, 110) = 2.37, p < .05$.

Each of the treatments led to expected changes (i.e., PT improved parent behavior, CT improved peer social skills and children’s behavior in the classroom, and TT improved teacher behavior). Spillover effects, particularly for the CT group (i.e., there were positive effects in the behaviors of parents and teachers of children who received CT only). Based on this study, it seems that combining PT with either CT or TT may be the most potent treatment for children with pervasive behavior problems.

Quality assessment

Randomisation: +
Allocation concealed: -
Patient and clinician Blinded: ?
Assessor blinded: +
Intervention and control groups were similar: +
Follow-up: +
Intention-to-treat:?

Finance: NIH National Center for Nursing Research Grant and Research Scientist Development Award from the National Institute of Mental Health

Quality of evidence

B

ANCOVA: analysis of covariance; CT: child training; PT: parent training; TT: teacher training
### Bewijstabellen bij hoofdstuk 6.3, Farmacologische behandeling

Voor de volledige literatuurbeschrijvingen van de onderzoeken, zie hoofdstuk 6.3, literatuur.

<table>
<thead>
<tr>
<th><strong>Biederman e.a. (2007) Effect of comorbid symptoms of oppositional defiant disorder on responses to atomoxetine in children with ADHD: A meta-analysis of controlled clinical trial data</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study aim</strong></td>
</tr>
<tr>
<td><strong>Study design</strong></td>
</tr>
<tr>
<td>Blinded: double blind</td>
</tr>
<tr>
<td>Analysis: meta-analysis (?)</td>
</tr>
<tr>
<td><strong>Number of studies</strong></td>
</tr>
<tr>
<td><strong>No ODD/CD as primary disorder. Children with ADHD, some have as comorbid ODD</strong></td>
</tr>
<tr>
<td><strong>Number of patients</strong></td>
</tr>
<tr>
<td><strong>158 were diagnosed with comorbid ODD (30,9%)</strong></td>
</tr>
<tr>
<td><strong>Patient characteristics</strong></td>
</tr>
<tr>
<td>Sex ratio: 139 girls</td>
</tr>
<tr>
<td><strong>Inclusion</strong></td>
</tr>
<tr>
<td>– Required to have a symptom severity score that was at least 1.0 standard deviations above age and sex norms on the ADHDRS-IV parent version.</td>
</tr>
<tr>
<td>– Assessed for lifetime psychiatric disorders, including ODD, by clinical history and structured interview, using the K-SADS-PL.</td>
</tr>
<tr>
<td>– IQ &gt; 80.</td>
</tr>
<tr>
<td><strong>Intervention(s)</strong></td>
</tr>
<tr>
<td>– atomoxetine once daily up to 1.8 mg/kg/day.</td>
</tr>
<tr>
<td>– In 2 of the 3 studies: atomoxetine maximum could increase to 1.2 mg/kg/day.</td>
</tr>
<tr>
<td>– in the other study: atomoxetine maximum could increased to 1.5-1.8 mg/kg/day.</td>
</tr>
<tr>
<td><strong>Control:</strong></td>
</tr>
<tr>
<td>– placebo.</td>
</tr>
<tr>
<td><strong>Follow-up (length):</strong></td>
</tr>
<tr>
<td>– 6 to 8 weeks</td>
</tr>
</tbody>
</table>
Outcome

Outcome:
– Effect of the presence of comorbid ODD symptoms on clinical outcomes with atomoxetine.

Researchers hypothesized that:
– treatment with atomoxetine will improve;
– symptoms of ADHD in children with and without comorbid ODD;
– higher daily doses of atomoxetine will be needed to treat children with ADHD and comorbid ODD;
– treatment with atomoxetine will improve symptoms of ODD in ADHD children with comorbid ODD.

Outcome measure:
– ADHDRS-IV, which comprises the 18 DSM-IV ADHD items, each rated 0-3 by the investigator, based on a semi-structured interview with parents (or primary caregivers) in two studies and with teachers in one study;
– Conners’ Parent RS, revised; which includes a subscale assessing oppositional behavior, and the CGI-S, keyed to ADHD severity (CGI-ADHD-S);
– Child Health Questionnaire (CHQ);
– a parent-rated health outcome scale

Results

ADHD with/without ODD:
– atomoxetine treatment significant reductions from baseline on the CPRS-R:S.

ODD-comorbid or non-comorbid subgroups:
– no significant treatment difference was seen.

Number of categorical responders in the ADHD and ODD domains (as defined by ≥ 25% reduction in symptoms):
– ADHD: 21.9% for the placebo group and 50% for the atomoxetine group;
– ODD: 31.3% for the placebo group and 50% for the atomoxetine group.

Modal daily doses were not statistically significantly different between ODD-comorbid and non-comorbid subjects taking atomoxetine
(ODD-comorbid: mean (SD) = 1.24 (0.37) mg/kg, median = 1.25 mg/kg;
non-comorbid: mean (SD) = 1.25 (0.36) mg/kg, median = 1.25 mg/kg)
Quality assessment

Study question: +
Search: ?
Selection:
- It is not described why the researchers selected these three articles.
Quality assessment: no information
Data-extraction: they showed different outcomes in tables.
They used: ADHDRS-IV; CGI-ADHD-S; CHQ, Parent rated health outcome scale.
Description of original studies: not much information
Handling heterogeneity: ?
- This is a methodological limitation: heterogeneity may have been introduced into the sample of convenience by virtue of differences in the inclusion criteria among the three studies from which data were pooled.
Statistical pooling: ?
Funding/conflicts of interest: Eli Lilly and Company

Quality of evidence

B
- It’s not clear why they took these three trials. No search described.
- Eli Lilly (pharmacist) funded the research.
- Different results calculated with different instruments.

ADHDRS-IV: ADHD Rating Scale-IV [parent ratings regarding the frequency of each ADHD symptom based on DSM-IV criteria]; CGI-ADHD-S: CHQ: Clinical Global Impressions-ADHD-Severity; CHQ: child health questionnaire; CPRS-R:S: Conners’ Parent Rating Scale, Revised: Short Form; K-SADS-PL: Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version
Connor e.a. (2006) Juvenile maladaptive aggression: A review of prevention, treatment, and service configuration and a proposed research agenda

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>154 trails, over psychosociale behandeling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient characteristics</td>
<td>Kinderen en adolescenten met agressief gedrag, CD, antisociaal gedrag en gewelddadig gedrag</td>
</tr>
<tr>
<td>Intervention(s)</td>
<td>Psychosociale en psychofarmacologische interventies. Medicatie in de onderzoeken naar farmacotherapie: lithium, carbamazepine, divalproex, risperidon, methylfenidaat, clomipramine, clonidine, valproaat, molindone, haloperidol</td>
</tr>
</tbody>
</table>
| Results | Er is uitsluitend een effectgrootte weergegeven:  
- psychosociale behandeling: effectgroottes variëren van 0,4 tot 0,9, afhankelijk van behandeling, leeftijd en termijn;  
- farmacologische artikelen: 2 meta-analyses van medicatie effecten van kinderen en adolescenten met heterogene diagnoses, effectgrootte varieert van 0,44 tot 3,0.  
Preventieprogramma's geven een vermindering aan van agressie in de risicovolle groep.  
Conclusies over farmacotherapie:  
- psychotherapeutische medicatie: 3 langetermijnonderzoeken duidden erop dat risperidon goed verdragen werd en zorgde voor effect bij kinderen met een onder gemiddeld IQ (tot 52 weken). De andere studie geeft ook positieve, robuuste effecten weer bij onaangepast gedrag bij kinderen;  
- bij olanzapine, quetiapine, ziprasidon en aripiprazol (atypische antipsychotica) hebben agressieve kinderen en adolescenten hun gedrag meer onder controle;  
- neuroleptica: effectief in reduceren van agressie molindon en haloperidol;  
- stemmingsstabilisatoren: bij lithium en divalproexsodium effectieve vermindering van agressie;  
- gecontroleerde onderzoeken indienen dat stemmingsstabilisatoren meer effectief zijn voor het reduceren van explosief gedrag in CD dan behandeling van early-onset bipolaire stoornissen;  
- verder onderzoek naar agressief gedrag bij kinderen en adolescenten is belangrijk voor de kinder- en jeugdpsychiatrie |

Study design
Review van 17 placebogecontroleerde onderzoeken en 6 open trials over alle bekende farmacotherapeutische interventies bij CD.
Follow-upduur: variabel

Number of patients
De onderzoeken betroffen minstens 8 patiënten, gemiddeld of benedengemiddeld intelligent, CD als (gedeelde) diagnose; ook comorbide stoornissen zoals Pervasive Developmental Disorder - Not Otherwise Specified (PDD-NOS) konden aanwezig zijn.
Enkel placebogecontroleerde resultaten werden weergegeven in tabellen (van de overige onderzoeken werden geen kenmerken gepresenteerd)

Intervention(s)
Toedienen van stemmingsstabilisatoren, antipsychotica of stimulantia

Outcome Results
Variabele meetlijsten
Lithium (tabel 1, p. 364):
- Campbel e.a. (1984) Haloperidol = lithium > placebo (meetlijsten: CPRS, CGI, CTQ, CPTQ, GCJ);
- Campbel e.a. (1995) Lithium > placebo (meetlijsten: GCJCS, CGI, CPRS, CTQ, CPTQ, POMS);
- Rifkin e.a. (1997) Lithium = placebo (meetlijsten: HDRS, OAS, BRS, CTRS, ADO/H Adolescent Self Report Rating Scale);
Lithium is de best gedocumenteerde medicatie voor CD bij jongeren (wordt niet onderbouwd door bronvermelding). Er zijn verscheidene placebogecontroleerde onderzoeken die aangetoond hebben dat lithium effectief is ter behandeling van agressie, met minder bijwerkingen dan antipsychotica (geen bronnen genoemd). Qua bijwerkingen is er weinig bekend. Sommige menen dat er sprake is van langetermijnveiligheid. Anderen menen dat er te weinig bekend is van de bijwerkingen bij gebruik op dergelijk jonge leeftijd.
Antipsychotica (tabel 2, p. 365):
- Broche (1980) Pimozide > placebo (meetlijst: authors behaviour scale);
- Campbel e.a. (1984) haloperidol = lithium > placebo (meetlijsten: CPRS, CGI, CTQ, CPTQ, GCJ);
- Greenhill e.a. (1985) thioridazine = molindone > placebo (meetlijsten: CPRS, CRS, DOTES, CTQ, CGI, IAS);
- Finding e.a. (2000) risperidon > placebo (meetlijsten: RAAPP, CGI, CPRS, CBCL);

Stimulantia (tabel 3, p. 365):
- Kaplan e.a. (1990) methylfenidaat > placebo (meetlijsten: AABC, CTRS);
- Gadow e.a. (1990) methylfenidaat > placebo (meetlijsten: classroom observation);
- Hinshaw e.a. (1992) methylfenidaat > placebo (meetlijsten: CBCL, personal behavioural measures);
- Klein e.a. (1997) methylfenidaat > placebo (meetlijsten: CPTQ, QBC);
- Kolko e.a. (1999) methylfenidaat (low dose = high dose) > placebo (meetlijsten: abbreviated-CRS, OAS);
- Connor (2000) methylfenidaat = clonidine = both (meetlijsten: DBS, APRS, HSQ, SSQ, GDS, GBP).

Onderzoeken zoals die van Klein en Hinshaw tonen aan dat methylfenidaat de symptomen van CD verbetert in geval van comorbiditeit van ADHD en CD. Oudere onderzoeken gaven negatieve resultaten (geen bronvermelding).

Klein toonde aan dat de symptomen van CD verbeterden zelfs zonder de aanwezigheid van ADHD.

Quality of evidence D

AABC: Adolescent Antisocial Behavior Checklist; APRS: Academic Performance Rating Scale; CGI: Clinical Global Impressions [Scale]; BRS: Behavior Rating Scale; CRS: Conners’ Rating Scale; CPRS: Conners’ Parent Rating Scale; CPTQ: Conners’ Parent Teacher Questionnaire; CTQ: Conners’ Teacher Questionnaire; CTRS: Conners’ Teacher Rating Scale; DBS: Disruptive Behavior Scale; DOTES: Dosage Record and Treatment Emergent Symptom Scale; GBP: gabapentine; GCJCS: Global Clinical Judgments (Consensus) Scale; GDS: Gordon Diagnostic System; HDRS: Hamilton Depression Rating Scale; HSQ: Home Situations Questionnaire; IAS: Inpatient Aggression Scale; OAS: Overt Aggression Scale; QBC: Quay revised Behavior Checklist; SSQ: School Situations Questionnaire.
### Greenhill e.a. (2006) Efficacy and safety of immediate-release methylphenidate treatment for preschoolers with ADHD

**Study aim**
To determine the efficacy and safety of immediate-release methylphenidate (MPH-IR), given three times a day to children ages 3 to 5.5 years with attention-deficit/hyperactivity disorder (ADHD).

**Study design**
The 8-phase, 70-week PATS protocol included two double-blind, controlled phases, a crossover-titration trial followed by a placebo-controlled parallel trial.

Blinding: double blind.

Analysis: intention-to-treat.

Duration of the study: 70-week.

Setting: from clinics, paid and public service advertisements in newspapers and on the radio, primary care physicians, nursery schools, day care centers, and kindergartens.

Location: six academic sites (Columbia University, Duke University, Johns Hopkins University, New York University, University of California, Irvine, and University of California, Los Angeles)

**Number of patients**
Of 303 preschoolers enrolled, 165 were randomized into the titration trial.

**Patient characteristics**
Age: 3 to 5.5 years old

Sex ratio titration trial: 76% male

**Inclusion**
- children of both sexes;
- ages 3 to 5.5 years;
- with a DSM-IV consensus diagnosis of ADHD;
- hyperactive-impulsive subscale T score of 65 (1.5 SDs above the age- and sex-adjusted means) on both the Revised Conners’ Parent and Teacher Rating Scales;
- IQ >70; participation in a preschool, day care group setting, or other school program at least 2 half-days per week with at least eight same-age peers; and the same primary caretaker for at least 6 months before screening.

**Exclusion**
- When there was current evidence of adjustment disorder, pervasive developmental disorders, psychosis, significant suicidality, or other psychiatric disorder in addition to ADHD that required treatment with additional medication; current stimulant or cocaine abuse in a relative living in the home; a confounding medical condition; inability of the parent to understand or follow study instructions, or history of bipolar disorder in both biological parents.
Intervention(s) Intervention:
- methylphenidate immediate release (MPH-IR): 1.25, 2.5, 5.0, or 7.5 mg.
Control:
- placebo.
Duration of follow-up:
- 70 weeks.
Outcome
The primary outcome measure for the crossover phase was the combined parent-teacher scalar report using the CLAM/SKAMP.
The primary outcome measure for the parallel group phase of the study was excellent responder status, a binary response variable, defined using the SNAP.
Results
During the crossover-titration, random-coefficient regression analyses of composite SKAMP/CLAM scores identified a statistically significant linear trend with dose. Significant decreases in ADHD symptoms were found on MPH at 2.5 mg (p < .01), 5 mg (p < .001) and 7.5 mg (p < .001) three times a day doses, but not for 1.25 mg (p < .06); all compared to placebo.
Effect sizes for MPH during titration with doses of 1.25, 2.5, 5, and 7.5 mg three times a day were 0.16, 0.34, 0.43, and 0.72, respectively.
Only 13/61 (22%) of subjects randomized to best-dose MPH and 7/53 (13%) of those randomized to placebo met criteria for excellent response on the SNAP composite score, a difference that did not reach statistical significance.
Effect sizes for MPH doses during the parallel phase (1.25, 2.5, 5, and 7.5 mg versus placebo) were 0.22, 0.48, 0.52, and 0.87, respectively.
The mean optimal MPH total daily dose for the entire group was $14.2 \pm 8.1$ mg/day ($0.7 \pm 0.4$ mg/kg/day).
Effect sizes (0.4-0.8) were smaller for the pre-school children than those cited for school-age children on the same medication.

Quality assessment
Follow-up: +
- 165 children entered the multisite trial.
Intention-to-treat analysis: +
- all analyses were run using the intent-to-treat principle.
Finance: this research was supported by a cooperative agreement between the National Institute of Mental Health and the 6 universities

Quality of evidence
A2
- This is a trail with ADHD children, no specific ODD/CD.
- PATS data suggest that preschoolers with ADHD need to start with low MPH doses. Treatment may best begin using MPH-IR at 2.5 mg twice a day and then be increased to 7.5 mg three times a day during the course of 1 week. The mean optimal total daily MPH dose for preschoolers was $14.2 \pm 8.1$ mg/day, lower than the mean found in school-age children in the MTA study.
CLAM: Conners, Loney and Milich Rating Scale; MPH-IR: immediate-release methylphenidate; PATS: Preschoolers with Attention Deficit/Hyperactivity Disorder (ADHD) Treatment Study; SKAMP: Swanson, Kotkin, Agler, M-Flynn and Pelham Scale; SNAP: Swanson, Nolan, and Pelham Questionnaire


<table>
<thead>
<tr>
<th>Study design</th>
<th>Meta-analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of studies</td>
<td>N = 14</td>
</tr>
<tr>
<td>Number of patients</td>
<td>N = 823</td>
</tr>
<tr>
<td>Inclusion</td>
<td>Inclusion/exclusion:</td>
</tr>
</tbody>
</table>

- pediatric disruptive behavior disorders;
- the presence of comorbid substance use, depression, hyperkinetic conduct disorder (in which features of both hyperkinetic disorder and conduct disorder are present), or ADHD were not used as exclusion criteria;
- sub-average IQs were included, provided the majority of the sample was dopamine antagonist thioridazine (one trial each). Only one trial included a comparison of medication with psychotherapy not diagnosed with mental retardation (IQ ≤ 70);
- diagnosis of hyperkinetic disorder were excluded from the meta-analysis, as were trials in which an augmenting medication was used in addition to the medication under study;
- a brief review of pediatric impulse control disorders, given the observation that both DBDs and impulse control disorders may be characterized by the poor control of impulsive behavior

Intervention(s) The trials included in the meta-analysis tested the following medications:

- stimulants (three methylphenidate, one mixed amphetamine salts extended release, one pemoline);
- antipsychotics (one haloperidol, one molindone, two risperidone);
- lithium (four trials);
- anticonvulsants (one carbamazepine, one divalproex);
- selective adrenergic agonist clonidine and the dopamine antagonist thioridazine (one trial each);
- only one trial included a comparison of medication with psychotherapy.

Placebo controlled

Follow-up:

- 4 to 12 weeks.
Outcome

Primary:
- treatment response (CGI-I).

Secondary:
- reduction off aggression.

Results

Lithium vs. placebo (N = 2, RR = 4.22, 95%CI = 1.83-9.74; n = 90).
Risperidone was effective in reducing overall symptom severity by 2.19 points on the CGI-S (N = 2, 95%-CI=−3.07 to −1.31; n=58.
There was limited evidence for the effectiveness of medication in reducing aggression (N = 4, SMD = −1.93, 95%-CI = −3.88 to 0.02, n = 172) despite significant variation in the efficacy of the different agents.
The tendency of medication to reduce aggression was largely attributable to the reduction of aggression scores in the single trial of methylphenidate.
There is little evidence of the effectiveness of other stimulants besides methylphenidate in treating disruptive behavior disorders.

Quality assessment

Study question: +
Search: -/+  
Selection: +  
Quality assessment: +  
Data extraction: ?  
Description of original studies: ?  
Handling heterogeneity : +  
Statistical pooling: +

Quality of evidence

A2

CGI-I: Clinical Global Impression, Global Improvement; CGI-S: Clinical Global Impression of Severity; CI: confidence interval [betrouwbaarheidsinterval] RR: risk ratio [relatieve risico]; SMD: standardized mean difference

Klein e.a. (1997) Clinical efficacy of methylphenidate in conduct disorder with and without attention deficit hyperactivity disorder

Study design
Het onderzoeksproject duurde 3 jaar. 297 patiënten werden verwezen; 62 hebben de behandeling niet voortgezet. (20 weigerden medicatie). 151 beantwoorden niet aan de inclusiecriteria. Bij start van uiteindelijke studie was N = 84. De duur van het onderzoek was 5 weken.

Number of patients
N = 84

Patient characteristics
Leeftijd: 6-15 jaar, schoolgaand, IQ > 70, medisch gezond, niet psychotisch, sporadisch gebruik van onwettige drugs was toegestaan, exclusie: middelengebruik

Inclusion
(Zie Patient characteristics)
Intervention(s) Interventie:
- methylfenidaat (N = 41);
- 1 patiënt stopte met het onderzoek voor de start van de behandeling;
- Verenigde Staten;
- duur: 5 weken.
- Einde van onderzoek methylfenidaat: N = 37;
- Op het einde van de studie was de gemiddelde dosis methylfenidaat: 41,3mg/d (1,0mg/kg), De ochtend- en middaggift waren ongeveer gelijk, wanneer verschillend scheelden ze maximaal 5mg
- bijwerkingen: 84% (31/37).
- Slechts bij enkelen was het vertraagd in slapen ernstig.

Placebo:
- N = 42;
- duur: 5 weken;
- einde van studie placebo N=37;
- bijwerkingen bij 46% v/d patiënten.

Outcome Zowel ouders, onderwijzers als onderzoekers werden betrokken bij de observatie

Results De symptomen van de CD reageren op kortwerkend methylfenidaat (1mg/kg). Er trad een significante vermindering op bij verschillende onderdelen van antisociaal gedrag. verschillende De effecten van het kortwerkende methylfenidaat op de verschillende aspecten van de CD zijn niet afhankelijk van de ernst van de ADHD-symptomen

Quality assessment 69% van de patiënten hadden ADHD en CD.

Reden (?): hetzij combinatie is bijna standaard, hetzij combinatie betreft patiënten die zich gemakkelijker laten verwijzen voor behandeling. Het onderzoek werd gedeeltelijk ondersteund door Public Health Service Grant MH-35779, National Institute of Mental Health, Rockville.

Quality of evidence A2

<table>
<thead>
<tr>
<th>Study aim</th>
<th>Assessing the efficacy of atomoxetine in preventing relapse in pediatric patients with ADHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>Double blind, placebo-controlled study.</td>
</tr>
<tr>
<td></td>
<td>Blinding: double blind.</td>
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<tr>
<td></td>
<td>Analysis: ITT.</td>
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<tr>
<td></td>
<td>Duration: 12 weeks and after that 9 months.</td>
</tr>
<tr>
<td>Setting:</td>
<td>33 academic investigative centers.</td>
</tr>
<tr>
<td>Locations:</td>
<td>Europe, Israel, South Africa and Australia</td>
</tr>
<tr>
<td>Patient characteristics</td>
<td>Clinical history and confirmed by a structured interview</td>
</tr>
<tr>
<td>Inclusion:</td>
<td>Symptom severity was at least 1.5 SD above U.S. age and gender norms.</td>
</tr>
<tr>
<td>Exclusion:</td>
<td>- patients with bipolar disorder or a psychotic illness;</td>
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<td></td>
<td>- patients with a condition that would require ongoing administration</td>
</tr>
<tr>
<td></td>
<td>of a psychoactive medication (beside atomoxetine) during the study</td>
</tr>
<tr>
<td>Intervention(s):</td>
<td>Children and adolescents who responded to an initial 12-week, open label period of treatment</td>
</tr>
<tr>
<td></td>
<td>with atomoxetine, were randomized to continued atomoxetine or placebo treatment for 9 months.</td>
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<tr>
<td></td>
<td>Patients who relapsed during the double blind portion of the study, were removed from the</td>
</tr>
<tr>
<td></td>
<td>study and offered the option of entering an open-label extension study that would allow them</td>
</tr>
<tr>
<td></td>
<td>to continue to receive treatment with atomoxetine.</td>
</tr>
<tr>
<td>Outcome:</td>
<td>Primary outcome: Symptom reduction of at least 25%.</td>
</tr>
<tr>
<td></td>
<td>Secondary outcome: Quality of Life measures.</td>
</tr>
<tr>
<td>Results:</td>
<td>Symptom severity:</td>
</tr>
<tr>
<td></td>
<td>- proportion relapsing; atomoxetine: 65 of 292; 22.3%;</td>
</tr>
<tr>
<td></td>
<td>- placebo 47 of 124, 37.9%.</td>
</tr>
<tr>
<td></td>
<td>Patients with a 50% worsening in symptoms post randomized:</td>
</tr>
<tr>
<td></td>
<td>- atomoxetine: 83 of 292, 28.4%. placebo: 59 of 124, 47.6%.</td>
</tr>
<tr>
<td></td>
<td>Atomoxetine-treated patients had better psychosocial functioning at end point.</td>
</tr>
<tr>
<td></td>
<td>Discontinuation for adverse events was low in both groups and tolerability was similar</td>
</tr>
<tr>
<td>Quality assessment</td>
<td>Blindness: +</td>
</tr>
<tr>
<td></td>
<td>Intervention and control group comparability: +</td>
</tr>
<tr>
<td></td>
<td>Follow-up: +</td>
</tr>
<tr>
<td></td>
<td>Intention-to-treat analysis: +</td>
</tr>
<tr>
<td>Financing:</td>
<td>Eli Lilly and Company</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>A2</td>
</tr>
<tr>
<td></td>
<td>- It looks like this is a well-conducted RCT (double blind), but it is risky that it is</td>
</tr>
<tr>
<td></td>
<td>funded by a pharmacist</td>
</tr>
</tbody>
</table>

ITT: intent-to-treat; RCT: randomized controlled trial
Bewijstabellen bij hoofdstuk 6.3, Farmacologische behandeling

Tcherenissine & Lieving (2006) Pharmacological aspects of the treatment of conduct disorder in children and adolescents

Study design
Overzichtsartikel van verschillende psychofarmaca bij CD. Bij elke psychofarmacologische interventies worden de verschillende onderzoeken beschreven, met de uitkomst.

Number of patients
Variabel, zie Results.

Patient characteristics
Variabel, zie Results.

Intervention(s)
Variabel, zie Results.

Results
Zie tekst onder tabel

Quality of evidence
A2

DBD-NOS: disruptive behavior disorder not otherwise specified [gedragsstoornis niet anderszins omschreven]; NCBRF: Nisonger Child Behavior Rating Form; RAAPP: Rating of Aggression Against People and/or Property

Antipsychotica

1. Klassieke antipsychotica
   – Molindon en thioridazide:
     SD: Double-blind, 8 weken, N = 31 gehospitaliseerde kinderen (6j-11j).
     Uitkomstmaat: Conners’ Rating Scale, the Inpatient Aggression Scale, Children’s Psychiatric Rating Scale.
     Uitkomst: Allebei gelijkwaardige goede effecten. Geen placebo controle, dus er kan niet besloten worden tot klinische relevante effectiviteit. Bijwerkingoproef verschilde significant met meer sedatie voor de kinderen behandeld met thioridazine.
   – Haloperidol (1mg tot 6mg/dag), lithium n (500-2000mg/dag) en placebo:
     SD: Double-blind, Placebo controlled, N = 61 behandelresistente, gehospitaliseerde kinderen (5,2j-2,9j)
     Uitkomstmaat: verschillende rating scales in verschillende settings
     Uitkomst: haloperidol en lithium significant beter dan placebo voor de afname van gedragsproblemen. Haloperidol was meer geassocieerd met bijwerkingen dan lithium.

2. Atypische antipsychotica (overzicht tabel 1, p 553)
   – Er is in toenemende mate evidentie voor de effectiviteit van atypische antipsychotica als eerstelijnsbehandeling voor gedragsstoornissen in bij patiënten zonder psychotische stoornis.
   – Risperidon:


Er is een groot placebogecontroleerd onderzoek gedaan naar de onderhoudsbehandeling met risperidon bij gedragsstoornissen (CD, ODD en DBD-NOS) bij kinderen en jongeren (Reyes e.a. (2006)). 527 patiënten (van 5-17 jaar) starten in een open label trial. 436 patiënten die reageerden op de behandeling met risperidon gingen verder in de volgende fase van het onderzoek: single blind behandeling voor de duur van 6 weken. 335 patiënten die een blijvende response hadden op de behandeling starten in de dubbel blinde fase van het onderzoek. De meetlijsten waren: CGI-I en de NCBRF, subschema ‘Conduct Disorder’. Uit de resultaten bleek dat het heroptreden van de symptomen significant vertraagd werd bij patiënten die initieel goed reageerden op de medicatie en de behandeling continueerden gedurende langere tijd.

– Aripiprazol:
  voorlopige resultaten suggereren dat aripiprazole de symptomen van een gedragsstoornis verbeteren bij kinderen en adolescenten.

– Olanzapine:
  60,9% van de patiënten reageerde positief op behandeling blijkt uit resultaten van retrospectief onderzoek. Met name het impulsieve-affectieve type van agressie was een voorspeller voor goed gevolg.

Stemmingsstabilisatoren

– Lithium:
  er is een groeiende evidentie dat voor de effectiviteit en tolerabiliteit van lithium bij de pediatrische populatie met gedragsstoornissen.
Twee RCT-PC-onderzoeken (Campbell e.a., 1995; Malone e.a., 2000). Litium was klinisch en statistisch superieur aan placebo, ook in soms zeer agressieve kinderen met CD. Alhoewel lithium goed werd verdragen waren er bijwerkingen: misselijkheid, overgeven en toegenomen urineren. Deze resultaten werden niet bevestigd bij adolescenten (Rifkin e.a. (1997)). Lithium verbeterde de symptomen niet tegenover placebo.

- Valproaat/ divalproexsodium:
  Donovan e.a. (1997), toonden met een open-labelonderzoek aan dat er verbetering optrad na behandeling van 10 adolescenten met valproaatsodium. Nadien werd een open label, double blind placebo controlled studie uitgevoerd met 20 jongeren tussen 10-18 jaar (crossoverdesign 2 maal 6 weken). Deze werden gekenmerkt door DBD en stemmingslabiliteit. Uiteindelijke dosis was 750-1.500 mg/dag. 5 patiënten vielen uit. Meetlijsten: Modified OAS, Symptom checklist-90 (anger hostility subscale). Bevinding: klinische significante verbetering na 6 weken behandeling. Aanwijzingen voor een significante dosisafhankelijke verbetering op de impulscontrole en zelfbeheersing. Dit werd zowel door clinici als patiënten gescoord na een RCT met divalproexsodium. (Steiner e.a. 2003, N=71 (13 patiënten stoppen); duur: 7 weken). Het betrof een RCT met een low dose group (125 mg/dag tot 250 mg/dag) en een high dose group (gemiddeld 1.000 mg/dag met variatie tussen 500 mg-1.500 mg)

- Carbamazepine:
  1 placebo-controlled, double blind studie (Cueva et al.1996) voor de duur van 6 week plus 1 week post-treatmentplacebo. Carbamazepine bleek niet superieur tegenover placebo.

**Antidepressiva**

Opmerking over de onderzoeken naar antidepressiva: vooral open-labeltrials!

- Trazodon
  Zubieta e.a. (1992). 1 open label trial bij gehospitaliseerde kinderen met de diagnose DBD. Gemiddelde leeftijd: 9 jaar (5-12 jaar); gemiddelde dosering: 241mg/dag (100-800mg/dag). 67% (n = 13) toonde verbetering op agressief en impulsvies symptomen. Bij follow up (gemiddeld 8,8 maanden (3-14 maand)) bleef het effect aanhouden.

- Fluoxetine:
  Riggs e.a. (1997) Open label, 8 patiënten (14 – 18 jaar) met CD, major depression en substance abuse disorder, dosis 20mg, duur: 7 weken. Uitkomst: 7/8 toonden duidelijke verbetering op de CGI-severity of Illness scale alsook op de afgenomen meetlijsten voor depressieve stoornis.

- Citalopram:
  Armenteros e.a. (2002) Open label trial (N=12), leeftijd gemiddeld: 10,22 (7-12 jaar), duur: 6 weken. Dosis start 10 mg per dag, gemiddeld 27mg (20-40 mg/dag). Er werd een significante verbetering gezien in openlijke agressie zowel door clinici als ouders. Bijwerkingen, 4 hadden milde klachten van slapeligheid, hoofdpijn, duizeligheid en nachtmerries.
- **Bupropon:**

- **Reboxetine:**

**Stimulantia**

- **D-amfetamine:**
  Eisenberg e.a. (1963) double blind, placebo controlled 28 geïnstitutionaliseerde mannelijke delinquent jongeren. Alle 14 jongeren die d-amfetamine hadden een significant positief effect volgens leerkrachten, bewakers en familie.

- **Methylfenidaat:**
  Kaplan e.a. (1990) cross-over studie gedurende 7 weken met 9 adolescenten (13-16jaar) met ADHD en CD. Methylfenidaat 30mg. Resultaat: significant minderen van de Adolescent Antisocial Behaviour Checklist.
  Klein e.a. (1997) gerandomiseerd waarbij ze of methylfenidaat of placebo ontvingen. Duur 5 weken, 83 kinderen (6-15jaar) met CD, 69% had ADHD. Gedrag werd geëvalueerd door ouders, leerkrachten, clinici en directe klas observaties. Resultaat: de frequentie van gedrag specifiek voor gedragstoornissen lag niet in het verlengde van de ernst van de ADHD symptomatologie. Er was dus geen relatie tussen de ernst van de ADHD en de verbetering in gedrag specifiek voor de CD.
  Kolko e.a. (1999) verkreeg gelijkwaardige resultaten in zijn placebo controlled, cross-over designed onderzoek waarbij methylfenidaat werd vergeleken met gedragsbeïnvloeding bij kinderen gediagnosticeerd met ADHD en CD/ODD. N = 16, deels gehospitaliseerd, leeftijd: 6,9-12,9, duur studie: 6 weken. Pas na drie weken studie werd begonnen met methylfenidaat. Er werden drie groepen vergeleken: placebo, lage dosis (0,3 mg/kg/dag) en hoge dosis (0,6 mg/kg/dag). De effecten werden gemeten via de OAS. Significante verschillen werden gemeten tussen methylfenidaat en placebo betreffende de OAS. Methylfenidaat leidde ook tot vermindering in negatief gedrag.
  Connor e.a. (2000) vergeleken in een 3 maand durende RCT (doubleblind, geen placebo) onderzoek de effectiviteit en tolerabiliteit van methylfenidaat, clonidine en de combinatie methylfenidaat-clonidine. Het betrof een onderzoek bij kinderen met ADHD met comorbiditeit voor agressieve ODD of CD, 8 deelnemers per groep.
Alle drie de groepen waren klinisch effectief, gemeten door ouders, en leerkrachten en via onderzoeksmateriaal. Clonidine en de combinatie methylfenidaat/clonidine werden door de onderzoekers als effectief bevonden voor de behandeling de combinatie ADHD en agressieve ODD/CD.

**Alpha-adrenerge medicatie**
- Clonidine:
  Hazel en Stuart (2003) RCT-PC onderzoek waarbij clonidine dan wel placebo werd toegevoegd aan een lopende behandeling middels psychostimulantia voor de behandeling van ADHD met comorbiditeit voor ODD, dan wel CD. N = 112 kinderen (6-14 jaar) die reeds minimal 3 maand behandeld werden middels stimulantia. Bij start van additietherapie waren er nog 60 patiënten, n = 35 clonidine, n = 25 placebo. Duur: 6 weken. De dosis stimulantia werd constant gehouden. De dosis clonidine langzaam opgehoogd 25pt: clonidine 0.2mg/dag, 4pt: clonidine 0.15mg/dag, 6: 0.1mg clonidine/dag. Resultaat: Bij de clonidine groep vond een grotere afname plaats bij de Conners’ Reports, subschaal Conduct and Hyperactive Index scores. Bijwerkingen: sufheid en duizeligheid significant verhoogd, echter van voorbijgaande aard.
  Kemph e.a. (1993) open pilotstudie (N = 17, leeftijd 5-15 jaar), 15 kinderen hadden een CD, allemaal vertoonden ze wreedzaam gedrag naar naderen. Meeting via RAAPP. Resultaat: bij 88% van de patiënten waren de scores bij de RAAPP significant verbeterd. T.g.v. behandeling middels clonidine (0,15-0,4 mg/dag, gemiddeld: 0,24 mg/dag; duur: 1-18 maanden, gemiddeld: 5,2 maand). Bijwerking: sedatie, voorbijgaand van aard.

<table>
<thead>
<tr>
<th>Turgay (2009)</th>
<th>Psychopharmacological treatment of oppositional defiant disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>Review</td>
</tr>
<tr>
<td>Number of patients</td>
<td>Variabel, zie Results</td>
</tr>
<tr>
<td>Intervention(s)</td>
<td>Variabel, zie Results</td>
</tr>
<tr>
<td>Outcome</td>
<td>Variabel, zie Results</td>
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<tr>
<td>Results</td>
<td>Zie tekst onder tabel</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>C</td>
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</tbody>
</table>

**Algemene beschouwingen bij de farmacologische behandeling van ODD**
Er zijn slechts weinig gecontroleerde onderzoeken naar de behandeling van ODD met psychofarmaca. Er zijn geen onderzoeken te vinden die de farmacotherapie behandelen bij patiënten met ODD zonder comorbiditeit. Vaak worden bij onderzoeken naar ADHD ook patiënten geïncludeerd. Dit betekent dat artikels die de effectieve farmacotherapeutische behandeling van OOD beschrijven vaak afgeleid zijn van onderzoeken ontwikkeld voor de behandeling van ADHD. Meer dan de helft van de patiënten met ADHD hebben eveneens ODD. De dosis van de medicatie voor patiënten met comorbide ADHD en ODD, dient waarschijnlijk hoger te zijn dan bij patiënten met ADHD zonder ODD (MTA Cooperative Group (1995), MTA Cooperative Group (1999), Newcorn e.a. (2005))
Bespreking van verschillende medicaties ter behandeling ODD

- Stimulantia:
  Eerste aanwijzingen voor gunstig effect van stimulantia uit 1937 door Bradley bij een groep kinderen die ADHD hadden en andere gedragsproblemen ernstig genoeg voor behandeling in residentiële setting. Bij behandeling met benzedrine (*a racemic mixture of d and l-amfetamine*) werd een dramatische verbetering. In 1967 werd het eerste double blind onderzoek gevoerd naar het gebruik van dexamfetamine bij gedragsproblemen (Conners e.a., 1967).
  (MTA Cooperative Group, 1995) Het is thans duidelijk dat bij kinderen met ADHD en ODD psychostimulantia effectief zijn in de behandeling/controle van zowel de ADHD als ODD symptomatologie. Terwijl kinderen met ADHD alleen even effectief kunnen reageren op psychosociale therapie als op medicatie, zullen kinderen met ADHD en ODD beter reageren op de combinatietherapie (psychosociaal + farmacotherapie). Er wordt geschat dat het therapiesucces stijgt met 20% indien psychosociale behandeling wordt toegevoegd aan farmacotherapie (Swanson e.a. (2001), Richters e.a. (1995)). Farmacotherapie alleen was superieur tegenover gedragstherapie en relatief superieur t.o.v. psychosociale als community standard interventions (MTA Cooperative Group, 1995).
  Symptomen van ODD reageren beter op langwerkende dan kortwerkende methylfenidaat. (Steele e.a. (2006))
  De meta-analyse (Pappadopulos e.a. (2006) waarbij alle onderzoeken die agressief gedrag behandelde bij kinderen en adolescenten concludeerden dat stimulantia een medium tot large effect uitoefenden (effectgrootte: 0,78) en risperidon een sterk effect: (effectgrootte: 0,9). Het beperkt aantal onderzoeken met atomoxetine toonde slecht een klein effect (effectgrootte: 0,18). Voor lithium (effectgrootte: 0,4) en voor guanfacine (effectgrootte: 0,4) waren deze matig. Voor de behandeling met antidepressiva waren deze klein (effectgrootte: 0,3).

- Atomoxetine:
  Spencer e.a. (2001) toonden aan dat atomoxetine effectief kon zijn in de behandeling van ODD en co morbid stoornissen van ADHD.
  Newcorn e.a. (2005) liet zien in hun onderzoek dat bij de behandeling van ADHD met comorbid ODD atomoxetine (1,8mg/kg/dag) superieur was tegenover placebo (atomoxetine 1,2mg/kg/dag was niet superieur). N = 297 kinderen en adolescenten (115 patiënten: ODD), die gerandomiseerd atomoxetine dan wel placebo kregen. Gemeten via ADHD Rating Scale IV-Parent Version.
  Het voordeel van atomoxetine is het langwerkende effect.
  Het bijwerkingenprofiel is acceptabel, zonder veel problemen. Er is wel gerapporteerd dat er sprake kan zijn van toegenomen risico op suïcidale ideaties. Zeer zelden zijn ernstige bijwerkingen bij lever en hart gerapporteerd.

- Antidepressiva
  Het is bekend dat antidepressiva een effect kunnen hebben bij de behandeling van ADHD. Echter de specifiek impact van antidepressieve op de ODD symptomen zijn nog niet duidelijk aangetoond.
- Bupropion
  Het enige antidepressivum dat in kleine mate onderzocht is en waarbij er aan wijzingen zijn dat het mogelijk een verbetering geeft voor hyperactiviteit en agressie, alsook een cognitieve verbetering bij kinderen met ADHD en CD.

- Alpha2-agonisten
  - Clonidine
    Connor e.a. (1999) een meta-analyse van 11 RCT-PC toonden een matige effectgrootte voor behandeling middels clonidine voor de symptomatologie van ADHD alleen alsook met comorbide CD.

- Stemmingsstabilisatoren
  - Lithium
    Campbell e.a. (1995) en Malone e.a. (2000): bij therapeutische dosis was lithium effectief en goed verdragen bij kortdurende behandeling voor agressief gedrag bij kinderen en adolescenten met CD.

- Carbamazepine
  Cueva e.a. (1996) toonde geen significant verschil aan tussen carbamazepine en placebo bij een RCT-PC studie aan (n = 22 kinderen, carbamazepine 400-800mg/dag, duur:?)

- Antipsychotica
  - Risperidon
    Findling e.a. (1997) rapporteerden dat risperidon superieur was tegenover placebo alsook goed verdragen werd bij de korte behandeling van een kleine groep ambulante kinderen en adolescenten met ODD en CD.
    Aman e.a. (2002) en Buitelaar e.a. (2001) toonden de effectiviteit van risperidon aan bij kinderen met ODD en CD met ook een zwakbegaafdheid, autisme of ontwikkelingsstoornis of andere gedragsstoornissen (DBD) met of zonder ADHD.
    Buitelaar e.a. (2002) toonden evenzeer aan dat risperidon effectief was in de behandeling van oppositioneel gedrag en agressie bij klinische opgenomen adolescenten met zwakbegaafdheid.
    Als bijwerkingen werden gezien: sedatie met secundaire cognitieve effecten, hypotensie, EPS, tardive dyskinesie en obesitas.
    Snyder e.a. (2002) concludeerden na RCT-PC dat risperidon adequaat verdragen werd en een effectieve behandeling was bij kinderen met zwakbegaafdheid en ernstige gedragstoornissen als agressie en destructief gedrag. N = 110, leeftijd
5-12 jaar, IQ: 36-84. 80% van de patiënten had ADHD. Dosis 0,02-0,06mg/kg/dag. Duur: 1 week singel blind, placebo run-in periode, waarna een 6 weken durende behandelfase. Bijwerkingen: slaperigheid, hoofdpijn, toegenomen eetlust en gewichtstoename.

Turgay e.a. (2002) concludeerden na een 48 weken durende open trial waarin dat risperidon effectief en veilig was in de behandeling van DBD bij kinderen met de leeftijd tussen 5 en 12 jaar, met en zonder ADHD. N = 77 kinderen gediagnosticeerd met DBD en zwakbegaafdheid of lichte tot matige zwakzinnigheid. De dosis was 0,02-0,06mg/kg/dag. Bijwerkingen waren: slaperigheid, hoofdpijn, gewichtstoename. De helft van de gemiddelde gewichtstoename (8,5kg) werd toegeschreven aan de normale groei. De mate van sedatie was van voorbijgaande aard. Op het einde van de studie was de gemiddelde prolactine concentratie statisch significant verhoogd tegenover de baseline bij mannelijke deelnemers. Het was echter < 20ng/ml, dit is binnen de normale marge.


Combinaties van medicatie ter behandeling ODD

- Stimulantia en clonidine
  Er bestaat slecht anekdotisch klinische evidentie en enkele gecontroleerde onderzoeken (Popper e.a. (1995), Hunt e.a. (1990)) die de bruikbaarheid van deze combinatie ondersteunen bij kinderen met ernstige ADHD en agressief gedrag die onvoldoende reageren op de standaard behandeling.
  Een voordeel van het gebruik van clonidine zou kunnen liggen in het verbeteren van de kwaliteit van het in slaap vallen.
  Er is evenwel een mogelijke zeer ernstige bijwerking die verder onderzocht wordt: 4 doden zijn gerapporteerd bij de FDA. Het betroffen 4 kinderen die op een moment tegelijkertijd (... at one time had been taken ...) clonidine en methylfenidaat tegelijkertijd innamen. Er wordt nu sowieso aangeraden om voorzichtig te zijn bij gebruik van clonidine met cardiaal belaste patiënten.

- Stimulantia en antidepressiva
  Combinatie van methylfenidaat en imipramine is geassocieerd met een verwardheid, affect labiliteit, toegenomen agressie en ernstige agitatie. Methylfenidaat kan ernstig interfereren met het hepatische metabolisme.
van imipramine wat resulteert in een langere halfwaardetijd en toegenomen bloedconcentratie.

Fluoxetine en methylfenidaat is enkel onderzocht in een kleine studie waarbij patiënten ADHD en een depressieve stoornis hadden. De combinatie werd goed verdragen en leek effectief. Het sample was echter klein.

- Stimulantia en antipsychotica

In 3 dubbelblinde, placebogecontroleerde onderzoeken van kinderen met ODD en/of CD (met of zonder ADHD) en een benedengemiddelde intelligentie werd de combinatie effectief bevonden en goed verdragen (Snyder e.a. (2002), Turgay e.a. (2002), Aman e.a. (2004)).