



# **Klinik und Poliklinik** **für Kinder- und Jugend-** **psychiatrie/Psychotherapie**

**Jörg M.Fegert Ulm**



# Pillen für die Störenfriede? Behandlungsansätze von aggressivem Verhalten

*Symposium Aggressive Verhaltensstörungen*

*Entwicklungspsychopathologie und  
Behandlungsansätze*

*J. M. Fegert (Ulm)*



**Referral**  
*Pre-school, School Child & Adolescent*

**DBD**

**Conduct Disorder**

**ADHD**

**Other Co-morbid Disorders**

**Working Hypothesis**

**Chronicity  
Pervasiveness  
Global Functioning  
Academic ? & Peer Problems**

**Impact**

**Symptoms**

**Aggression**

**Defiance**

**Impulsivity**

**Hyperactivity**

**Distractability**

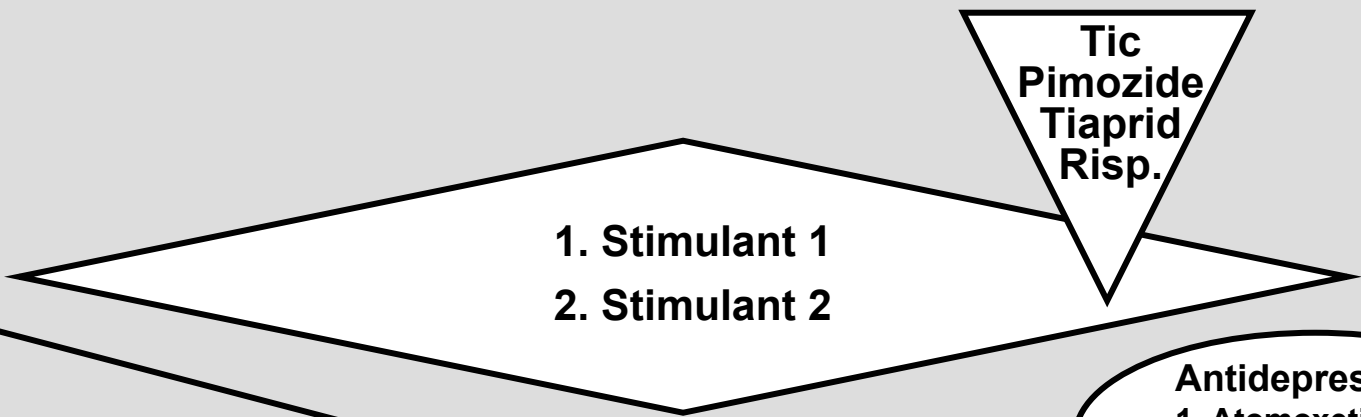
**Neuro/Tic**

**Affective Symptoms**

**Psychosocial Interventions e.g. Parent Training, Symptom Specific Interventions**

**Treatment**

**Atypicals  
Risperdone  
Lithium**



# Prävention, Sekundärprävention

- Allgemein ( Eltern )
  - Triple P (Sanders e al. 2000)
  - Partners, Basic und Advance
    - Webster-Sratton 1998 Video basiert
- Externale Störungen
  - Eltern
    - Z.B. Fast Tack (Conduct problem research group 1999)
  - Kind:
    - z.B. Peer coping skills training (Prinz et al. 1994)

# Prävention, Sekundärprävention

- Gruppe
  - Social relations program (Lochman et al, 1993)
  - Good behaviour game NIMH/H. Brown 2002
- Übersicht in Heinrichs et al. (2002) :  
Prävention kindlicher Verhaltensstörungen
  - Psychologische Rundschau ,53 (4) 170 - 183

- **Selbstinstruktion**
  - Z.B. Petermann & Petermann 1997
  - Einzel- und Gruppentraining
  - Umgang mit Ärger und impulsivem Verhalten
  - Manualisiert, Videotraining
  - Entspannungskomponente

# Soziale Problemlösung und Ärgermanagement

- Spivack und Shure 1974
  - Verbesserung von Problemlösefertigkeiten
  - Nicht automatisch feindselige Absichten unterstellen
  - Differenzierte Wahrnehmung sozialer Situationen erlernen
    - Modelllernen
    - Gemeinsame Diskussion von Gruppenprozessen
- Lochman et al. 1993
  - Anger management Training

# Nur Pillen für den Störenfried?

- Pharmakotherapie Teil eines Behandlungskonzepts insbesondere bei impulsiver Aggressivität
  - Stationäre Aufnahme + Placebogabe zeigt bei der Hälfte der Patienten auch schon deutliche Erfolge (Malone et al. 1997)
- Substanzgruppen
  - (atypische) Neuroleptika
  - Methylphenidat insbesondere bei Komorbidität
  - SSRI
  - Lithium und Antiepileptika

# (atypische) Neuroleptika

- TRAAAY (2003) Treatment Recommendations for the use of antipsychotics for aggressive youth
- Kutcher et al. 2003 treatment algorithm for disruptive behaviour disorders
- Risperidon 1 – 3 mg /die
  - Findling et al 2000, Snyder et al. 2002, Buitelaar et al 2001, Aman et al. 2002, Fegert et al. 2003
- Haleridol, Pipamperon ...



## Patient Selection

Age 5–14 years

Subaverage IQ (between 35 and 84, inclusive)

**DSM-IV Axis I diagnosis of disruptive behavior disorder, eg, conduct disorder (312.8), oppositional defiant disorder (313.81), or disruptive behavior disorder not otherwise specified (NOS) (312.9)**

Total rating  $\geq 24$  in the Conduct Problem subscale of the Nisonger Child Behavior Rating Form (N-CBRF)

Vineland Adaptive Behavior Scale score  $\leq 84$

Subjects who had previously participated in a double-blind placebo-controlled study of risperidone had to have completed at least 2 weeks of double-blind treatment

Targeted enrollment: 500 subjects

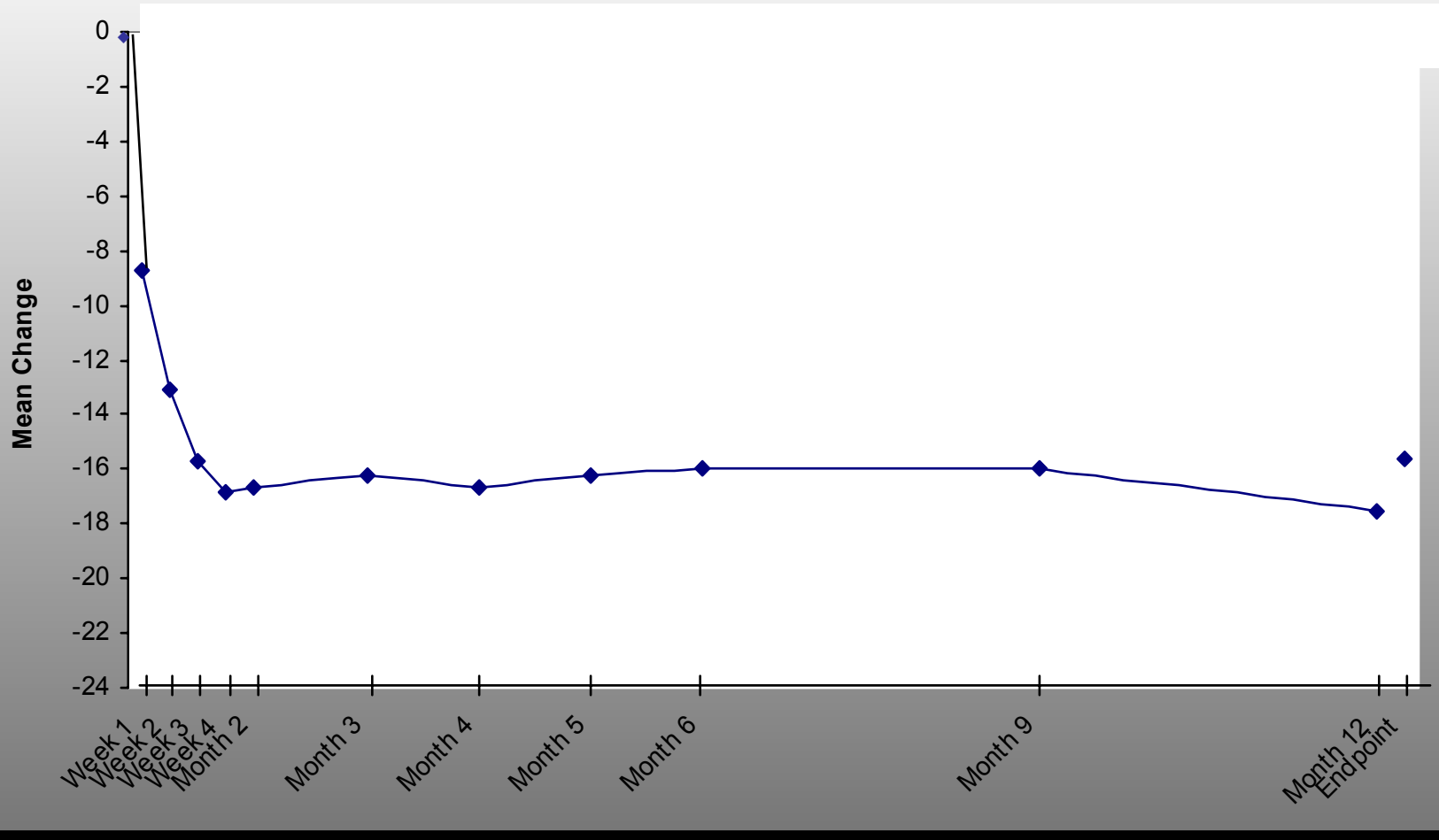
The **319 subjects** who entered the trial received risperidone at a mean modal dose  $\pm$  SE of **1.64  $\pm$  0.04 mg/day (range: 0.2-4.0 mg/day), or 0.021  $\pm$  0.001 mg/kg/day**. Mean treatment duration  $\pm$  SE for the study population was 261.0  $\pm$  7.2 days (range: 1-498 days).

**60 subjects withdrew** from the trial:

- ⇒ 22 because of adverse events,
- ⇒ 10 because of insufficient response
- ⇒ 28 for a variety of reasons, including loss to follow-up, withdrawal of consent, noncompliance, and protocol ineligibility.

# Results

Figure 1. NCBRF Conduct Problem Subscale Score: Mean Change From Baseline



Most common adverse events reported:

- **somnolence in 28.2%**
- **rhinitis in 24.5%**
- **headache in 17.2%**

**Body weight** increased by an average of **6.3 kg** at endpoint from a baseline of 35.6 kg.

**Weight increase was reported as an adverse event in 15.4% of subjects.**

**Extrapyramidal-like symptoms** (eg, tremor, hypertonia, involuntary muscle contractions, dyskinesia, dystonia) were reported in **22.3% of subjects.**

Two subjects reported **tardive dyskinesia-like symptoms** that resolved after treatment discontinuation.

Mean **ESRS score** decreased significantly ( $P=0.006$ ) during treatment, from 1.2 at baseline to 0.7 at endpoint.

# Adverse Events II (Prolactin)

**Peak increases** in mean **prolactin levels** occurred at **week 4**

- **Boys: 20.7 ng/mL**
- **Girls: 27.1 ng/mL**

Prolactin levels declined thereafter.

Adverse events that were possibly related to risperidone and **hyperprolactinemia included:**

- **10 cases of mild to moderate gynecomastia**
- **1 case of galactorrhea**
- **1 case of amenorrhea**
- **1 case of menorrhagia**

**global incidence of 5%.**

All symptoms were transient and resolved without intervention except the amenorrhea, which resolved with treatment.

# Mögliche Indikationen

- F 84.4 hyperactive disorders in mentally retarded children with stereotyped behavior
- F 91 conduct disorder (not F 91.3 oppositional defiant disorder) ~ DSM IV 312.8 & 312.9
- F 92 conduct and emotional disorder combined
- F 94.2 early attachment problems with disruptive behavior (~ DSM IV 313.89)
- F 60.3 emotionally instable personality disorders
  - F 60.30 impulsive type
  - F 60.31 borderline type ~ DSM IV 301.83
- F 98.4 stereotyped movement dis. (~ DSM IV 307.3)

The New England Journal of Medicine

## RISPERIDONE IN CHILDREN WITH AUTISM AND SERIOUS BEHAVIORAL PROBLEMS

RESEARCH UNITS ON PEDIATRIC PSYCHOPHARMACOLOGY AUTISM NETWORK\*

### ABSTRACT

**Background** Atypical antipsychotic agents, which block postsynaptic dopamine and serotonin receptors, have advantages over traditional antipsychotic medications in the treatment of adults with schizophrenia and may be beneficial in children with autistic disorder who have serious behavioral disturbances. However, data on the safety and efficacy of atypical antipsychotic agents in children are limited.

**Methods** We conducted a multisite, randomized, double-blind trial of risperidone as compared with placebo for the treatment of autistic disorder accompanied by severe tantrums, aggression, or self-injurious behavior in children 5 to 17 years old. The primary outcome measures were the score on the Irritability subscale of the Aberrant Behavior Checklist and the rating on the Clinical Global Impressions — Improvement (CGI-I) scale at eight weeks.

**Results** A total of 101 children (82 boys and 19 girls; mean [±SD] age, 8.3±2.7 years) were randomly assigned to receive risperidone (49 children) or placebo (52). Treatment with risperidone for eight weeks (dose range, 0.5 to 3.5 mg per day) resulted in a 56.9 percent reduction in the irritability score, as compared with a 14.1 percent decrease in the placebo group ( $P<0.001$ ). The rate of a positive response, defined as at least a 25 percent decrease in the irritability score and a rating of much improved or very much improved on the CGI-I scale, was 69 percent in the risperidone group (34 of 49 children had a positive response) and 12 percent in the placebo group (6 of 52,  $P<0.001$ ). Risperidone therapy was associated with an average weight gain of 2.7±2.9 kg, as compared with 0.8±2.2 kg with placebo ( $P<0.001$ ). Increased appetite, fatigue, drowsiness, dizziness, and drooling were more common in the risperidone group than in the placebo group ( $P<0.05$  for each comparison). In two thirds of the children with a positive response to risperidone at eight weeks (23 of 34), the benefit was maintained at six months.

**Conclusions** Risperidone was effective and well tolerated for the treatment of tantrums, aggression, or self-injurious behavior in children with autistic disorder. The short period of this trial limits inferences about adverse effects such as tardive dyskinesia. (N Engl J Med 2002;347:314-21.)

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**A**UTISM, a chronic condition that develops in early childhood, is characterized by a marked impairment in the ability to relate to others, delayed language, and restricted patterns of behavior. The disorder affects as many as 20 children per 10,000.<sup>1</sup>

In addition to core symptoms, children with autism frequently have serious behavioral disturbances, such as self-injurious behavior, aggression, and tantrums in response to routine environmental demands.<sup>2</sup> These behavioral problems interfere with rehabilitative efforts and pose enormous challenges to parents and educators. Although behavior therapy may reduce aggression and self-injury, it tends to be highly individualized and has not been evaluated in randomized clinical trials.<sup>3</sup> Attempts to treat autism with several medications in various chemical classes have had limited success.<sup>4</sup> To date, only haloperidol, a potent postsynaptic dopamine-receptor antagonist, has been shown in more than one study to be superior to placebo for the treatment of serious behavioral problems.<sup>5,6</sup> However, many clinicians avoid using haloperidol in children because of concern about its short- and long-term side effects.<sup>7</sup>

Unlike haloperidol, atypical antipsychotic agents block postsynaptic serotonin receptors. The affinity of these agents for serotonin receptors may enhance their efficacy and provide protection against extrapyramidal symptoms.<sup>8</sup> Alternatively, atypical antipsychotic agents may be more easily displaced by endogenous dopamine, which reduces the risk of neurologic side effects.<sup>9</sup> Given the lower frequency of extrapyramidal symptoms with atypical antipsychotic agents and

Address reprint requests to Dr. Lawrence Scullin at the Yale Child Study Center, P.O. Box 207900, New Haven, CT 06520, or at lawrence.scullin@yale.edu.

Dr. Scullin accepts responsibility for the overall content and integrity of the manuscript.

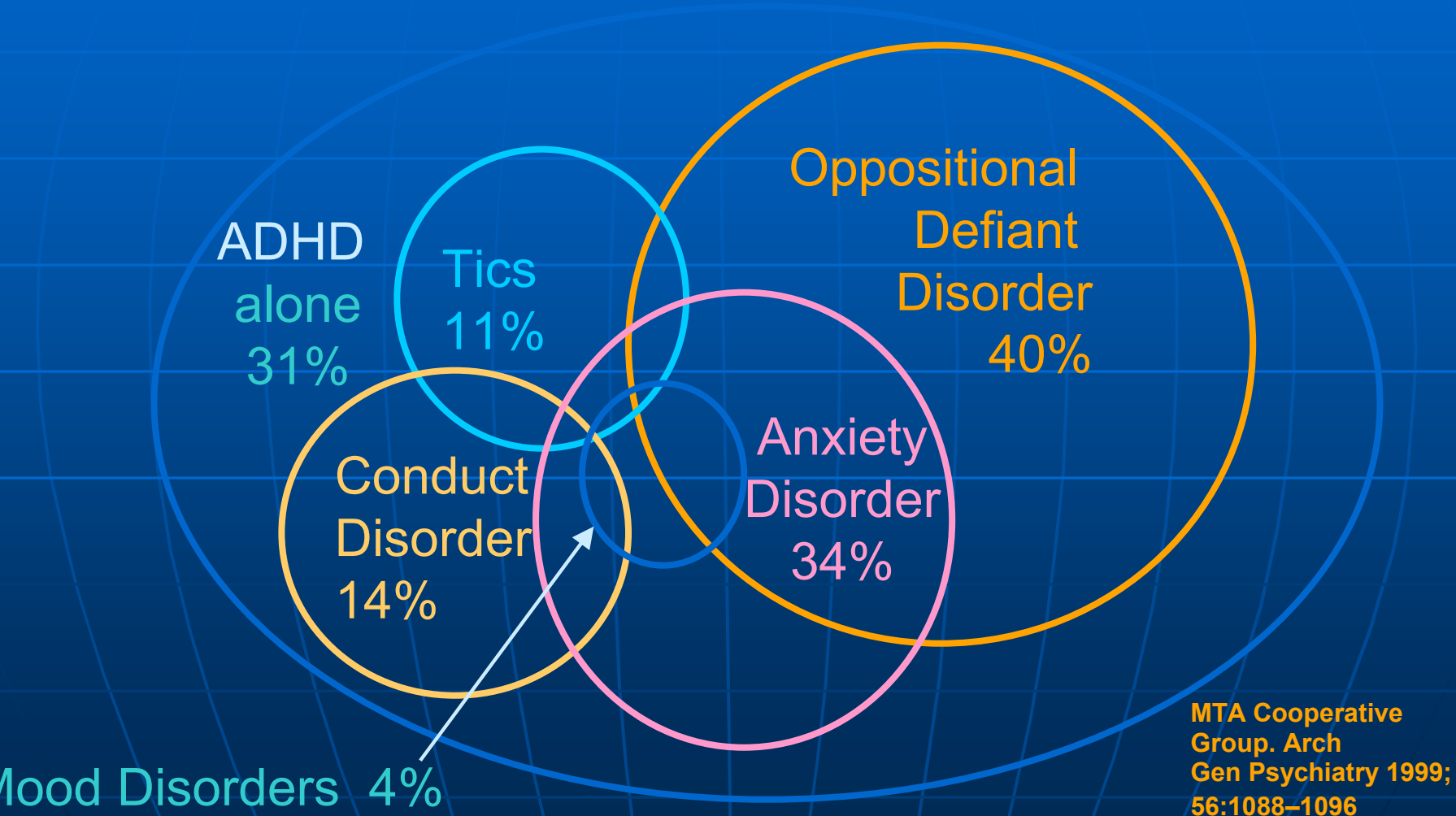
\*The authors of this report are James T. McCracken, M.D., James McGough, M.D., Bhavik Shah, M.D., Fegen Croom, Ph.D., and David Hong, M.A., University of California, Los Angeles; Michael G. Aman, Ph.D., Eugene Arnold, M.D., Ronald Lindsay, M.D., Patricia Nash, M.D., and Jill Hollway, B.A., Ohio State University, Columbus; Christopher J. McDougle, M.D., David Posey, M.D., Naomi Sweeney, Ph.D., and Arlene Kohn, B.A., Indiana University, Indianapolis; Lawrence Scullin, M.S.N., Ph.D., Andrei Marun, M.D., Kathleen Kotias, M.S.N., Fred Volkmar, M.D., D'andre Carroll, M.S.N., and Allison Lanox, B.S., Yale University, New Haven, Conn.; Elaine Tierney, M.D., Jawinder Chhoman, M.D., Nilda M. Gonzalez, M.D., and Marco Grados, M.D., Kennedy Krieger Institute, Baltimore; Benedetto Vitiello, M.D., and Louise Ruz, M.B.A., National Institute of Mental Health, Bethesda, Md.; Mark Davies, M.F.H., Columbia University, New York; and James Robinson, M.E.D., and Don McMahon, M.S., Nathan Kline Institute, Orangeburg, N.Y.

- *Largest medication trial in youths with autism.*
- *5-site RCT*
- *N=101 (8-week Double Blind)*
- *N=37 (6-month Open Label)*
- *Age: 8.8(2.7), range 5-17*
- *Dose: 1.8(0.7), range 0.5-3.5*
- *Most common adverse event: Appetite increase*

# Disruptive behaviours in PDD

- Haloperidole <A> Anderson et al. 1989
- Naltrexone <A> Kolmen et al. 1995, Willemsen-Swinkels et al. 1996
- MPH <A> Quintana et al 1995, Handen et al. 2000
- Risperidone <C> Fisman & Steele, 1996, Hardan et al. 1996, Mc Dougle et al. 1997, Perry et al. 1997, Zuddas et al. 2000, RUPP 2002 <A>
- Olanzapine <C> Horrigan et al. 1997 Malek-Ahmadi and Simonds 1998

# Co-occurring Disorders in Children ( $n=579$ )



# F90.1 hyperactivity and conduct disorder combined (~ DSM IV 314.01 & 312.8; DBD)

- Pharmacological treatment
  - Methylphenidate ... <A>
  - MPH in combination with
    - „low-potent“ conventional neuroleptics (pipamperone)
    - Atypical neuroleptics: risperidone is licenced by the german regulatory agency BFARM since summer 2001 for the use in children age 5 and older with CD and disruptive behavior
  - 2nd line lithium <A > clonidine, carbamazepine
- Non – pharmalogical treatment
  - School based interventions (e.g. Barkley et al. 2000) <A>
  - Self control & Family based interventions

# Stimulants and treatment of aggressive symptoms

- Meta-analysis Connor et al. (2002)
  - J.Am.AcadChildAdolescent Psychiatry 41 (3) 253 – 261
  - 28 studies included 683 young patients
  - Combined Z-test : reduction of clinicians rating of aggression ( $Z=6,53$ ;  $p< .0,0001$ ) and parent rating ( $Z = 6,09$ ,  $p< .0001$ )
  - Only 7 trials reported effects on covert aggression
  - Comorbid ODD or CD led to significantly diminished effect sizes

## Methods/Characteristics

- 83 youths (6–15 years of age) with DBD (DSM-III)
  - 2/3 also met criteria for ADHD
  - Mean age 10 years (74 males)
- 5 weeks of placebo vs. 60 mg/d forced titration (BID): outpatients
  - 41 received MPH
  - Average MPH dose = 41 mg/d (1 mg/kg)
    - MPH was generally well-tolerated

Klein et al., 1997

## Results

- Less symptoms of aggression, conduct problems, ADHD symptoms with MPH when compared to placebo (parent, teacher, & observers)
- No positive correlation between initial symptoms of overall activity and improvement

Klein et al., 1997

## Limitations

- Reductions in socialized aggression were not statistically significant (parent and teachers)
- Responses were “clinically significant”, but “normalisation...almost never occurred...”

Klein et al., 1997

- Citalopram (20 – 40 mg/d) Armenteros & Lewis 2002 Reduktion impulsiver Aggressivität bei Kindern mit ODD, CD, ADHD
- Erwachsenenbefunde bzw. laufende Studien mit Fluoxetin, Sertralin (Coccaro & Kavoussi 1997) und Escitalopram

# Carbamazepine in Conduct Disorder

- Carbamazepine = placebo in 24 inpatients with 22 completing trial
  - mean age 9 years (Range = 5–11)
  - 2-week placebo baseline and post-treatment periods
  - 6 week double-blind
  - Mean CBZ levels = 6.8  $\mu\text{g/ml}$
  - Carbamazepine = placebo

Cueva et al., 1996



# Lithium vs Placebo: Children

- 5–12 years old, DBD, undersocialised, aggressive type
- 6-week study
- 50 children completed the study
  - Average age = 9.4 years
- Mean Li TDD = 1,248 mg
- Lithium superior to placebo

Campbell et al., 1995



# Lithium vs Placebo: Adolescents

- 33 inpatient teenagers with DBD with aggression
  - (12–17 years, mean = 15)
- 1 week placebo followed by 2 weeks lithium (levels 0.6–1.0)
- Lithium = placebo
  - In-patient setting/brief course

Rifkin et al., 1997

# Handlungsrepertoire in akuten Krisen mit „Störenfrieden“

- Absicherung und Dokumentation der Entscheidung
  - akut: Anordnung durch Behandler, Doku in Pflegebericht
  - perakut: Eingreifen des Stationspersonals sofortige Info des Stationsarztes bzw. Dienstarztes, Entscheidung zur Behandlung gegen den Willen nur nach Info der Sorgeberechtigten und/oder (wenn diese nicht zu erreichen sind) auf Anordnung eines Facharztes (OA) und gerichtl. Anordnung
  - Regelfall: Visitenentscheidung (Dokumentation und Übergabe, gezielte Planung für Bedarfsfall)

# AACAP Practice Parameter for the prevention and management of aggressive behaviour in child and adolescent psychiatric institutions, with special reference to seclusion and restraint

J.Am.Acad 41:2 Supplement Feb.2002

- **Level 1 Nichtrestriktive Interventionen**
  - Prompting, Belohnungsprogramme, time-out unter 30min, verhandeln
    - Selbstkontrollaspekt
- **Level 2 Restriktive Interventionen**
  - Extinction, Zimmerarrest
    - Sicherheitsaspekt (Interventionen sollten vorher geplant und angekündigt sein, das Scheitern auf Level 1 sollte dokumentiert werden)
- **Level 3 Restriktivste Interventionen**
  - Festhalten, Einschließen, Fixieren und „chemical restraint“
    - Schutz anderer und des Betroffenen

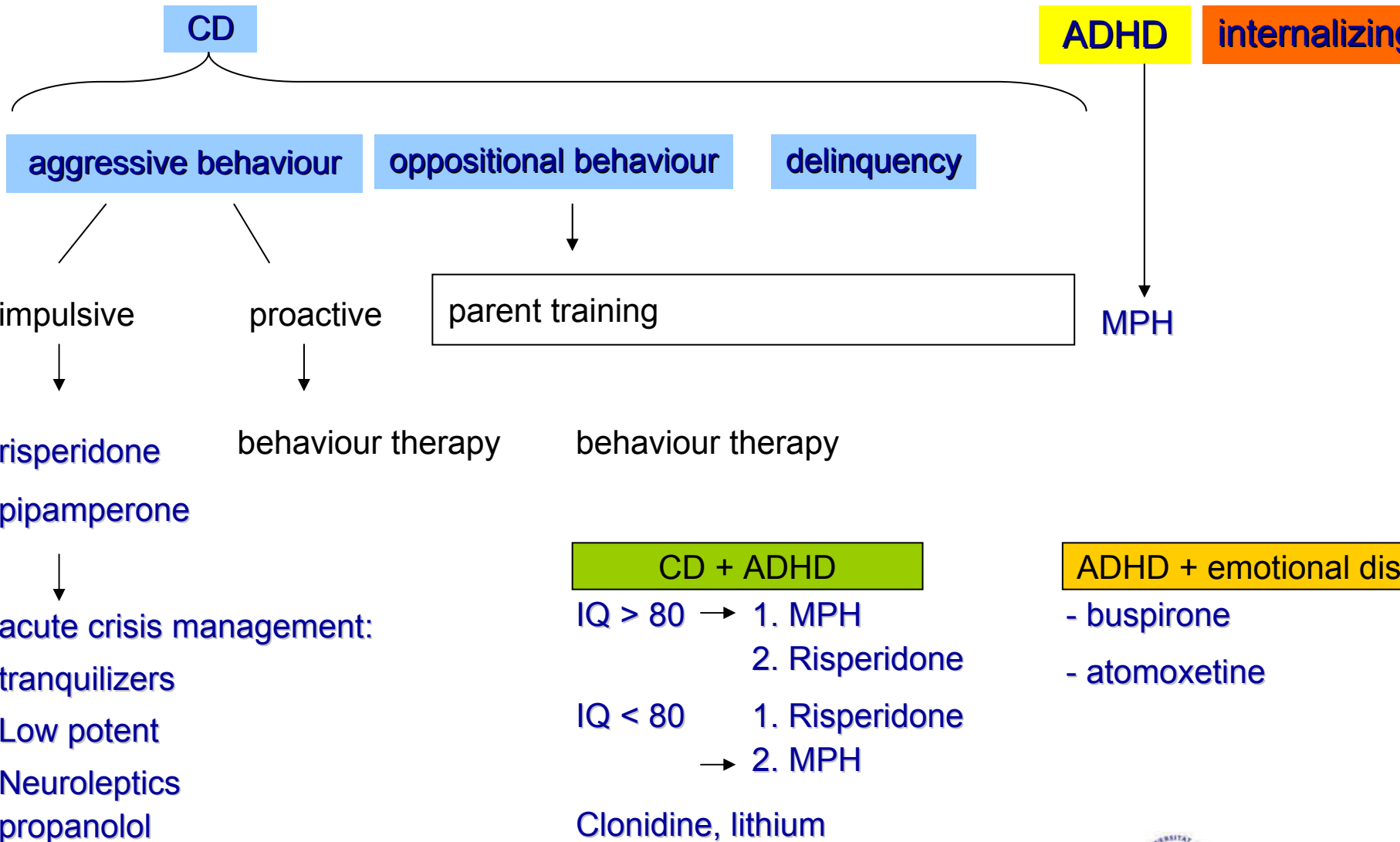


- **Problemdefinition (3 Stufen)**
  - **Definition der Zielsymptome**
  - **Feststellung des Schweregrads**
  - **„why now“ (Besuch, Wechsel im Betreuungsteam, Familieninteraktion etc.)**
- **Zielbeschreibung**
  - **Reduktion von Zielsymptomen**
  - **Aufrechterhaltung von:**
    - **Sicherheit**
    - **Autonomie**
    - **Milieu**

# Festlegung des unmittelbar notwendigen Interventionsniveaus

- **Level 1 Verhaltensmanagement, Gespräch**
  - Zielsymptome: opp. Verh., Ärger, Wut, selbstberichtete Verzweiflung, verbale Attacken
  - Schweregrad: nicht gefährlich, Bedrohung des Milieus
  - Primäres Ziel: Autonomie und Milieu bewahren
- **Level 2 Räumliche Trennung, erhöhte Personalpräsenz, symptom spezifische Medikation**
  - Z.: Stress, Angst, Agitation, Zerstörung von Sachen, Bedrohung
  - S.: potentielle aber nicht perakute Gefahr
  - Z.: Reduktion der Zielsymptome
- **Level 3 Sedierende Medikamente, Festhalten, Isolation, Fixierung, Einschluss**
  - Z.: Aggressives Verhalten mit Selbst- u./oder Fremdgefährdung
  - S.: akute Gefahr
  - Z.: Sicherheit
- **Anschließend: Monitoring und Feedback**

# differential indication of treatments



**CD + ADHD**

IQ > 80 → 1. MPH  
2. Risperidone

IQ < 80 1. Risperidone  
→ 2. MPH

Clonidine, lithium

# Zusammenfassung

## Ja, auch Pillen für den Störenfried

- Akute Reaktionen auf Krisen von Interventionen unterscheiden
  - Transparenz, Stufenplan
- Elternarbeit
- Reduktion von Vorbehalten gegenüber einer rationalen Psychopharmakotherapie, die in ein Konzept eingebunden ist
- Vermeidung von Abbrüchen
- Nicht zuviel erwarten (Fegert 1996 für Jugendhilfemaßnahmen)



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Prof. Dr. med. Jörg M. Fegert

Steinhövelstraße 5  
89075 Ulm

Tel. 0731/500-33544/45

Fax 0731/500-33546

e-mail: [joerg.fegert@medizin.uni-ulm.de](mailto:joerg.fegert@medizin.uni-ulm.de)