

# Treatment of Attention-Deficit/Hyperactivity Disorder (ADHD): Are U.S. Cost-Effectiveness Findings based upon the MTA Study Relevant to Mental Health Care Policy Makers in Germany?

Michael Schlander<sup>1,2</sup>, Oliver Schwarz<sup>1,3</sup>, Goetz-Erik Trott<sup>1,4</sup>, Eric Taylor<sup>5</sup>, Paramala J. Santosh<sup>6</sup>, Peter S. Jensen<sup>7</sup>, E. Michael Foster<sup>8</sup>, Joe A. Garcia<sup>7</sup>, Sherry Glied<sup>7</sup>, Maura Crowe<sup>7</sup>, MTA Cooperative Group

<sup>1</sup>Institute for Innovation & Valuation in Health Care (INNOVAL<sup>HC</sup>), Aschaffenburg and Eschborn (Germany);

<sup>2</sup>University for Applied Economic Sciences (Ludwigshafen); <sup>3</sup>University of Cooperative Education (Mannheim); <sup>4</sup>University of Wuerzburg; <sup>5</sup>King's College (London); <sup>6</sup>Great Ormond Street Hospital (London);

<sup>7</sup>Columbia University (New York, NY); <sup>8</sup>University of North Carolina (Chapel Hill, NC)

## Rationale

The NIMH MTA Study represents the most important randomized trial of the major clinically proven ADHD treatment strategies. It has been used to estimate the cost-effectiveness of ADHD treatment in the United States (Jensen et al. 2005, Schlander et al. 2005). Yet U.S. results are not readily portable to the German health care system since there are distinct differences between the United States and most European countries regarding diagnostic criteria recommended (Europe, Hyperkinetic Disorder, ICD-10; USA, ADHD, DSM-IV), ADHD treatment preferences and standards of care, health care utilization patterns, and unit costs.

**Objectives:** To evaluate, based on the MTA (providing patient-level data for a time horizon of 14 months), the cost-effectiveness of ADHD treatment strategies from the perspective of the statutory health insurance (SHI) in Germany, and to provide first cost-utility estimates for Germany.

**Methods:** 579 children with ADHD, combined type (DSM-IV), aged 7-10, were assigned to 14 months of routine community care (CC), medication management (MedMgt), intensive behavioral treatment (Beh), or the two combined (Comb) – cf. right. “The NIMH MTA Study”. Study entry documentation was used to identify patients meeting the stricter ICD-10-based diagnostic criteria for Hyperkinetic (Conduct) Disorder (HKD, F90.0, or HKCD, F90.1; n=145; cf. below: “Patient Population”). Clinical effectiveness was determined using ADHD symptom normalization rates as determined by a score  $\leq 1$  on the SNAP-IV<sup>1</sup>, a narrow band symptom scale, integrating parent as well as teacher ratings and capturing DSM-IV defined core symptoms of ADHD (inattention, hyperactivity/impulsivity; also opposition/defiance). Quality-Adjusted Life Year (QALY) estimates were calculated from SNAP-IV response rates in combination with health-related quality of life (“utility”) weights derived from expert estimates<sup>2</sup> (best case analysis,  $\Delta = 0.117$ ) and parent proxy ratings<sup>3</sup> (base case analysis:  $\Delta = 0.064$ ). Costs were calculated from the perspective of the German SHI, excluding the research component of the study.

<sup>1</sup>J. Swanson et al. 2001; <sup>2</sup>J. Lord and S. Paisley 2000; <sup>3</sup>D. Coghill et al. 2004

## Patient Population

European guidelines (Taylor et al. 2004) emphasize ICD-10-based diagnostic criteria (“Hyperkinetic Disorder, HKD”) instead of DSM-IV-based criteria for ADHD as commonly used in the United States. Since DSM-IV criteria were used to determine MTA study eligibility, data from the study entry documentation were used to identify the subgroup of patients fulfilling the stricter ICD-10 criteria:

### “ADHD” (DSM-IV): n=579



- Inattention
  - $\geq 6/9$  symptoms
- and/or
- Hyperactivity and Impulsivity
  - $\geq 6/9$  symptoms
- Symptoms causing impairment
  - Have persisted for  $\geq 6$  months
  - Are present before 7 years of age
  - Are “pervasive”, i.e., present in  $\geq 2$  settings
  - Are not better accounted for by another mental disorder

### “HK[C]D” (ICD-10): n=145

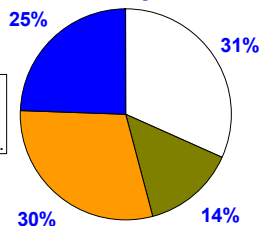


- Inattention ( $\geq 6/9$  symptoms)
- and
- Hyperactivity ( $\geq 3/5$  symptoms)
- and
- Impulsivity ( $\geq 1/4$  symptoms)
- Symptoms criteria like DSM-IV (left)
  - Hyperkinetic Disorder:
    - If criteria above are met ( $\rightarrow$  F90.0)
  - Hyperkinetic Conduct Disorder:
    - If additional symptoms of conduct disorder are present ( $\rightarrow$  F90.1)

## Psychiatric Comorbidity in MTA Study Population

### DSM-IV:

- ADHD w/o comorb.
- ADHD + int. comorb.
- ADHD + ext. comorb.
- ADHD + both comorb.



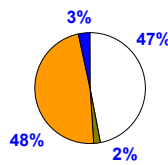
### Internalizing Comorbidity:

anxiety, depression

### Externalizing Comorbidity:

conduct disorder, oppositional defiant disorder

### ICD-10:



## The NIMH MTA Study

### A Randomized Clinical Trial

- of Treatment Strategies
  - Psychosocial Treatment Alone [BEH]
  - Pharmacological Treatment Alone [MM]
  - Combined Psychosocial and Pharmacological Treatment [COMB]
  - Community Comparison Group [CC]
- 579 Subjects
  - Entered between January and May of three consecutive years
  - Six sites (in the United States and Canada)
- Treatment for 14 Months
  - Follow-up for +22 months
- Extensive Standardization
  - Treatment manuals
  - Coordinated staff training
  - Extensive measures of treatment fidelity for all components

### Medication Treatment Strategies in the MTA<sup>4</sup>

- A Structured Set of Detailed Strategies (Algorithms) ...
  - ... rather than a test of a single medication
  - Considerable relevance for office practice
  - Yet, “difficult to mount in real-world office practice”
- In the MTA, n=289 Children Were Assigned to a Medication Management Arm [MM, COMB]
  - Of those, 256 adhered to and completed the full titration trial protocol
  - 77% (198/256) of those who completed titration responded to one of the methylphenidate (MPH) titration doses
  - 88% (174/198) of those children were still taking MPH at the end of maintenance (after 14 months)
- Mean MPH Doses End of Titration:
  - COMB: 29.1 mg/d; MM: 32.2 mg/d (both t.i.d.; n.s.)
- Mean MPH Doses End of 14 Months:
  - COMB: 31.1 mg/d; MM: 38.1 mg/d (both t.i.d.; p<0.001)

<sup>4</sup>L. Greenhill et al. 1996; L.L. Greenhill et al. 2001; B. Vitiello et al. 2001. Note that in the CC arm, 67.4% of subjects (97/146) received medication; n=84 (87%) of those MPH at a mean total daily dose at study completion of 22.6mg, divided into an average of 2.3 daily doses

### Psychosocial Treatment in the MTA<sup>5</sup>

- Three Integrated Psychosocial Treatment Components
  - Aiming to deliver comprehensive treatment coverage
- Parent Training
  - Group sessions (each full-time Therapist-Consultant [Ph.D. level psychologist or equivalent] treated 12 cases divided in two, six-family, parent groups in each annual cohort, beginning 3x/month (lasting 1.5-2h each) and then gradually being tapered (total: 27)
  - Individual sessions (1 h each, 8x over 14 m)
  - Telephone sessions (15 min, weekly)
- School Intervention
  - Teacher Consultation: 16 meetings over 14 months by Therapist-Consultants (who also supervised school paraprofessional aides); built-in flexibility
  - Irvine Paraprofessional Program (IPP): an educational intervention based on behavior modification techniques; paraprofessionals went through three preparatory phases and participated in the STP; in the fall of children's second school year, each paraprofessional was assigned to 2 children and implemented the program over 12 weeks
- Summer Treatment Program (STP)
  - Extensively manualized child-focused treatment program
  - An 8-week program that met daily on weekday from 8:00 am until 5:00 pm
  - Children were placed in age-matched groups of 12
  - Treatments were implemented by teams of 2 classroom staff and 5 paraprofessional counselors for each group
  - Each group spent 3 h daily in classroom sessions and the remainder of each day in recreationally based therapeutic group activities
  - Interventions included implementation of a points system for (appropriate / inappropriate) behavior, positive reinforcement, peer interventions, sports skills training, daily report cards, management of classroom behavior, and individualized programs

<sup>5</sup>K.C. Wells et al. 2000; K.C. Wells 2001

## Cost-Effectiveness Analysis (CEA)

### Effectiveness

#### Response Rates by Diagnostic Criteria and by Comorbidity

Patient Group	n	CC		MedMgt		Beh		Comb	
		n	%	n	%	n	%	n	%
ADHD (all)	579	25	145	56	144	34	144	68	146
HK[C]D	145	24	33	50	36	29	41	71	35
ADHD w/o comorbidity	184	31	42	57	46	42	43	70	53
ADHD w/ int. comorb.	81	21	19	80	20	39	23	74	19
ADHD w/ ext. comorb.	136	28	54	58	40	19	42	67	36
ADHD w/ both comorb.	142	16	31	39	38	39	36	62	37

### Costing

#### Average Costs per Patient by Diagnostic Criteria

	DSM IV				ICD10			
	CC	MedMgt	Beh	Comb	CC	MedMgt	Beh	Comb
Costs of Medication	189 €	583 €	98 €	475 €	183 €	588 €	161 €	567 €
Medication Visit Costs	100 €	429 €	37 €	445 €	100 €	430 €	67 €	441 €
Psychosocial Costs	230 €	49 €	11,635 €	11,660 €	256 €	52 €	11,254 €	11,941 €
Total	518 €	1,061 €	11,770 €	12,580 €	540 €	1,070 €	11,481 €	12,950 €

Costs were calculated in € (2005) from the perspective of the German SHI, using resource utilization data from the MTA (excluding its research component), the “EBM 2000 plus” fee schedule for physicians, ex-pharmacy drug prices (“Gelbe Liste” 1/2005), and STP costs per day from Schmeck et al. 2004.

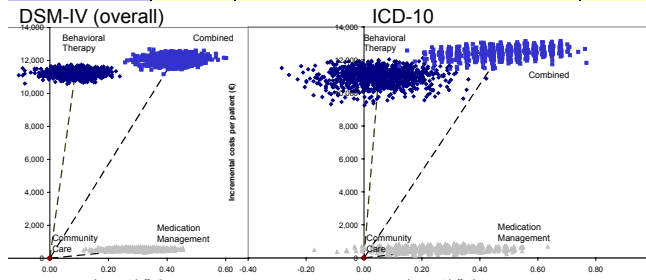
### Methods for CEA

- Incremental Cost-Effectiveness Ratios:  $ICER = \frac{C_B - C_A}{U_B - U_A}$
- One- and Two-Way Deterministic Sensitivity Analyses for various cost assumptions did not change overall results; for details please contact us at www.innoval-hc.com.
- Probabilistic Sensitivity Analyses were performed by non-parametric bootstrapping using patient-level data:
  - Ellipsoid ICER Confidence Regions (Scatter Plots) reflecting the covariance in cost and effect differences;
  - Cost-Effectiveness Acceptability Curves (CEACs) representing the probability that a strategy is most cost-effective given the MTA data (as a function of “willingness-to-pay”, WTP), taking parameter uncertainty into account

### Incremental Cost-Effectiveness

#### Incremental Cost per Patient “Normalized”

	DSM-IV		DSM-IV			ICD-10
	MTA overall	ADHD only	ADHD & Internalizing	ADHD & Externalizing	ADHD & Both Comorbidities	
MedMgt vs. CC	1,798	2,032	1,223	1,674	2,381	2,058
Comb vs. MedMgt	95,743	83,359	inferior	130,944	50,447	55,440
Beh vs. CC	129,547	105,277	59,993	inferior	49,379	217,702
Comb vs. CC	28,553	29,845	32,145	26,071	26,300	866,250
Comb vs. Beh	2,414	407	5,407	2,567	3,278	3,484
Beh vs. MedMgt	inferior	inferior	inferior	inferior	inferior	inferior



#### Incremental Cost per QALY (“Base Case”, dimension only)

MedMgt vs. CC	28,094	31,750	n.a.	n.a.	n.a.	32,156
Comb vs. MedMgt	1,495,984	1,302,484	n.a.	n.a.	n.a.	866,250
Comb vs. Beh	37,719	6,359	n.a.	n.a.	n.a.	54,438

#### Incremental Cost per QALY (“Best Case”, dimension only)

MedMgt vs. CC	15,388	17,388	n.a.	n.a.	n.a.	17,590
Comb vs. MedMgt	818,316	712,470	n.a.	n.a.	n.a.	473,846
Comb vs. Beh	20,632	3,479	n.a.	n.a.	n.a.	29,778

### Sensitivity Analysis for STP

#### Incremental Cost per Patient “Normalized”

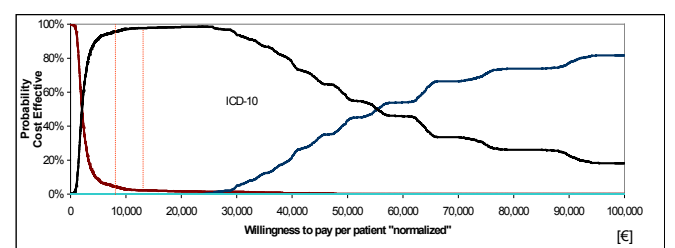
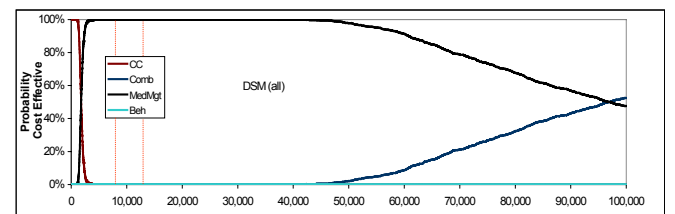
	DSM			ICD-10		
	incl. costs for STP	incl. half of costs for STP	without costs for STP	incl. costs for STP	incl. half of costs for STP	without costs for STP
MedMgt vs. CC	1,798	1,798	1,798	2,058	2,058	2,058
Comb vs. MedMgt	95,743	58,081	20,418	55,440	33,523	11,606
Beh vs. CC	129,547	77,396	25,244	217,702	130,591	43,481
Comb vs. CC	28,553	17,827	7,101	26,300	16,347	6,394
Comb vs. Beh	2,414	2,410	2,405	3,484	2,728	1,973
Beh vs. MedMgt	inferior	inferior	inferior	inferior	inferior	inferior

#### Incremental Cost per QALY (“Base Case”, dimension only)

MedMgt vs. CC	28,094	28,094	28,094	32,156	32,156	32,156
Comb vs. MedMgt	1,495,984	907,516	319,031	866,250	523,797	181,344
Comb vs. Beh	37,719	37,656	37,578	54,438	42,625	30,828

### Cost-Effectiveness Acceptability

#### Probability for Strategies Being Most Cost-Effective



100,000 200,000 WTP [€/QALY] / Best Case  
100,000 200,000 WTP [€/QALY] / Base Case

### Implications

The NIMH MTA Study continues to provide insights into ADHD treatment effectiveness and cost-effectiveness, also internationally.

From the perspective of the German statutory health insurance (SHI), an “MTA style” medication management strategy clearly shows acceptable cost-effectiveness. This observation holds irrespective of diagnostic criteria used (ICD-10 vs. DSM-IV). It also holds when medication management is added to intense behavioral treatment (cf. “Comb vs. Beh”). This finding points to a need to educate physicians involved in ADHD treatment about the benefits of a high-quality medication management strategy.

Sensitivity analyses indicate that behavioral management remains inferior to medication management even when removing the high costs associated with the summer treatment program (STP). This hypothetical case, however, is not supported by empirical evidence.

By way of caution, we note that cost-effectiveness ratios may change when broader clinical endpoints or longer time horizons are applied.