Cost-Effectiveness of Clinically Proven Treatment Strategies for Attention-Deficit/Hyperactivity Disorder (ADHD) in the United States, Germany, The Netherlands, Sweden, and United Kingdom

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Objectives

- To evaluate the **cost-effectiveness** of clinically proven **treatment strategies** (neither placebo nor single drugs) for **attention-deficit hyperactivity disorder** (ADHD) and **hyperkinetic** (conduct) **disorder** (HKD/HKCD) **in four European jurisdictions** (and to compare findings to primary U.S. results), using patient-level data over 14 months from the NIMH MTA Study, which was conducted at six sites in North America (see MTA Cooperative Group, 1999a, 1999b).
- **Analytic challenges include the following:**
  - Preferred diagnostic criteria vary between jurisdictions
  - Standards of care / treatment preferences vary between jurisdictions
  - Unit costs vary between jurisdictions (and by perspective, payers' versus societal)
  - Psychiatric comorbidity is common and known to moderate treatment effectiveness
  - Broad range of clinical effectiveness (and "response") criteria
  - Absence of reliable utility estimates for QALY calculation based on "responders"

Methods

- Analyzing the total study population (with ADHD according to DSM-IV criteria)
- Identifying and analyzing **patient subpopulations** meeting ICD-10 criteria for **hyperkinetic disorder** [or hyperkinetic conduct disorder] (Santosh, 2002)
- Identifying and analyzing **patient subpopulations without comorbidity** (i.e., "pure" ADHD and "pure" HKD; cf. Jensen et al., 2001, 2005; Santosh, 2002),in order to explore the potential impact of different comorbidity profiles associated with ADHD and HKD
- Modeling a hypothetical **"Do Nothing" alternative** (to account for context-specific "Community Care" arm of the MTA Study)
- **Effectiveness** (1) - **symptomatic normalization** (using SNAP-IV scores <1 as a categorical outcome measure; Swanson et al., 2001), capturing teacher and parent ratings of inattention (items 1-9), hyperactivity/impulsivity (items 10-18), and oppositional defiant symptoms (items 19-26)
- **Effectiveness** (2) – **QALYs gained** based on utility estimates for responders and nonresponders (parent proxy ratings, Coghill et al., 2004; expert estimates, Lord and Paisley, 2000)
- **Resource utilization** data from the MTA Study, excluding its research component, substituting its initial double-blind titration protocol with a clinically proven algorithm (Klein et al., 2004)
- **Unit costs** (direct medical expenditures) determined from a societal perspective (D, NL, S, UK, USA) and from a payers perspective (D, NL)
- **Incremental Cost-Effectiveness Ratios** (ICERs; cost per patient normalized; cost per QALY)
- **Probabilistic Sensitivity Analyses** (non-parametric bootstrapping using patient-level study 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 (as a function of "willingness-to-pay", WTP), taking parameter uncertainty into account

ADHD: Diagnostic Criteria

"ADHD" (DSM-IV)

- **Inattention**
  - ≥ 6/9 symptoms

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

"HKD" / "HKCD" (ICD-10)

- **Inattention** (≥ 6/9 symptoms)

  and
- **Hyperactivity** (≥ 3/5 symptoms)

  and
- **Impulsivity** (≥ 1/4 symptoms)
- **Symptoms** criteria like DSM-IV (see left)
  - **Hyperkinetic Disorder**:
  - If criteria above are met (-> F90.0)
  - **Hyperkinetic Conduct Disorder**:
  - If additional symptoms of conduct disorder are present (-> F90.1)

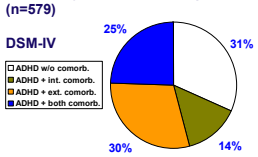
Hyperkinetic Disorder (HKD) broadly corresponds to the "impaired combined" subtype of ADHD (Tripp et al., 1999). ICD-10 criteria for HKD result in lower prevalence estimates, reports of which converge on about 1.5 percent in primary school age children (compared to 3-6% for ADHD according to DSM-IV), and these patients tend to be more pervasively hyperkinetic and neurologically impaired (cf. Garland, 1998; Taylor et al., 2004).

MTA: Patient Population

Instead of DSM-IV-based criteria for ADHD commonly used in the United States, European physicians have traditionally used ICD-10-based diagnostic criteria for "Hyperkinetic Disorder", HKD (cf. Taylor et al., 2004). 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 (cf. Santosh, 2002):

MTA Study Population (Subgroups) (n=579)

DSM-IV



Subgroup Meeting ICD-10 Criteria (HKD/HKCD, n=145)

Internalizing Comorbidity:
anxiety, depression

Externalizing Comorbidity:
conduct disorder, oppositional defiant disorder

MTA: Study Design

A Randomized Clinical Trial

- **of Treatment *Strategies***
  - Psychosocial Treatment Alone [BEH]
  - Pharmacological Treatment Alone [MM]
  - Combined BEH and MM ["COMB"]
  - Community Comparison Group [CC] (n=146) – 67% received medication, principally MPH (n=84), average dose 22.6mg/d (divided in 2.3 doses per day)
- **579 Subjects with ADHD, age 6-9.9**
  - Entered at six sites between January and May of three consecutive years
- **Treatment for 14 Months**
- **Extensive Standardization**

Medication Treatment Strategies in the MTA

A structured set of detailed strategies (algorithms) rather than a test of a single medication

In the MTA Study, n=289 children were assigned to a Medication Management Arm [MM, COMB], which comprised a range of measures including monthly specialist consultations (≥30 min. each)

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 study:
COMB: 31.1 mg/d;
MM: 38.1 mg/d (both t.i.d.; p<0.001)

Psychosocial Treatment

Three integrated psychosocial treatment components aiming to deliver comprehensive treatment coverage

Parent Training
Group sessions, individual sessions, telephone sessions

School Intervention
Teacher consultation, Irvine Paraprofessional Program

Summer Treatment Program (STP)

ADHD: Treatment Strategies

U.S. Guidelines

- **American Academy of Pediatrics (2001)**
  - Stimulant medication (strength of evidence: good) and/or behavior therapy (strength of evidence: fair), as appropriate, to improve target outcomes in children with ADHD
- **AACAP Practice Parameters (1997)**
  - Support, education, and psychopharmacology as cornerstones, "other treatments such as behavior therapy to address remaining symptoms"

European Guidelines

- **European Network on Hyperkinetic Disorders (EUNETHYDIS)**
  "First Upgrade" (Taylor et al., 2004)
  - Education and advice as basis; behavioral interventions
  - Psychopharmacological treatment (principally stimulants) "should be considered (…) when psychological treatments are insufficient alone" or when problems are severe enough to meet criteria for a diagnosis of hyperkinetic disorder

Neither U.S. nor European clinical guidelines have been informed by economic evaluations.

Results: Cost-Effectiveness Analysis (CEA)

Clinical Effectiveness

Symptomatic Normalization ("Response") Rates:

Patient Group		CC		MedMgt		Beh		Comb	
	n	%	n	%	n	%	n	%	n
ADHD (DSM-IV, "all")	579	25	145	56	144	34	144	68	146
HK[C]D (ICD-10, "all")	145	24	33	50	36	29	41	71	35
ADHD "pure" (w/o comorbidity)	184	31	42	57	46	42	43	70	53
HKD ("pure") (w/o comorbidity)	77	27	15	55	22	50	20	85	20

Cost Estimates

ADHD (DSM-IV, "all")	Average Cost per Patient				
	Germany	Sweden	Netherlands	UK	US
Community Care	819 €	1,699 €	876 €	1,434 €	1,030 €
Behavourial Treatment	12,358 €	10,906 €	9,728 €	8,257 €	6,719 €
Medication Management	1,533 €	2,876 €	1,062 €	2,558 €	1,214 €
Combined	13,593 €	13,369 €	10,569 €	10,516 €	7,605 €

HKD/HKCD (ICD-10, "all")	Average Cost per Patient				
	Germany	Sweden	Netherlands	UK	US
Community Care	856 €	1,828 €	928 €	1,541 €	1,104 €
Behavourial Treatment	12,034 €	10,606 €	9,437 €	8,018 €	6,586 €
Medication Management	1,550 €	2,910 €	1,093 €	2,571 €	1,214 €
Combined	13,957 €	13,417 €	10,705 €	10,569 €	7,693 €

ADHD ("pure")	Average Cost per Patient				
	Germany	Sweden	Netherlands	UK	US
Community Care	852 €	1,852 €	929 €	1,557 €	1,087 €
Behavourial Treatment	12,601 €	11,256 €	9,976 €	8,519 €	6,899 €
Medication Management	1,468 €	2,784 €	1,020 €	2,462 €	1,117 €
Combined	13,068 €	12,814 €	10,109 €	10,118 €	7,230 €

HKD ("pure")	Average Cost per Patient				
	Germany	Sweden	Netherlands	UK	US
Community Care	1,114 €	2,556 €	1,335 €	2,127 €	1,564 €
Behavourial Treatment	12,166 €	11,041 €	9,666 €	8,396 €	6,795 €
Medication Management	1,530 €	2,883 €	1,068 €	2,551 €	1,178 €
Combined	14,008 €	13,416 €	10,709 €	10,608 €	7,706 €

All cost data given above refer to the "societal perspective".

Costs were calculated in local currencies and then transformed into Euro (year 2005).

Note that overall results did not change when a payers' perspective was adopted (Germany, Netherlands).

Further details are available on request from the first author.

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ICERs: Cost per Patient "Normalized"

Germany	ADHD all	ADHD only	HKD/HKCD	HKD only
MedMgt vs CC	€ 2,363	€ 2,410	€ 2,693	€ 1,490
Comb vs MedMgt	€ 100,253	€ 87,283	€ 57,898	€ 40,980
Beh vs CC	€ 132,791	€ 107,694	€ 222,226	€ 47,370
Comb vs CC	€ 30,235	€ 31,436	€ 27,763	€ 22,105
Comb vs Beh	€ 3,680	€ 1,670	€ 4,562	€ 5,264
Beh vs MedMgt	inferior	inferior	inferior	inferior
CC vs DoNothing	€ 3,232	€ 2,752	€ 3,531	€ 4,178
Beh vs DoNothing	€ 36,316	€ 30,103	€ 41,114	€ 24,331
MedMgt vs DoNothing	€ 2,759	€ 2,597	€ 3,099	€ 2,804
Comb vs DoNothing	€ 20,112	€ 18,719	€ 19,540	€ 16,480

Netherlands	ADHD all	ADHD only	HKD/HKCD	HKD only
MedMgt vs CC	€ 682	€ 354	€ 638	dominant
Comb vs MedMgt	€ 78,862	€ 68,390	€ 44,854	€ 31,664
Beh vs CC	€ 101,860	€ 82,915	€ 169,158	€ 35,709
Comb vs CC	€ 22,942	€ 23,622	€ 20,717	€ 16,071
Comb vs Beh	€ 2,507	€ 478	€ 3,007	€ 2,982
Beh vs MedMgt	inferior	inferior	inferior	inferior
CC vs DoNothing	€ 3,458	€ 3,003	€ 3,830	€ 5,006
Beh vs DoNothing	€ 28,586	€ 23,831	€ 32,241	€ 19,332
MedMgt vs DoNothing	€ 1,948	€ 1,805	€ 2,185	€ 1,957
Comb vs DoNothing	€ 15,637	€ 14,481	€ 14,986	€ 12,599

Sweden	ADHD all	ADHD only	HKD/HKCD	HKD only
MedMgt vs CC	€ 3,894	€ 3,645	€ 4,198	€ 1,171
Comb vs MedMgt	€ 87,224	€ 75,475	€ 49,030	€ 34,593
Beh vs CC	€ 105,939	€ 86,196	€ 174,504	€ 36,367
Comb vs CC	€ 27,621	€ 28,211	€ 24,557	€ 18,619
Comb vs Beh	€ 7,342	€ 5,577	€ 6,667	€ 6,788
Beh vs MedMgt	inferior	inferior	inferior	inferior
CC vs DoNothing	€ 6,706	€ 5,982	€ 7,542	€ 9,585
Beh vs DoNothing	€ 32,047	€ 26,888	€ 36,234	€ 22,081
MedMgt vs DoNothing	€ 5,177	€ 4,925	€ 5,819	€ 5,285
Comb vs DoNothing	€ 19,780	€ 18,356	€ 18,783	€ 15,784

UK	ADHD all	ADHD only	HKD/HKCD	HKD only
MedMgt vs CC	€ 3,720	€ 3,535	€ 3,998	€ 1,522
Comb vs MedMgt	€ 66,148	€ 57,605	€ 37,324	€ 26,459
Beh vs CC	€ 78,515	€ 63,811	€ 128,767	€ 26,872
Comb vs CC	€ 21,495	€ 22,029	€ 19,132	€ 14,540
Comb vs Beh	€ 6,731	€ 5,720	€ 6,052	€ 6,319
Beh vs MedMgt	inferior	inferior	inferior	inferior
CC vs DoNothing	€ 5,658	€ 5,030	€ 6,357	€ 7,975
Beh vs DoNothing	€ 24,263	€ 20,351	€ 27,393	€ 16,792
MedMgt vs DoNothing	€ 4,604	€ 4,356	€ 5,142	€ 4,676
Comb vs DoNothing	€ 15,558	€ 14,493	€ 14,797	€ 12,480

US	ADHD all	ADHD only	HKD/HKCD	HKD only
MedMgt vs CC	€ 609.19	€ 116.83	€ 427.60	dominant
Comb vs MedMgt	€ 53,123.19	€ 45,996.21	€ 30,231.14	€ 21,438.93
Beh vs CC	€ 65,463.23	€ 53,269.56	€ 108,985.14	€ 22,422.30
Comb vs CC	€ 15,561.70	€ 15,807.44	€ 13,962.04	€ 10,530.72
Comb vs Beh	€ 2,640.23	€ 1,184.48	€ 2,625.08	€ 2,604.13
Beh vs MedMgt	inferior	inferior	inferior	inferior
CC vs DoNothing	€ 4,063.75	€ 3,512.90	€ 4,554.90	€ 5,863.53
Beh vs DoNothing	€ 19,742.90	€ 16,481.01	€ 22,501.06	€ 13,589.85
MedMgt vs DoNothing	€ 2,184.76	€ 1,976.50	€ 2,428.52	€ 2,159.88
Comb vs DoNothing	€ 11,251.03	€ 10,356.70	€ 10,769.69	€ 9,066.32

Cost-Utility Estimates

Cost per QALY Estimates:

Cost-utility estimates in pediatric populations should be interpreted with caution (cf. Griebsch et al., 2005).

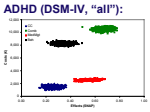
Applying utility estimates for responders and nonresponders reported by two studies from the United Kingdom (see Methods), the following "reasonable ranges" (values presented are the respective best and worst cases across assumptions and jurisdictions) for cost per QALY gained may be obtained from the MTA Study data:

Medication Management versus Community Care:
from €4,500 to €52,000 for ADHD ("all") and from €3,200 to €57,000 for HKD;

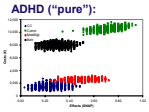
Combined Treatment versus Medication Management:
from €390,000 to €1,300,000 for ADHD and from €220,000 to €770,000 for HKD.

Sensitivity Analysis

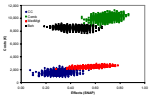
ADHD (DSM-IV, "all"):



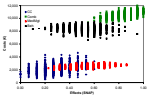
ADHD ("pure"):



HKD/HKCD (ICD-10, "all"):



HKD ("pure"):



Cost-effectiveness findings for ADHD hold for HKD as well (left).

Explorative analysis of "pure" subgroups (ADHD and HKD without psychiatric comorbidity, right) mirrors overall results. While ICERs (see left column) are suggestive of a similar pattern of cost-effectiveness (in favor of intense medication management) for patients with "pure" HKD, probabilistic analyses reveal considerable uncertainty due to the small sample size (n=77) .

Key Conclusions

Primary cost-effectiveness findings from the NIMH MTA Study (for the United States) appear robust across jurisdictions.

From a European perspective (i.e., D, NL, S, UK), an "MTA style" intense medication management strategy is broadly associated with acceptable to attractive cost-effectiveness ratios. This observation holds irrespective of diagnostic criteria used (ICD-10 vs. DSM-IV). Cost-effectiveness ratios are disappointing for behavioral management as administered in the MTA Study.

By way of caution, we note that cost-effectiveness ratios may change when (1) when broader clinical endpoints (i.e., therapeutic objectives other than symptomatic normalization) are considered,
(2) in the presence of psychiatric comorbidity,
(3) when longer time horizons are applied.

More research is needed to determine the cost-effectiveness of less intense, better tailored psychosocial interventions, since the NIMH MTA Study was designed to maximize their clinical effectiveness, not their cost-effectiveness.