



Leistungsfähigkeit und Limitationen gesundheitsökonomischer Evaluationen am Beispiel der ADHS

Öffentliche Antrittsvorlesung
für das Fach Gesundheitsökonomie
an der Medizinischen Fakultät Mannheim
der Ruprecht-Karls-Universität Heidelberg

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Universitätsklinikum Mannheim, 14. Dezember 2007



Economic Evaluation

Cost Analysis

- ▭ **Burden of Disease (BoD)**
 - ▭ Duration and quality of life lost
 - ▭ Measures: HALYs (DALYs, QALYs; unweighted)
- ▭ **Cost of Illness (CoI)**
 - ▭ Total (direct / indirect / ?) cost to society due to a disorder
- ▭ **Budgetary Impact Analyses (BIAs)**
 - ▭ Predicted impact of adopting a technology on a health care budget (payer's perspective)

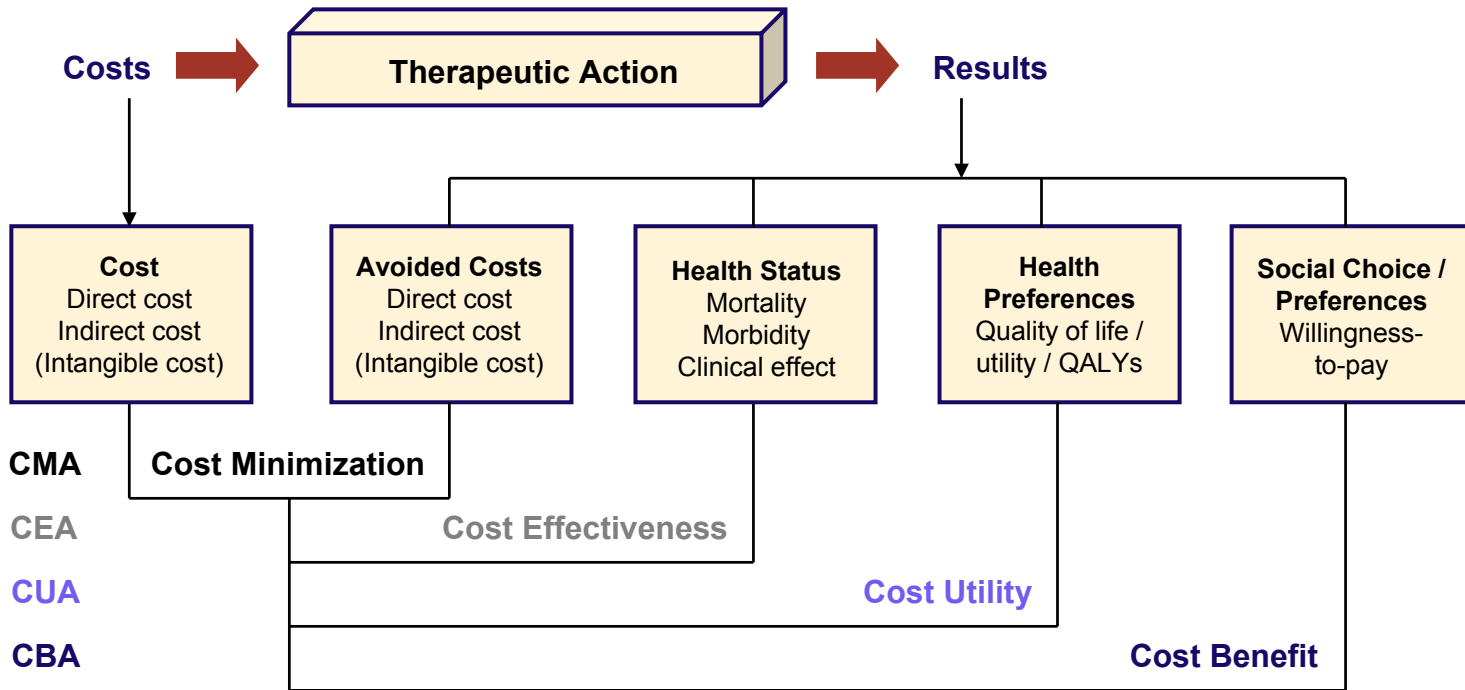
Comparative Analysis

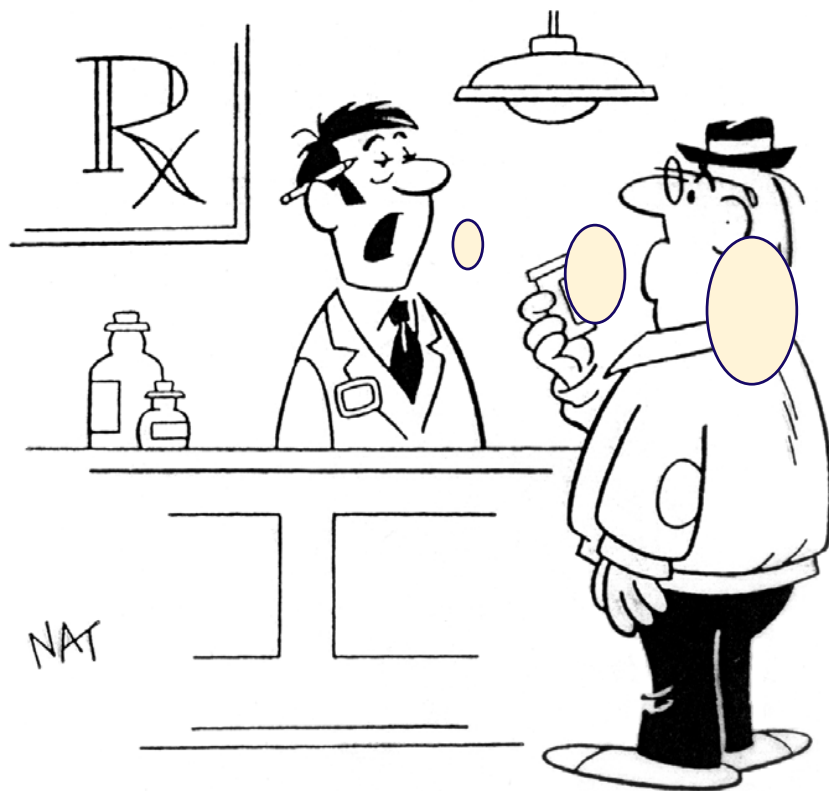
- ▭ **Cost Benefit Analysis (CBA)**
- ▭ **Cost-Effectiveness Analysis (CEA)**
 - ▭ Cost Utility Analysis (CUA)
 - ▭ Cost Consequence Analysis (CCA)
- ▭ **Cost Minimization Analysis (CMA)**



Economic Evaluation

“A comparative analysis of alternative courses of action in terms of their costs and consequences”





**“The drug itself
has no side
effects
–
but the number
of health
economists
needed to
prove its value
may cause
dizziness and
nausea.”**



ADHD – A Challenge for Economic Analysis

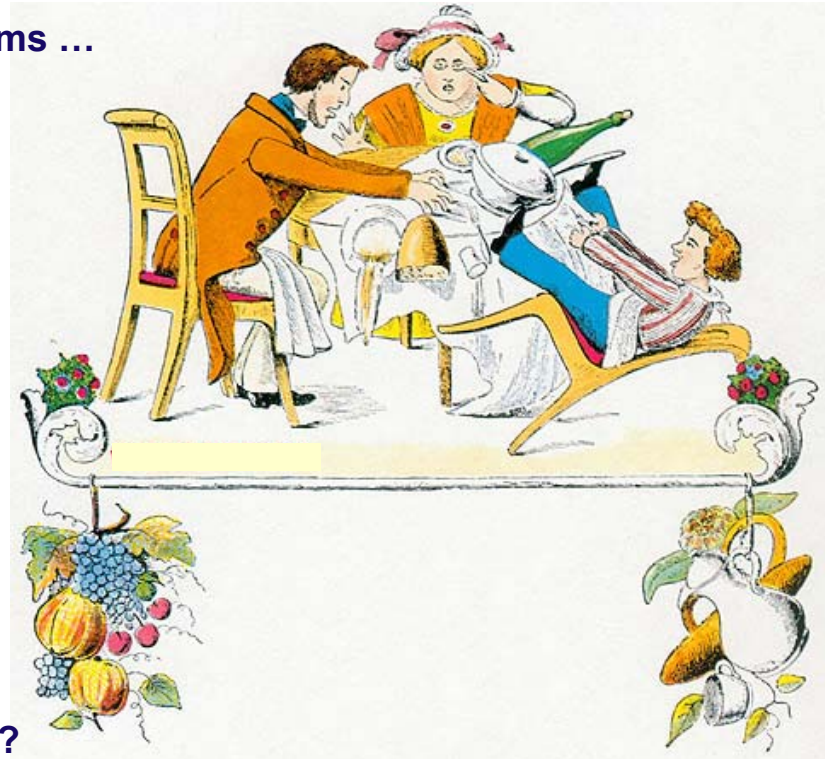
- International variation in preferred diagnostic criteria
- International variation in standards of care
- Co-existing disorders (comorbidity)
- Increasing diagnostic prevalence
- Variety of instruments to measure clinical outcomes
- Controversial validity of QALYs in pediatric populations
- Changing therapeutic landscape
- New medications with improved dosing schedules
(and higher acquisition costs)



Attention-Deficit/Hyperactivity Disorder (ADHD)

▸ Cores Symptoms ...

- Inattention
- Impulsivity
- Hyperactivity



▸ ... and beyond?

Source: www.sagen.at



ADHD: Burden of Disease (Overview)

▸ Health Care System

- Increased health care utilization and direct medical costs (reported to be comparable to children with asthma); including emergency room visits (...)
- Increased risk of substance abuse disorders (including earlier onset and lower probability to quit in adulthood)
- Increased risks of bike and more motor vehicle accidents

▸ School and Occupation

- Many expelled; increased drop-out rates; impaired educational outcomes and lower occupational status

▸ Family and Employers

- Parental divorce (or separation) rates increased; sibling fights
- Parental absenteeism and productivity

▸ Society

- Criminal behavior; justice and legal system costs, substance abuse disorders



Nordbaden Project: Research Objectives¹

- ▭ **“Real World” Prevalence of ADHD**
 - ▭ Administrative prevalence rate by age, gender, and severity
 - ▭ Physician groups (specialties) involved in patient care
- ▭ **Co-Existing Conditions**
- ▭ **Treatment Patterns**
 - ▭ Quality of care compared with existing guidelines
- ▭ **Direct Medical Costs Attributable to ADHD**
 - ▭ Perspective of the Statutory Health Insurance
 - ▭ Types of cost (physicians, medication, psychotherapy, etc.)
- ▭ **Baseline for Future Health Care Utilization Research**

¹cf. Study Protocol (“Projektbeschreibung”), InnoVal^{HC}, September 2004



Nordbaden Project: Design¹

- **Retrospective Database Analysis**
- **Case Control Technique**
 - Matched pairs (by age, gender, type of health insurance)
 - For examination of co-morbidity, utilization, and costs
- **Cross-Sectional Study**
 - Integrating patient-related data from four quarters of 2003
- **Study Protocol**
 - Including prospectively defined Data Analysis Plan
- **Data Transfer Protocol**
 - Detailed description of procedures for data transfer
 - Approval by Data Protection Officers

¹cf. Study Protocol (“Projektbeschreibung”), InnoVal^{HC}, September 2004



Nordbaden Project: Database

▸ Population

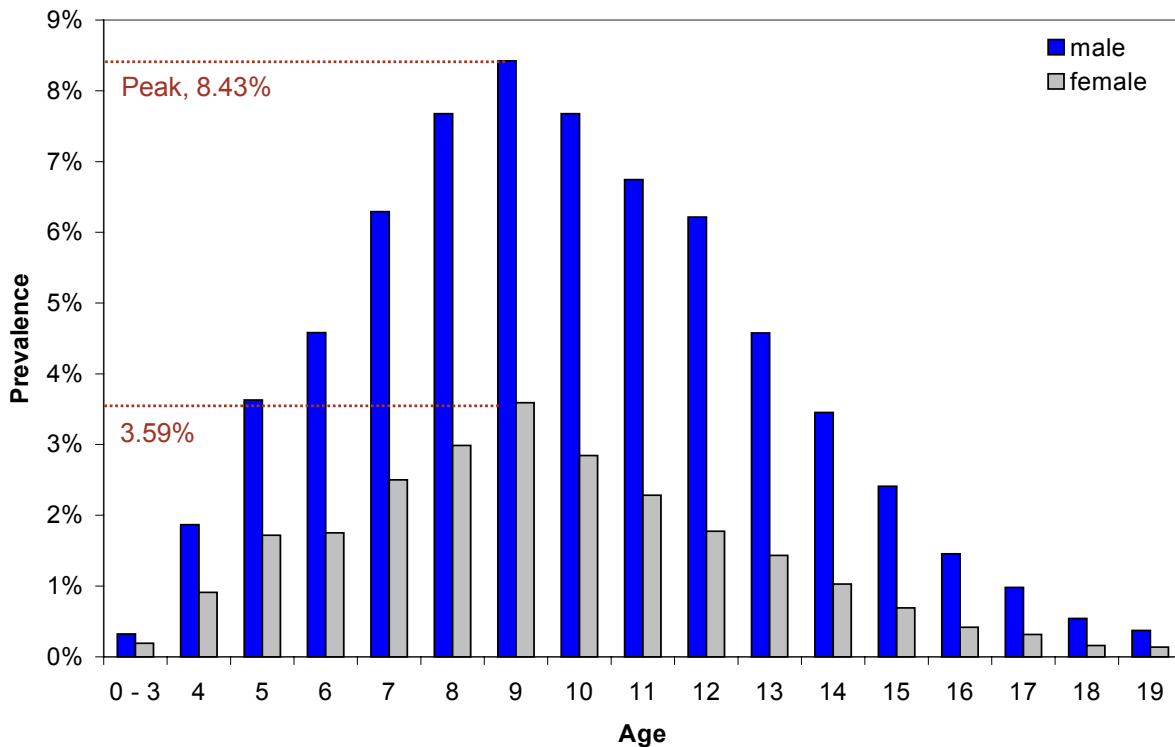
- 2.238m persons covered by Statutory Health Insurance
- Full coverage of the regional SHI insured population
- Representing 82% of the total population in Nordbaden
- Sample representing
~3% of the total population of Germany

▸ Generalizability

- Research Issue:
- (To what extent)
Can we assume the Nordbaden population sample
to be representative of the total German population?



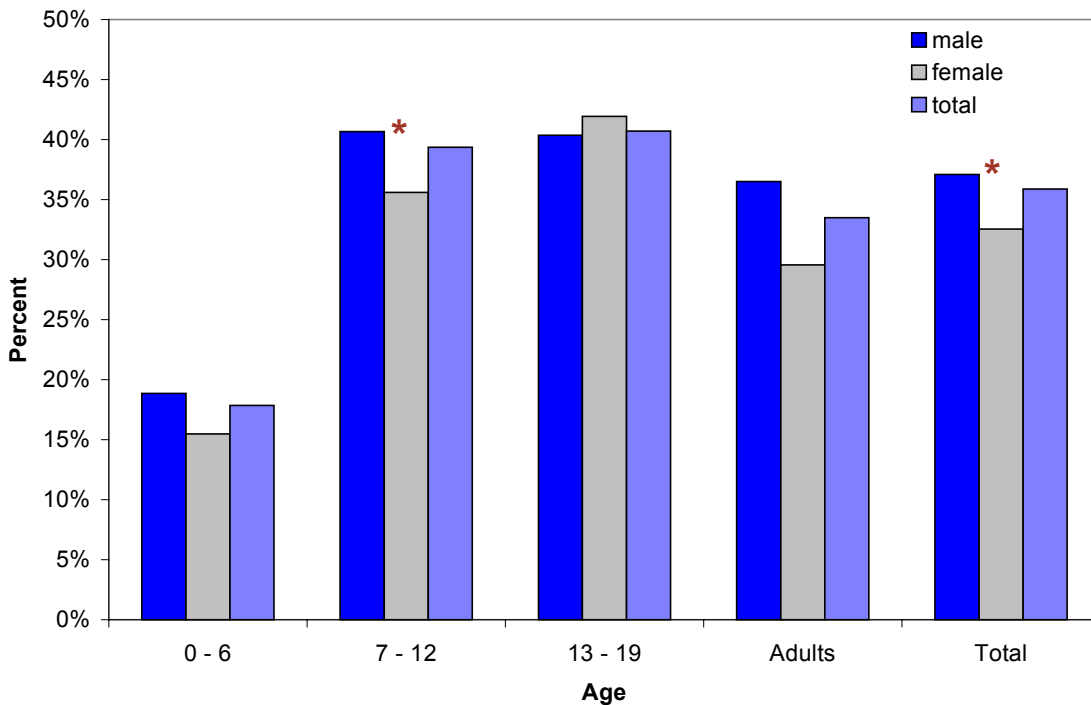
ADHD: Prevalence (Nordbaden, 2003)¹



¹M. Schlander, O. Schwarz, G.-E. Trott, et al. (2007)



ADHD: “Who Cares?” Specialist Involvement in Diagnosis and Treatment¹

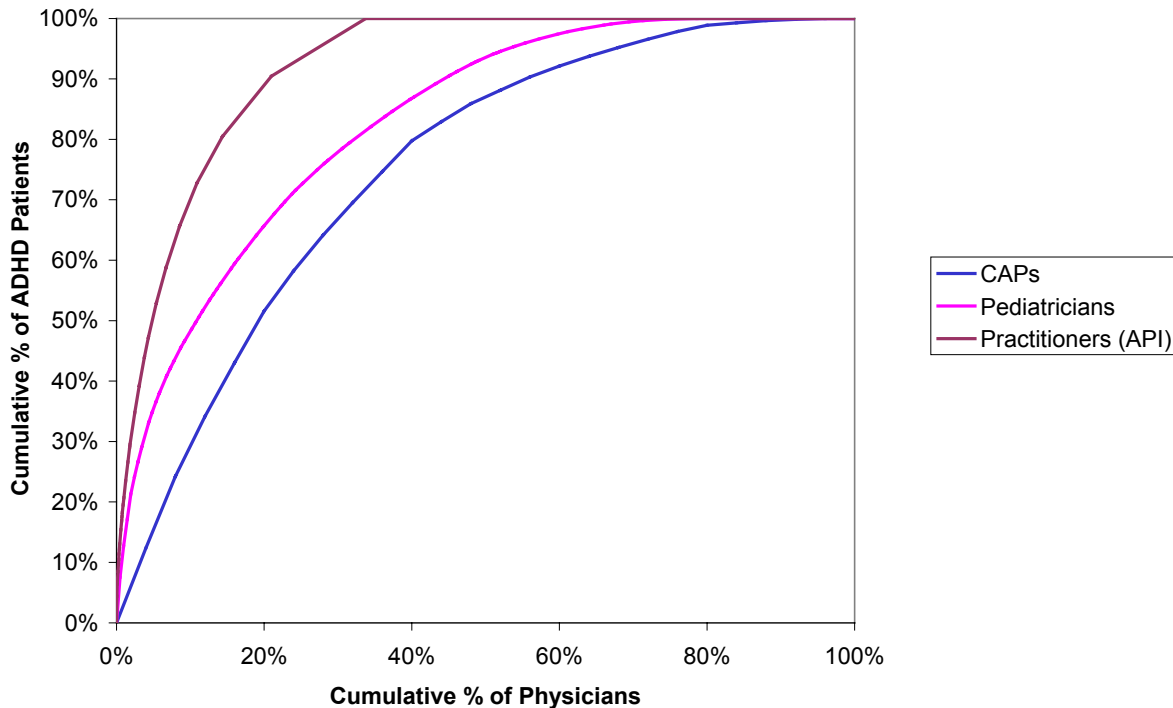


¹M. Schlander, O. Schwarz, G.-E. Trott, et al. (2007)



ADHD: “Who Cares?”

Concentration of Care Among Physician Groups¹



¹M. Schlander, O. Schwarz, G.-E. Trott, et al. (2007)



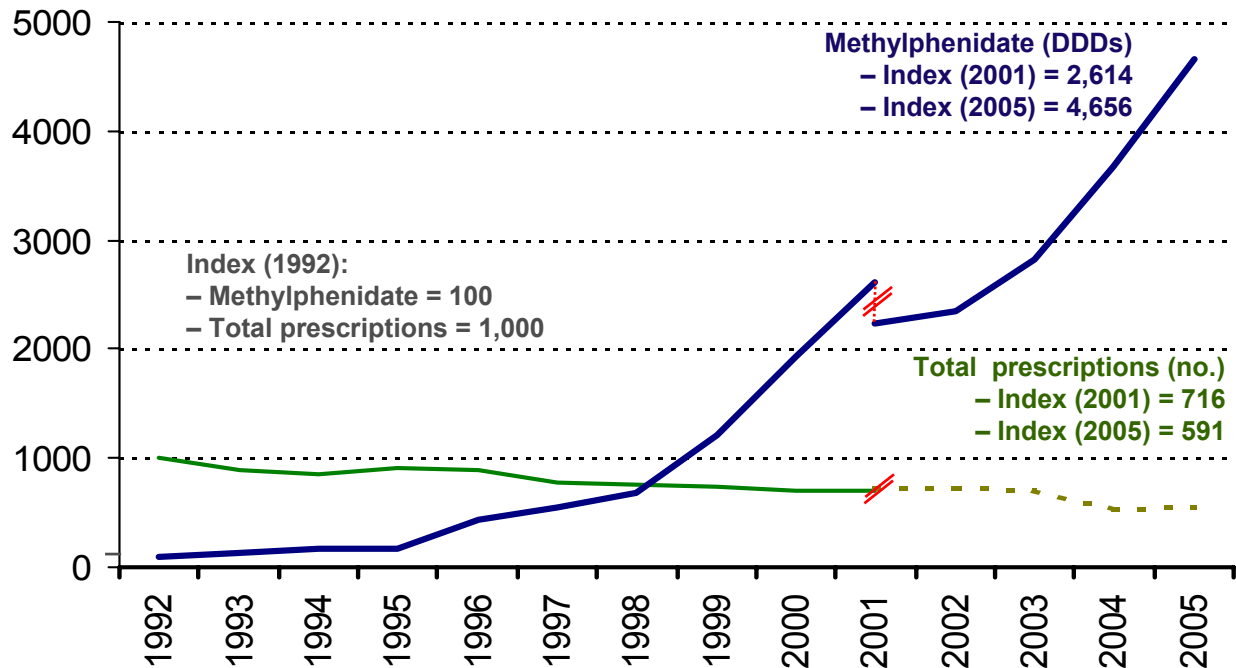
ADHD: Co-Existing Conditions (Administrative Data from Nordbaden, 2003)¹

- **Conduct & personality disorders**
 - 39.3% vs. 3.9%
- **Mood and affective disorders**
 - 38.0% vs. 8.9%
 - Emotional disorders, neurotic disorders, depression, phobia, anxiety
- **Specific development disorders**
 - 37.4% vs. 13.4%
- **Specific developmental disorders of scholastic skills**
 - 23.0% vs. 2.8%

¹in children adolescents (n=11,245), compared to control group matched by age, gender, and type of health insurance.
M. Schlander, O. Schwarz, G.-E. Trott, et al. (2006)



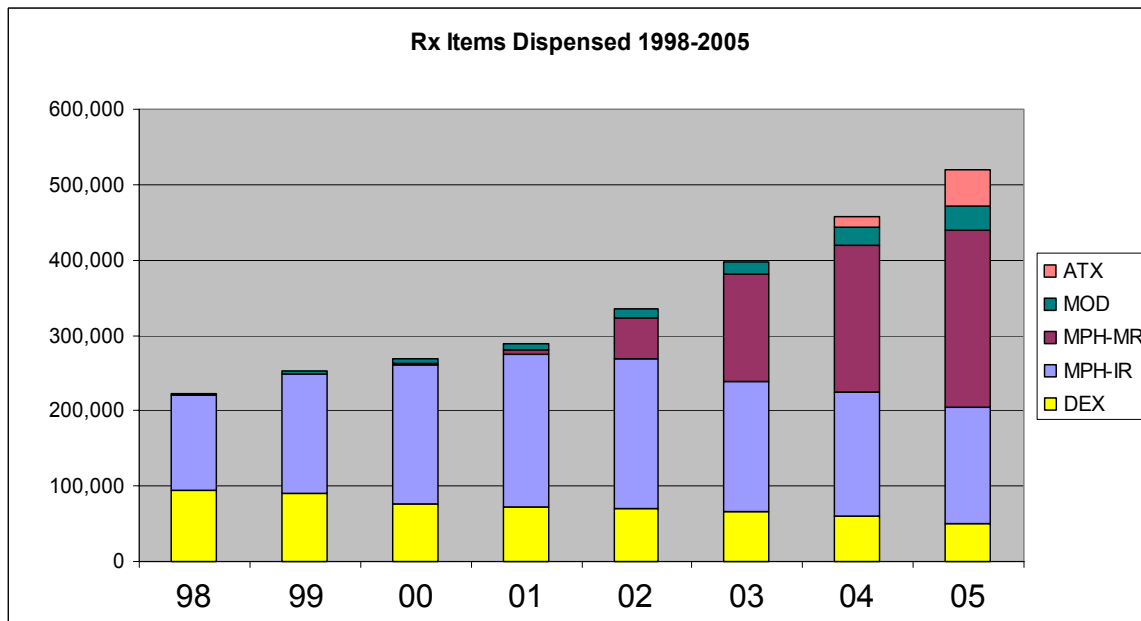
Methylphenidate (MPH) Prescription Trend (Germany)¹



¹Methylphenidate prescriptions grew >26-fold from 1995 to 2005. During the same period, total prescriptions in Germany declined by 35 percent. Data source: WiDo (U. Schwabe, D. Paffrath, 1993 – 2006); note change of database for year 2001/2002. All data refer to prescriptions reimbursed by statutory health insurance (SHI, “GKV”, covering ~85 percent of German population); excluding parallel imports. Note that these data include prescriptions for adults with ADHD and also for some other indications (narcolepsy).



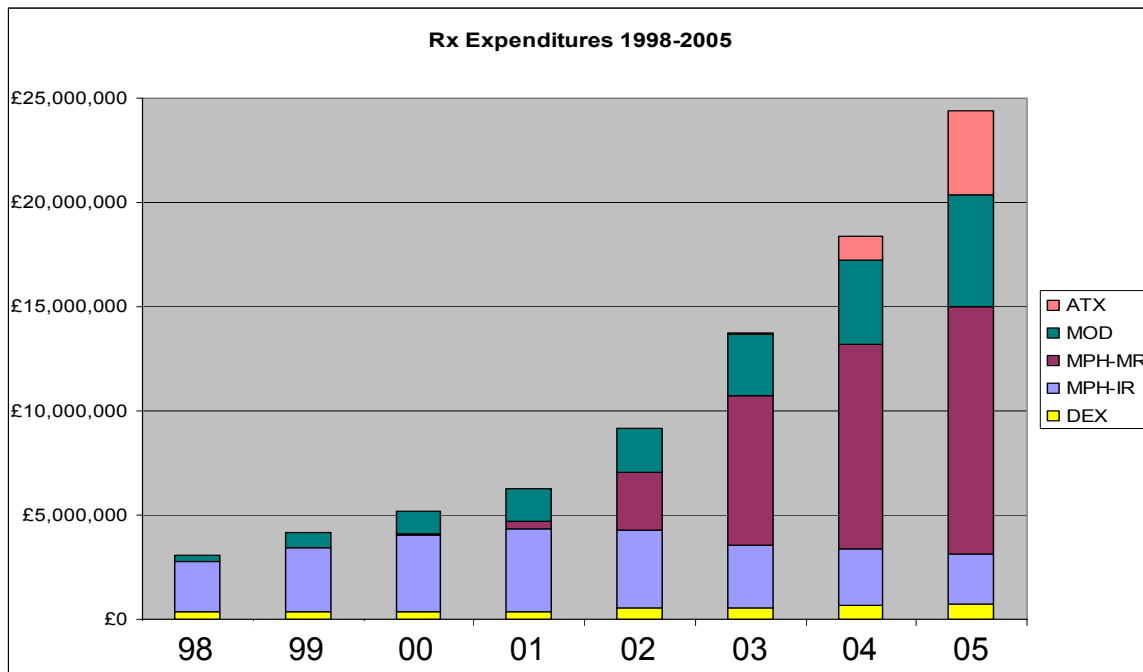
ADHD-Related Prescriptions (NHS England, 1998-2005)¹



¹Prescription items dispensed in the community p.a.; DEX: dexamphetamine (Dexedrine[®] and others); MPH: methylphenidate; IR: immediate-release formulations (Ritalin[®] and generics); MR: modified-release formulations (Concerta[®] XL, Equasym[®] XL; Ritalin[®] SR imports); MOD: modafinil (Provigil[®], licensed for daytime sleepiness); ATX: atomoxetine (Strattera[®]); PEM: pemoline (Volital[®], before 2002 only, not shown due to small volume); data source: NHS Prescription Cost Analysis 1999-2006



ADHD-Related Expenditures (NHS England, 1998-2005)¹



¹Expenditures by category p.a.; DEX: dexamphetamine (Dexedrine[®] and others); MPH: methylphenidate; IR: immediate-release formulations (Ritalin[®] and generics); MR: modified-release formulations (Concerta[®] XL, Equasym[®] XL; Ritalin[®] SR imports); MOD: modafinil (Provigil[®], licensed for daytime sleepiness); ATX: atomoxetine (Strattera[®]); PEM: pemoline (Volital[®], before 2002 only, not shown due to small volume); data source: NHS Prescription Cost Analysis 1999-2006.



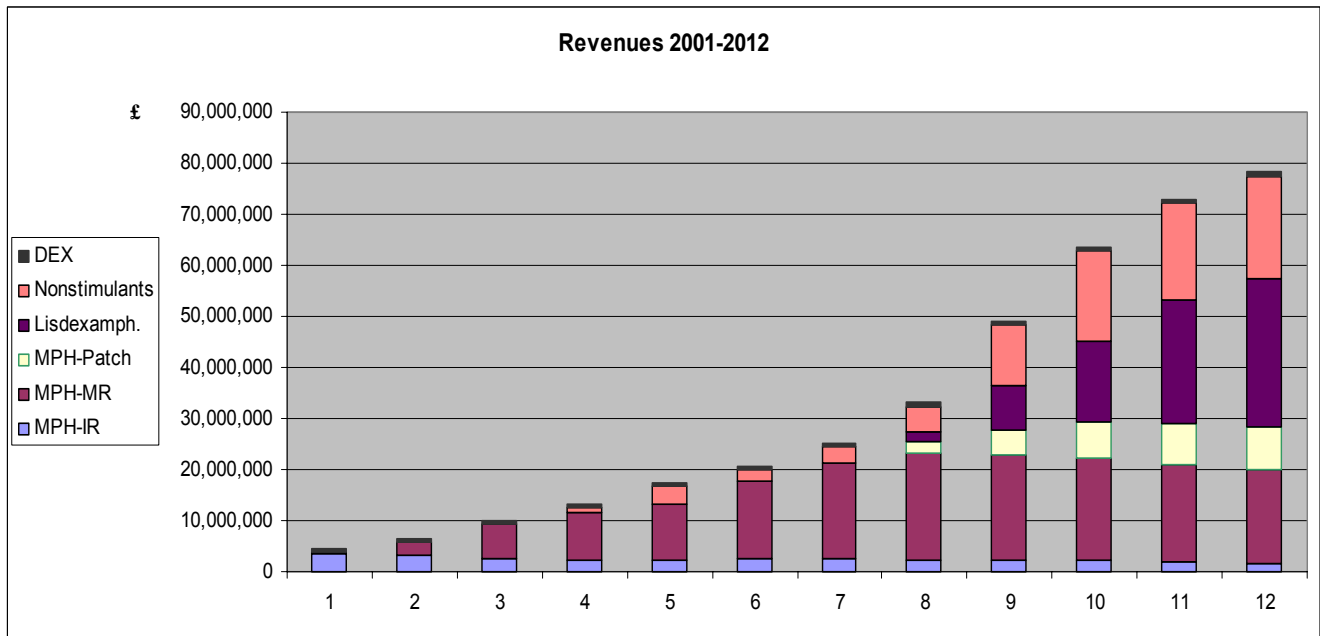
Reasons for Increased Spending on ADHD Treatment¹

1. Growing awareness (education & promotional efforts by industry)
 - **ADHD being diagnosed more frequently (and earlier)**
 2. Growing acceptance of pharmacotherapy
 - **More patients receiving pharmacotherapy**
 3. Increasing intensity of pharmacotherapy
 - **More prescriptions per diagnosed and treated patient**
 4. Improved therapeutic options
 - **Higher unit cost per DDD**
- These factors combined exert a **multiplicative effect**, leading to the expectation of a pronounced increase of drug expenditures.
 - **Other cost components (including, but not limited to, diagnostic procedures and behavioral therapy) are likely to increase as well.**

¹Schlander (2007)



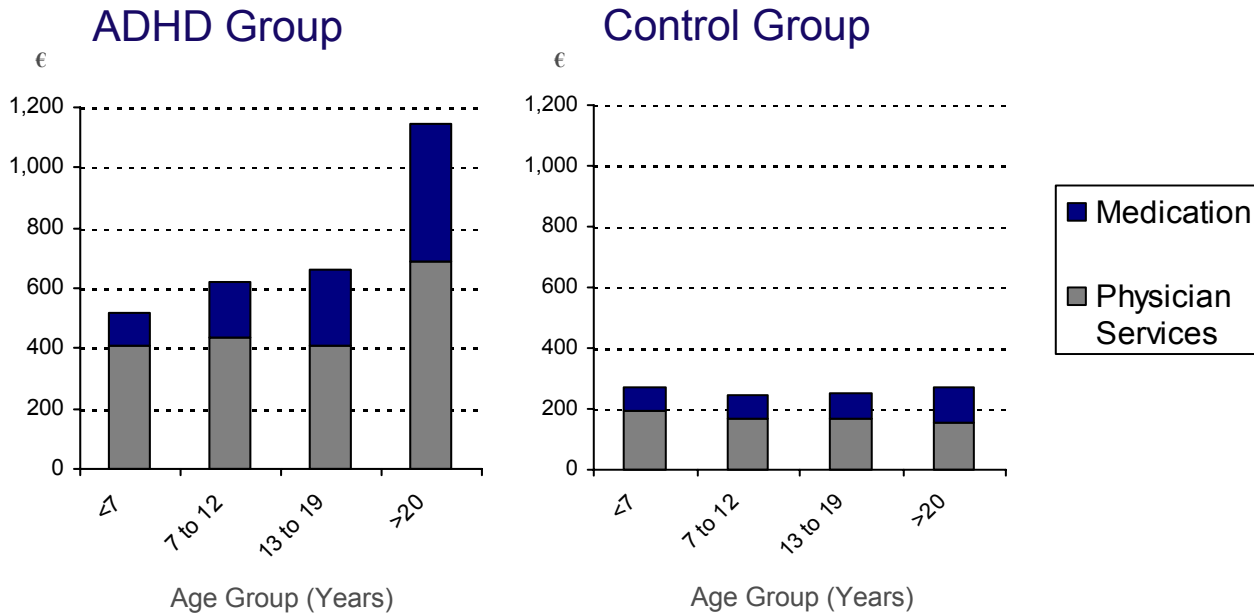
ADHD Treatment of Children and Adolescents: Drug Spending Projection –2012 (England)¹



¹Expenditures by category p.a.; MPH: methylphenidate; IR: immediate-release formulations (Ritalin[®], branded generics [Equasym[®]], generics; Focalin[®]); MR: modified-release formulations (Concerta[®] XL, Equasym[®] XL, Medikinet[®] retard, Focalin[®] XR; MPH-Patch: transdermal system (Daytrana[®]); LisDEX: lisdexamphetamine (NRP104); Nonstimulants: atomoxetine (Strattera[®]), armodafinil (Nuvigil[®]); DEX: dexamphetamine. Base case scenario, from M. Schlander (2007)



ADHD-Related Health Care Expenditures: Average Cost per Patient (Nordbaden, 2003)¹



¹M. Schlander et al. (unpublished data)



Economic Evaluation: The Logic of Cost-Effectiveness

1.



2.



3.



4.



Safety

- ▭ **Does it harm?**
(controlled conditions)

Efficacy

- ▭ **Can it work?**¹
(controlled conditions)

Effectiveness

- ▭ **Does it work and is it safe?**¹
(normal practice)

Efficiency

- ▭ **Do its benefits outweigh its costs?**
(often: "Is it cost-effective"?)

EBM²:
How sure
can we
be?

¹cf. D. Schwartz and J. Lellouch (1967); ²EBM: "evidence-based medicine"



Evidence-Based Treatment¹

▫ Pharmacologic Treatment

- Psychostimulants
 - > 250 studies (mostly cross-over trials)
 - N > 5,000
- Noradrenergic compounds

▫ Behavior Modification

- ~48 classroom studies (N > 900)
- ~80 parent training studies (N > 5,000)

▫ The combination of pharmacologic treatment and behavior modification

- 25 studies (N > 5,000)

¹From W.E. Pelham 2005



How Should These Evidence-Based Treatments be Sequenced?

- ▭ **Begin medication first?**
 - ▭ Physician practice in USA
- ▭ **Begin behavior therapy first?**
 - ▭ Parents' preference
- ▭ **Begin simultaneously?**
 - ▭ Physician preference in some European countries



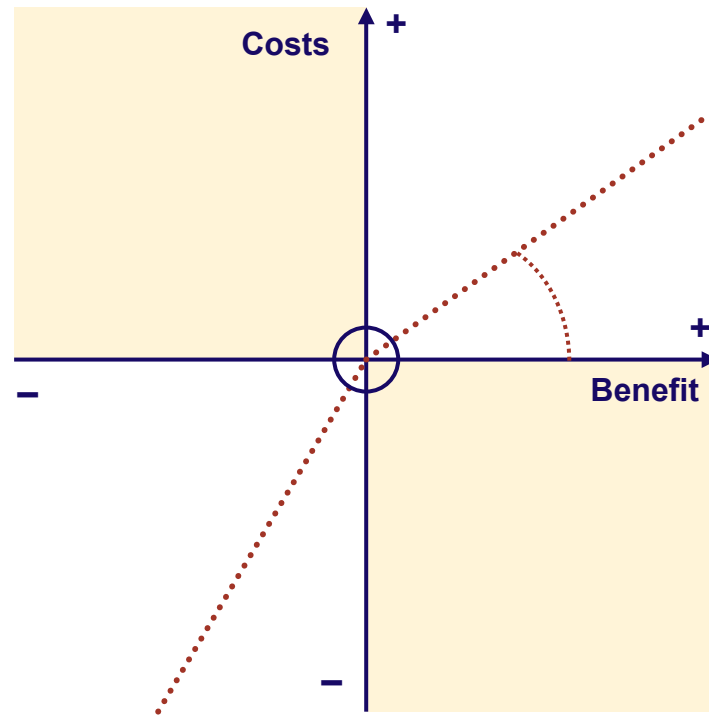
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 - ▭ Parents' preference
- ▭ **Begin simultaneously?**
 - ▭ Physician preference in some European countries

- ▭ **What would you prefer to do with your own child?**
- ▭ **What can we afford as a society?**
- ▭ **What is the cost-effectiveness of these options?**



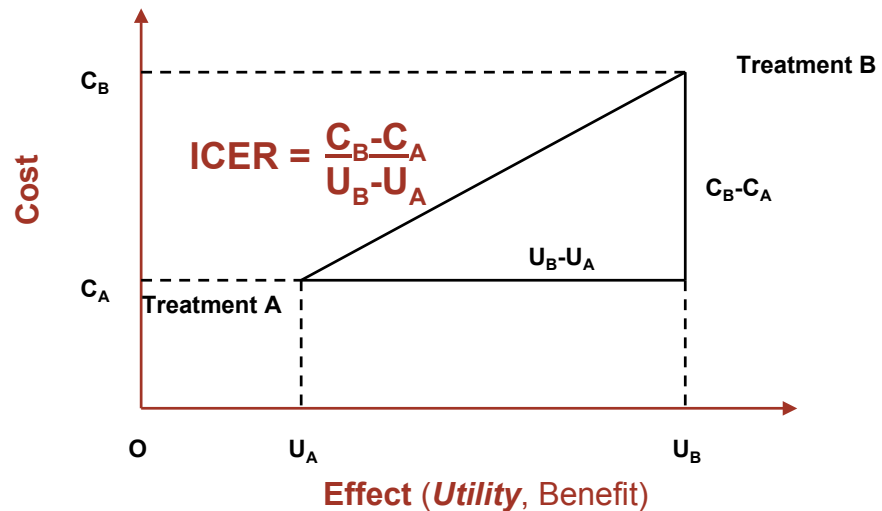
The Logic of Cost-Effectiveness: The C/E Plane¹



¹W.C. Black (1990)



The Logic of Cost-Effectiveness: Incremental Analysis



ICER: Incremental Cost-Effectiveness Ratio



The NIMH MTA Study¹

- **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

¹MTA Cooperative Group 1999a, 1999b



NIMH MTA Study: European Evaluation Strategy¹

- ▭ **Preferred diagnostic criteria vary between jurisdictions**
 - ▭ Analyzing subgroups with hyperkinetic disorder (with and without comorbidity)
- ▭ **Standards of care / treatment preferences vary between jurisdictions**
 - ▭ Adding a hypothetical “Do Nothing” alternative for modeling
- ▭ **Unit costs vary between jurisdictions (and by perspective)**
 - ▭ Costing by country and by perspective; sensitivity analyses
- ▭ **Psychiatric comorbidity is common and known to moderate treatment effectiveness**
 - ▭ Analyzing subgroups by internalizing and/or externalizing comorbidity
- ▭ **Broad range of clinical effectiveness (and “response”) criteria**
 - ▭ Focusing on symptomatic and functional improvement
- ▭ **Absence of reliable utility estimates for QALY (and cost per QALY gained) calculation based on “responders”**
 - ▭ Using expert estimates and parent proxy ratings to establish a reasonable range

¹M. Schlander et al., 2006a, 2006b, 2006c



NIMH MTA Study: Effectiveness Data⁴

▢ Response Rates (SNAP-IV Normalization)

- ▢ Narrow band symptom scale, integrating parent and teacher scores
- ▢ Capturing DSM-IV defined core symptoms of ADHD (inattention, hyperactivity/impulsivity; also opposition/defiance)¹

▢ Quality-Adjusted Life Year (QALY) Estimates

- ▢ Response rates defined by symptomatic normalization (SNAP-IV)
- ▢ Health-related quality of life (“utility”) weights derived from
 - ▢ Expert estimates (“best case” analysis): $\Delta = 0.117^2$
 - ▢ Parent proxy ratings (“base case” analysis): $\Delta = 0.064^3$
- ▢ Note underlying normative assumption (“extrawelfarism”) of QALY maximization; “a QALY is a QALY is a QALY”...

▢ Columbia Impairment Scale (CIS) Scores

- ▢ Global measure of impairment, tapping four domains: interpersonal relations, psychopathology, (job or) schoolwork, use of leisure time

¹Swanson et al. 2001; ²Lord, Paisley 2000; ³Coghill et al. 2004; ⁴M. Schlander et al., 2006a, 2006b, 2006c



NIMH MTA Study: Cost Data¹

- ▭ **Excluding the research component of the study**
 - ▭ Adding three dose titration visits in the medication management and combined treatment arms (cf. Klein et al., 2004)
- ▭ **Direct medical costs only**
 - ▭ Real treatment costs of the NIMH MTA Study
 1. Measured from a “payers’ perspective” (D, NL)
 2. Measured from a “societal perspective” (D, NL, S, UK, USA)
 - ▭ Adjusted for inflation to year 2005 €
 - ▭ Provider costs calculated on an hourly basis
 - ▭ Costs of the STP were calculated per attending day using the hourly wages of the staff needed for the program.
- ▭ **Sensitivity analyses ...**
 - ▭ Probabilistic sensitivity analyses using patient-level data; nonparametric bootstrapping

¹M. Schlander et al., 2006a, 2006b, 2006c; time horizon: 14 months



NIMH MTA Study: Economic Evaluation¹

▸ Incremental Cost-Effectiveness Ratios (ICERs)

$$\text{ICER} = \frac{C_B - C_A}{U_B - U_A}$$

▸ One- and Two-Way Deterministic Sensitivity Analyses ...

- ... for various cost assumptions did not change overall results
- Details available on request (contact Michael.Schlender@INNOVAL-HC.com)

▸ Probabilistic Sensitivity Analyses

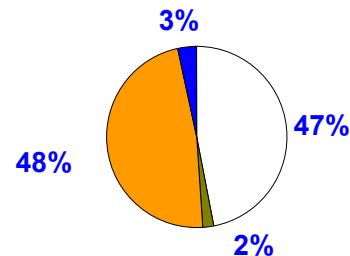
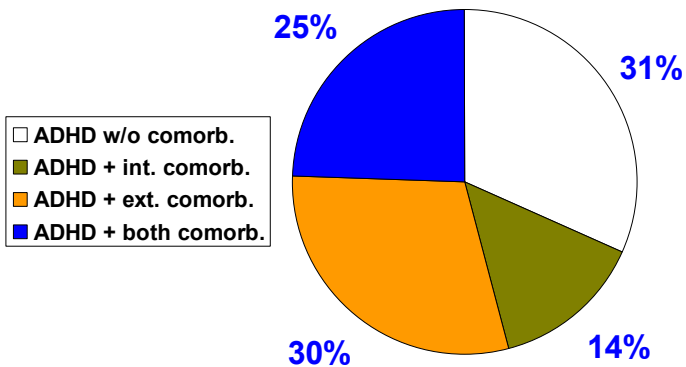
- Non-parametric bootstrapping using patient-level data
- **Ellipsoid ICER Confidence Regions / Scatter Plots**
 - Reflecting the covariance in cost and effect differences
- **Cost-Effectiveness Acceptability Curves (CEACs)**
 - Representing the probability that a strategy is most cost-effective given the MTA data (as a function of “willingness-to-pay”, WTP), taking parameter uncertainty fully into account

¹M. Schlender et al., 2005, 2006a, 2006b, 2006c



NIMH MTA Study: Study Population¹

	ADHD DSM IV								HKD/HKCD ICD10							
Pure ADHD	Total 184								Total 68							
	CC	42	MedMgt	46	Beh	43	Comb	53	CC	13	MedMgt	16	Beh	18	Comb	21
ADHD & Internalizing	Total 81								Total 3							
	CC	19	MedMgt	20	Beh	23	Comb	19	CC	0	MedMgt	0	Beh	3	Comb	0
ADHD & Externalizing	Total 136								Total 69							
	CC	54	MedMgt	40	Beh	42	Comb	36	CC	19	MedMgt	17	Beh	19	Comb	14
ADHD & Both Comorbidities	Total 142								Total 5							
	CC	31	MedMgt	38	Beh	36	Comb	37	CC	1	MedMgt	3	Beh	1	Comb	0
Total	Total 579								Total 145							
	CC	145	MedMgt	144	Beh	144	Comb	146	CC	33	MedMgt	36	Beh	41	Comb	35

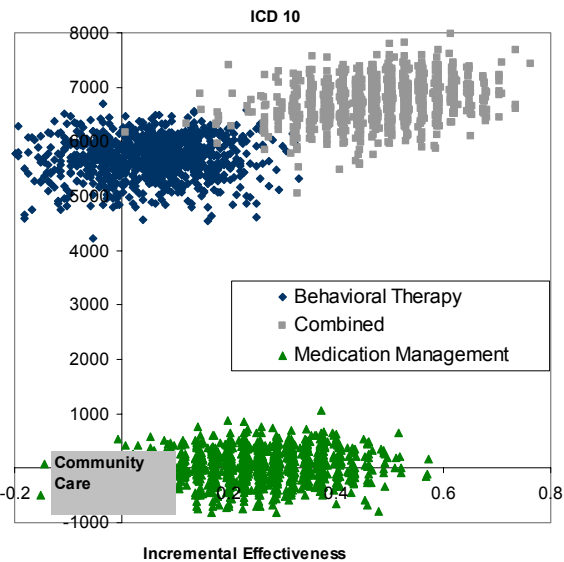
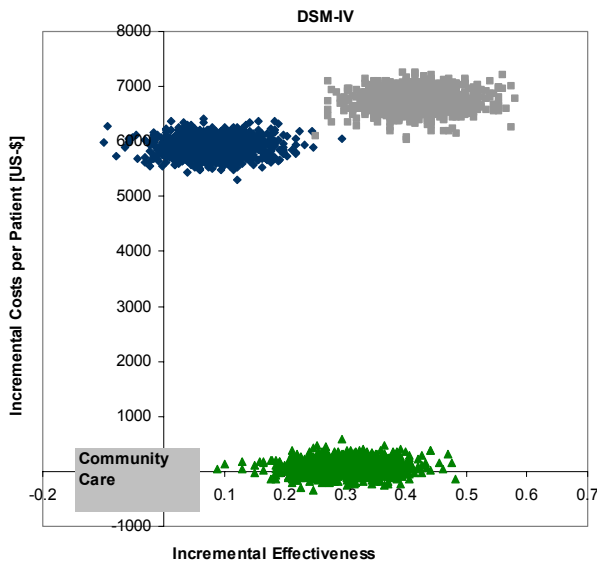




NIMH MTA Study: Primary Economic Evaluation (United States)

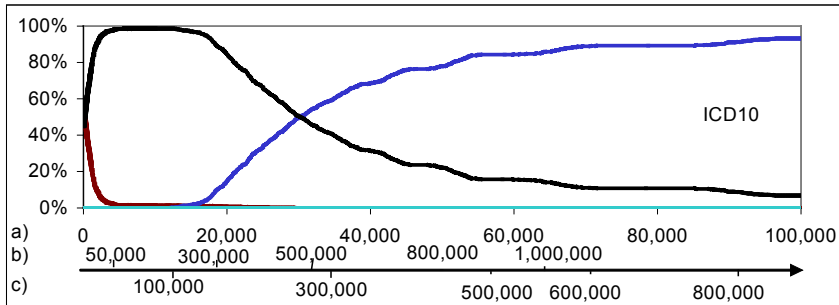
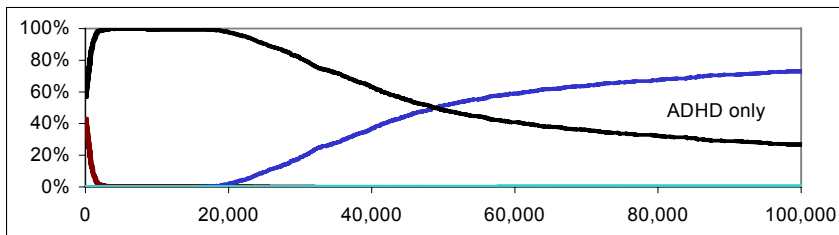
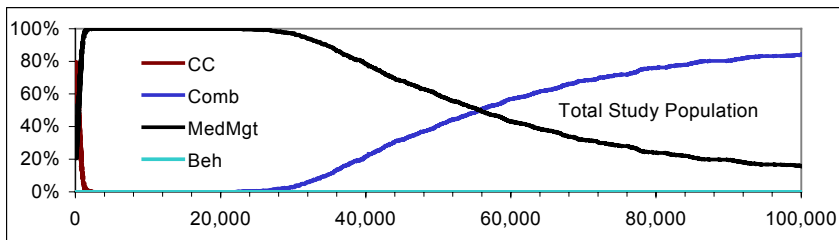
ADHD (n=579)

HKD (n=145)





Cost-Effectiveness Acceptability Analysis (U.S.)



Likelihood
"Best Option"

Decision Makers'
Willingness To Pay [US-\$]

- a) per patient "normalized"
- b) per QALY gained (base case)
- c) per QALY gained (best case)



Cost per Patient “Normalized”: Incremental Cost-Effectiveness (Germany)¹

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

¹M. Schlander et al., 2005, 2006a, 2006b, 2006c



Estimates: Cost per QALY Gained: Incremental Cost-Effectiveness (Germany)¹

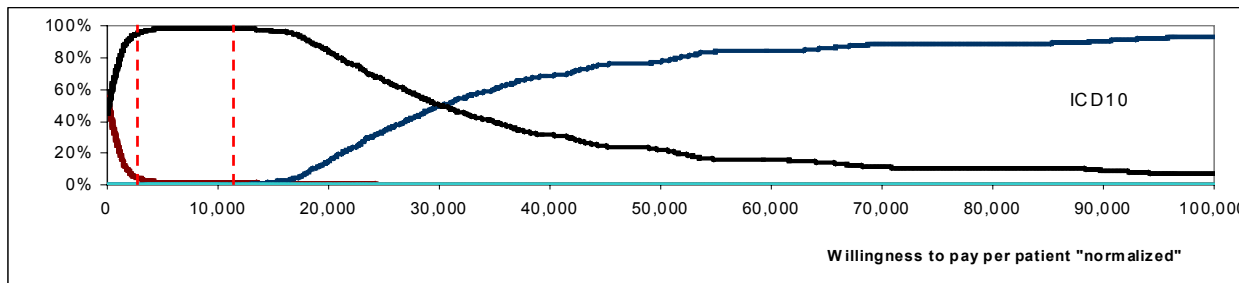
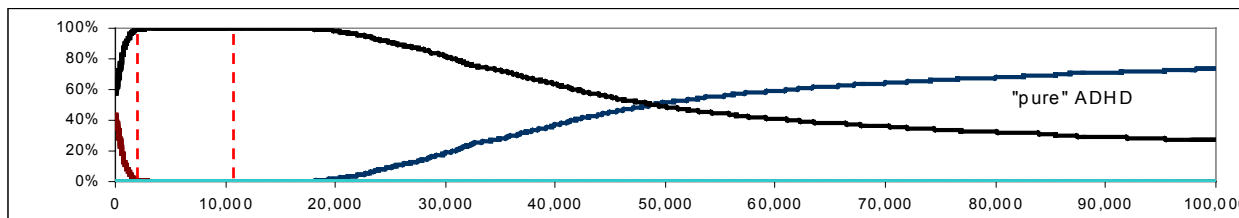
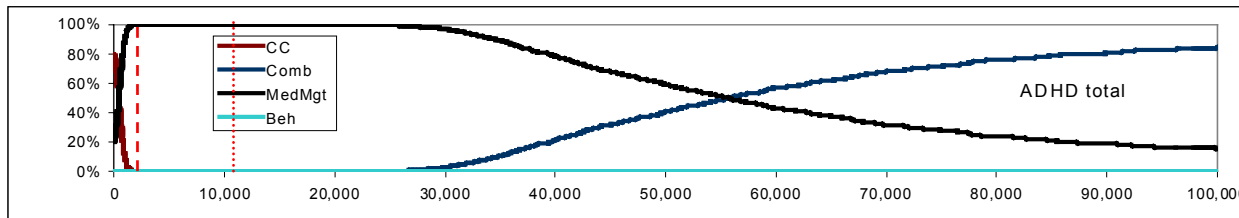
		ADHD all	ADHD only	HKD / HKCD	HKD only
MedMgt versus Do Nothing	Best Case	€ 20,138	€ 18,956	€ 22,620	€ 20,467
	Worst Case	€ 36,787	€ 34,627	€ 41,320	€ 37,387
Comb versus MedMgt	Best Case	€ 731,774	€ 637,102	€ 422,613	€ 299,124
	Worst Case	€ 1,336,707	€ 1,163,773	€ 771,973	€ 546,400

¹M. Schlander et al., 2005, 2006a, 2006b, 2006c



Cost-Effectiveness Acceptability (Germany)

Probability Best Option



¹M. Schlander et al., 2005, 2006a, 2006b, 2006c



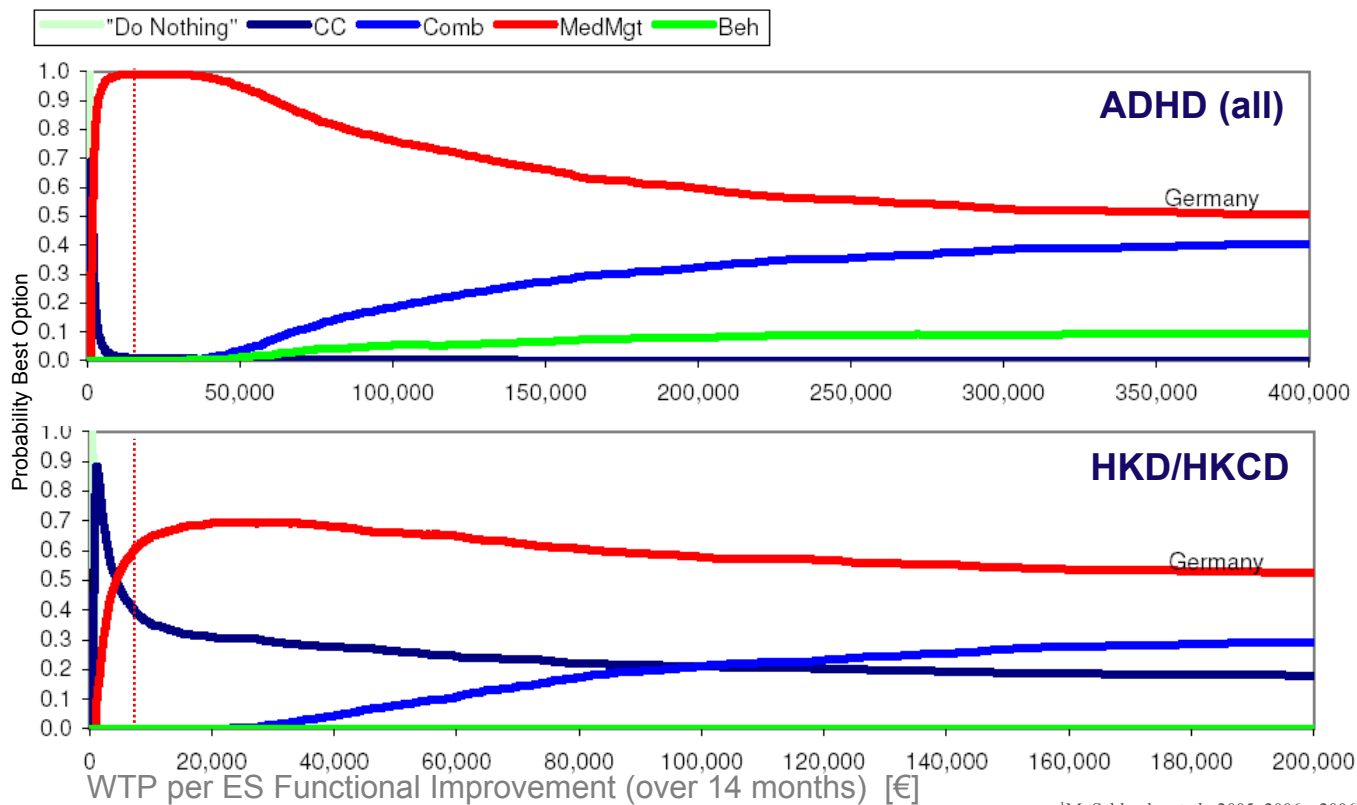
Functional Improvement as Therapeutic Objective of Interest: Cost per Effect Size (CIS): Incremental Cost-Effectiveness (Germany)¹

Germany	ADHD all	ADHD only	HKD/HKCD	HKD only
MedMgt vs CC	€ 1,854.52	€ 1,771.31	€ 4,535.73	€ 622.39
Comb vs MedMgt	€ 1,050,909.58	inferior	inferior	inferior
Beh vs CC	€ 42,528.66	€ 210,739.26	inferior	inferior
Comb vs CC	€ 34,526.17	€ 78,291.13	€ 110,018.26	€ 98,145.31
Comb vs Beh	€ 14,253.07	€ 14,356.15	€ 3,736.45	€ 14,993.88
Beh vs MedMgt	inferior	inferior	inferior	inferior
CC vs DoNothing	€ 1,227.32	€ 1,486.02	€ 792.17	€ 1,514.12
Beh vs DoNothing	€ 12,386.39	€ 18,163.97	€ 14,584.25	€ 13,200.33
MeMgt vs DoNothing	€ 1,436.46	€ 1,583.09	€ 1,170.56	€ 1,255.97
Comb vs DoNothing	€ 12,566.29	€ 17,624.35	€ 10,283.79	€ 13,474.59

¹M. Schlander et al., 2005, 2006a, 2006b, 2006c



Functional Improvement: CEA for Germany¹



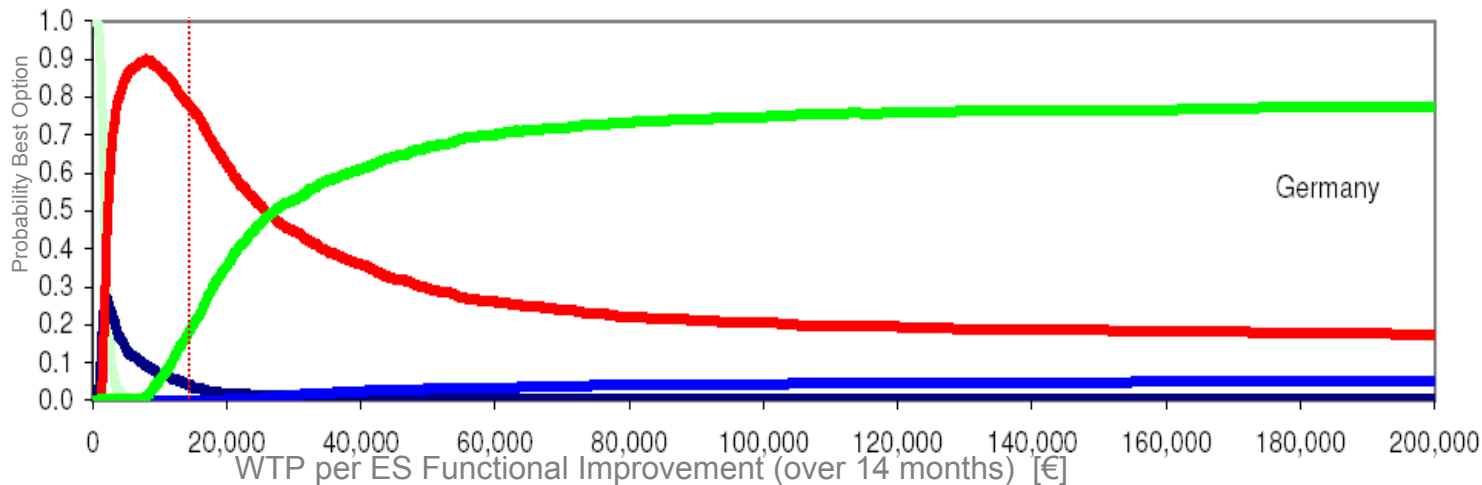
¹M. Schlander et al., 2005, 2006a, 2006b, 2006c



Functional Improvement, Internalizing Comorbidity and Cost-Effectiveness: CEA for Germany¹

■ "Do Nothing"
 ■ CC
 ■ Comb
 ■ MedMgt
 ■ Beh.

ADHD & Intern. Comorb.



¹M. Schlander et al., 2005, 2006a, 2006b, 2006c



What Have We Learnt? Currently Available Evidence (1)

▸ Medication Management

- Generally acceptable to attractive cost-effectiveness ratios
- Most attractive options may differ locally
- MPH-MR appears broadly acceptable in terms of cost-effectiveness
 - Providing compliance advantages translate into superior effectiveness¹
- ATX supported by less compelling data
 - Controversial cost-effectiveness
 - Most likely economically inferior to MPH-MR

Data from

- USA, UK, D, S, NL, CAN, AUS
- Product availability and unit costs
- CAN, UK, D
- Suggestive US data¹
- CAN?
- England +?; Scotland (SMC), AUS (PBAC) -?



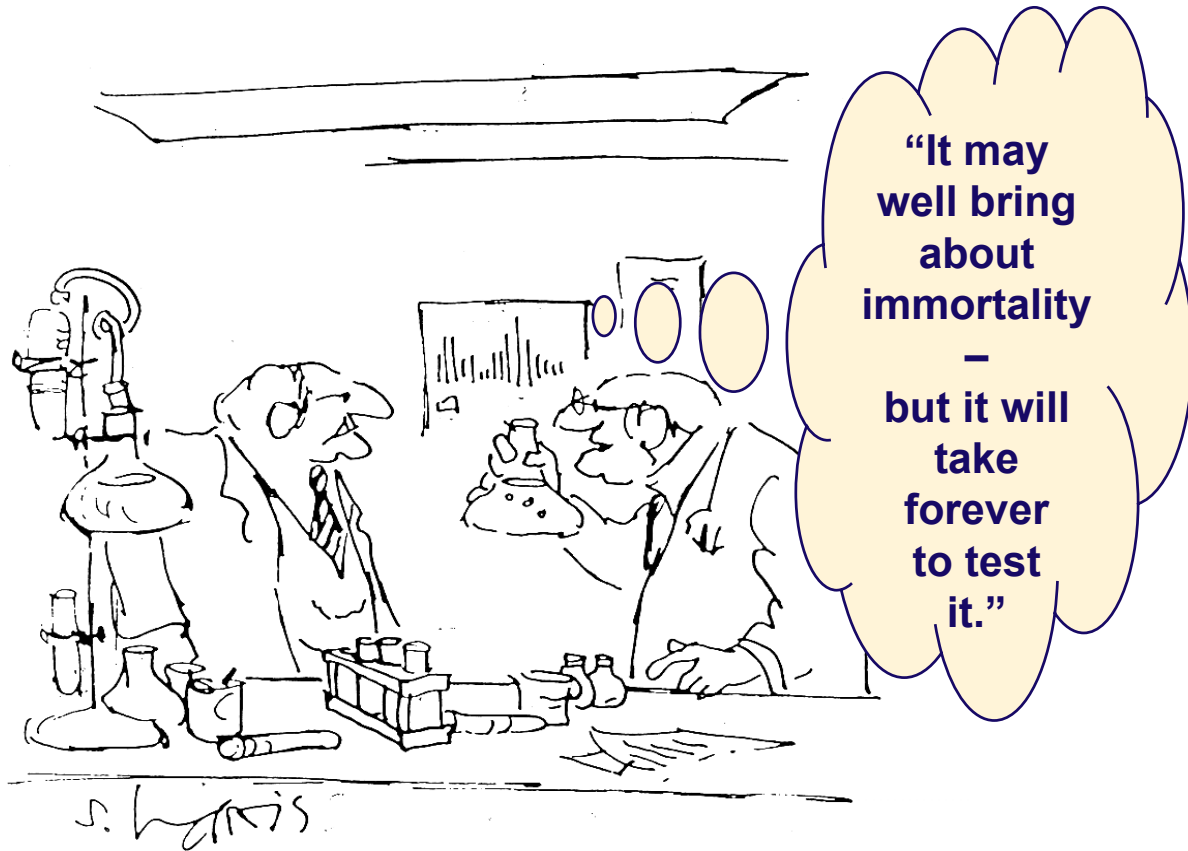
What Have We Learnt? Currently Available Evidence (2)

- ▭ **Psychosocial Interventions**
 - ▭ **Few data available**
 - ▭ Mostly disappointing cost-effectiveness:
 - ▭ Inferior to intense medication management in terms of symptomatic normalization
 - ▭ Mostly inferior to intense medication management in terms of functional improvement
 - ▭ **May be a cost-effective option for patients with internalizing and (in combination with medication management) externalizing comorbidities at higher levels of willingness-to-pay**
 - ▭ **Data needed ...**
 - ▭ ... on better targeted psychosocial interventions
 - ▭ ... on long-term outcomes



Towards a More Complete Analysis: What We (Still) Do Not Know

- ▭ **Effect of treatment on long-term outcomes**
 - ▭ Evaluation of economic implications
- ▭ **Surrogate parameters: which variables might be useful predictors of long-term outcomes (and treatment success)**
- ▭ **Psychosocial Interventions**
 - ▭ Data on cost-effectiveness desperately needed
 - ▭ Assess (better) targeted interventions (compared to MTA protocol)
- ▭ **Analyses from the perspectives of individuals (patients), families (caregivers), economies and societies as a whole**
 - ▭ Treatment preferences of patients and caregivers?
- ▭ **Currently, still no data for many jurisdictions**
 - ▭ Assess transferability of existing economic data
 - ▭ Determine relative cost-effectiveness of atomoxetine





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