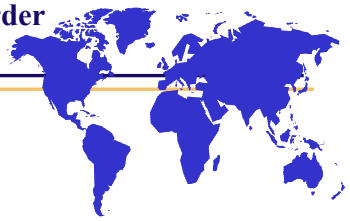
17th World Congress of the **International Association for Child and Adolescent Psychiatry and Allied Professionals** (IACAPAP)

Melbourne, September 12, 2006

Cost-Effectiveness of Treatment Options for Attention-Deficit/Hyperactivity Disorder (ADHD) in Children and Adolescents

What Have We Learnt?



Michael Schlander

University of Applied Economic Sciences Ludwigshafen (Germany)
Institute for Innovation & Valuation in Health Care (INNOVAL^{HC})

IV

BACKGROUND

Institutional Background

- Institute for Innovation & Valuation in Health Care (INNOVAL^{HC}) e.V.
  - Founded in Aschaffenburg/Germany in June 2005
  - Formally associated with the University of Applied Economic Sciences Ludwigshafen
  - Independent Not-For-Profit Research Organization (Not a Commercial Contract Research Organization)
  - Funding of Research Projects
    - Accepted under an "unrestricted educational grant" policy only
    - Receiving support from National Institutes of Mental Health (NIMH, Bethesda, Md.), Physician and Payer Organizations (~80% international projects – USA, Canada, United Kingdom, Sweden, Netherlands)
- Chairman: Prof. Dr. med. Michael Schlander, M.B.A. (Ludwigshafen)
- Vice-Chairman: Prof. Dr. rer. pol. Oliver Schwarz (Mannheim)

BACKGROUND

Personal

- **Institute for Innovation & Valuation in Health Care**
  - Founder and Chairman of INNOVAL[HC], since 2005
- **University of Duisburg / Essen**
  - Scientific Steering Committee "Pharmaceutical Medicine" & Member of Medical Faculty, since 2005
  - Previously at University of Witten/Herdecke (1996-2005)
- **University of Applied Economic Sciences Ludwigshafen**
  - Professor of Health Care Management, since 2002
- **Pharmaceutical Industry**
  - General Management (Germany) 1999-2002
  - Commercial Roles (in USA, Belgium, and Germany) 1993-1999
  - Clinical Research & Development (Europe) 1987-1993
- **Experimental Brain Research**
  - Academia (University of Frankfurt a.M.) 1982-1987
- **Diploma in Health Economics**
  - Stockholm School of Economics (2002)
- **Master of Business Administration (M.B.A.)**
  - City U of Bellevue/Washington, Valedictorian of the class of 1994
- **M.D. (Dr. med.)**
  - University of Frankfurt am Main, summa cum laude (1985/87)

OUTLINE

Agenda

- **Rationale**
  - Some Principles of Economic Thinking
  - Increasing Relevance of Economic (Cost-Effectiveness) Evidence in ADHD
- **Health Technology Assessments (HTAs) and Cost-Effectiveness Analyses (CEAs)**
  - International Overview
  - What Have We Learnt?
- **Research Needs**

RATIONALE

- Principles of Economic Thinking
- Increasing Relevance
- Critical Review
- What Have We Learnt?
- An Emerging Pattern?
- Research Needs

INTRODUCTION

Economic evaluation of new medical technologies

Key Questions Addressed

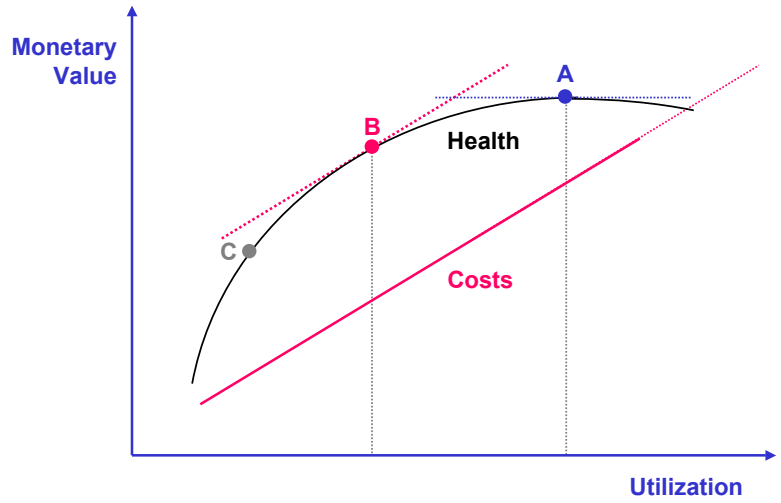
1. **Safety**
   - Does it harm? (controlled conditions)
2. **Efficacy**
   - *Can* it work?[1] (controlled conditions)
3. **Effectiveness**
   - *Does* it work[1] and is it safe? (normal practice)
4. **Efficiency**
   - Is it cost-effective?

How sure can we be? (evidence-based medicine)

[1]cf. D. Schwartz & J. Lellouch 1967

INTRODUCTION

Determining the optimal level of health care utilization:
(A) evidence based medicine, (B) economic evaluation[1]

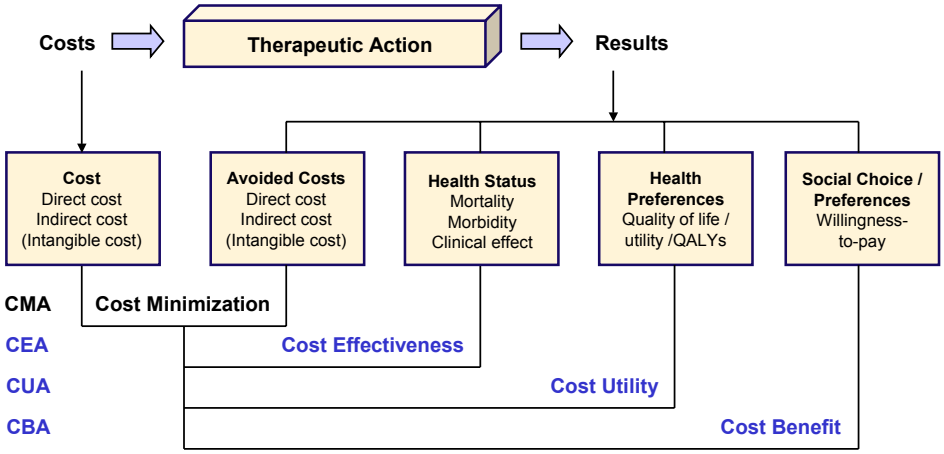


[1]cf. Victor R. Fuchs: "Health Care and the United States Economic System",
The Milbank Memorial Fund Quarterly, April 1972, pp. 211-237.

INTRODUCTION

Economic Analysis

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



INTRODUCTION

Economic evaluation of new medical technologies[1]

Cost-Effectiveness

A medical intervention is never cost-effective in itself, but only ...

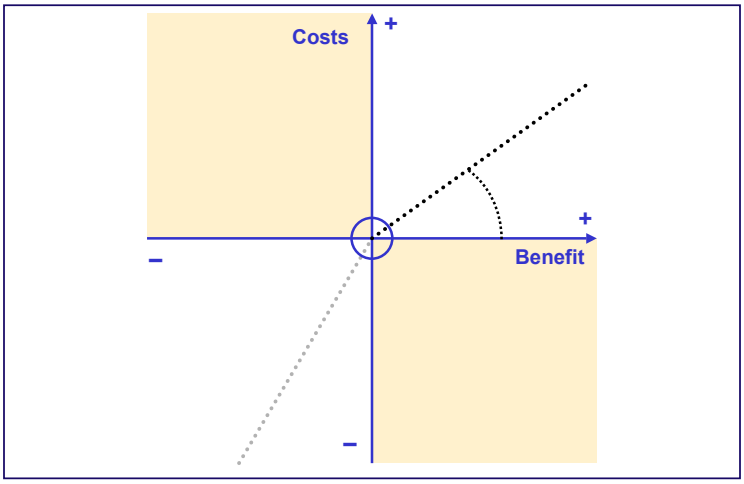
- … in relation to a defined alternative
- … in a defined indication
- … for a specific patient group
- … from a specific perspective

[1]Chart ccourtesy of G. Kobelt (2002)

INTRODUCTION

Economic evaluation of medical interventions

The Cost-Effectiveness Plane[1]

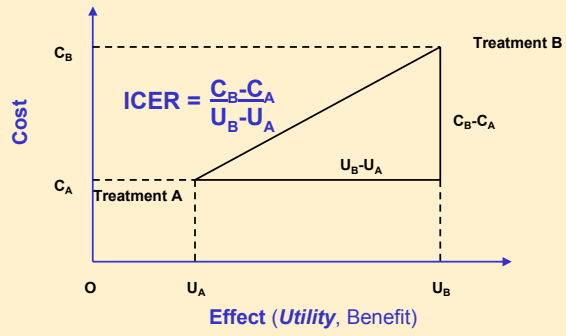


[1]W.C. Black (1990)

INTRODUCTION

Economic evaluation of new medical technologies[1]

Incremental Analysis



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

ICER: ***Incremental Cost-Effectiveness Ratio***

[1]Ccourtesy of G. Kobelt (2002)

INTRODUCTION

© THE NEW YORKER (1990)

Not *so* new:

The evaluation of human life time in economic / monetary terms

INTRODUCTION

Economic evaluation of new medical technologies[1]

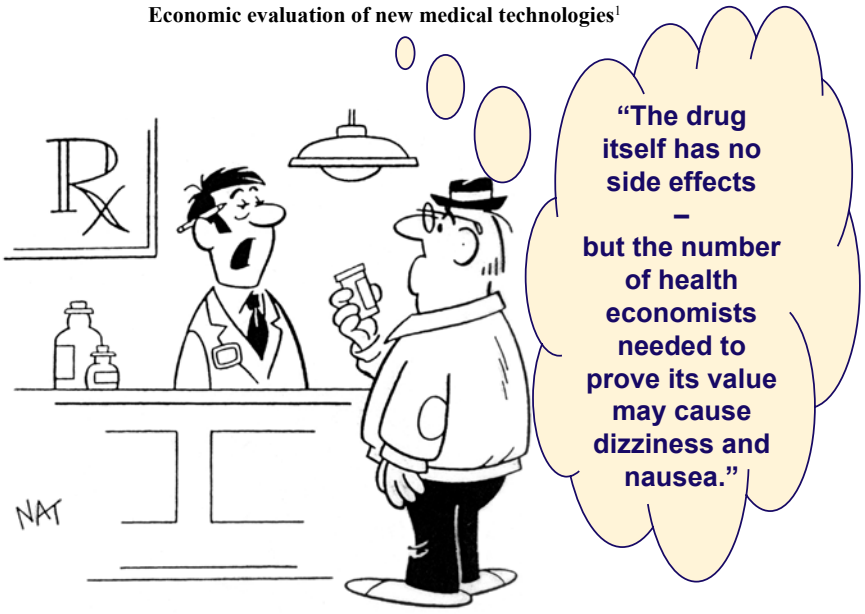
Some Cost-Effectiveness Benchmarks

- **No scientific basis**
- **International de facto standards:**
  - **New Zealand** (PHARMAC):
    NZ-$ 20,000 / QALY[1]
  - **Australia** (PBAC):
    AUS-$ 42,000 / LYG to AUS-$ 76,000 / LYG[2]
  - **England and Wales** (NICE):
    £ 20,000 – £ 30,000 / QALY
  - **United States** (MCOs):
    US-$ 100,000 / QALY[3]

[1]C. Pritchard (2002); QALY: "quality-adjusted life year"; [2]George et al. (2001); LYG: "life year gained"
[3]D.M. Cutler, M. McClellan (2001)

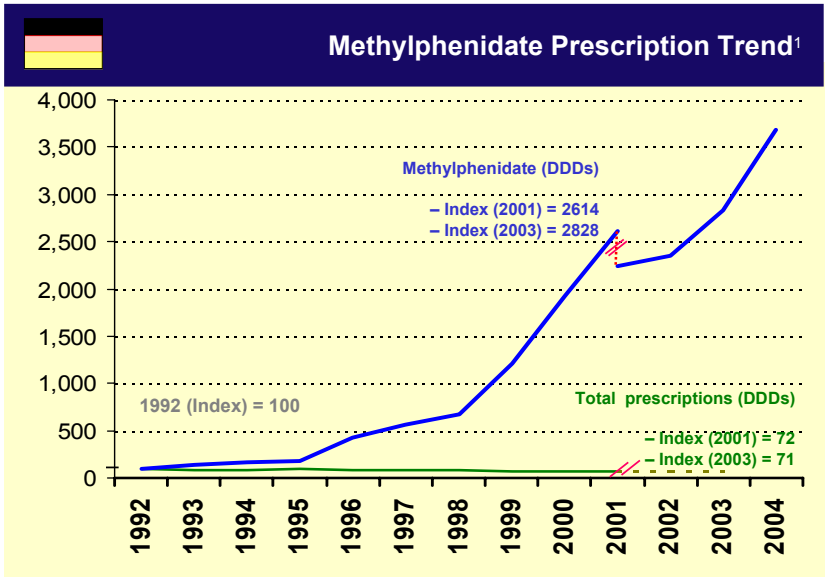
INTRODUCTION

Economic evaluation of new medical technologies[1]



AN ECONOMIC PERSPECTIVE

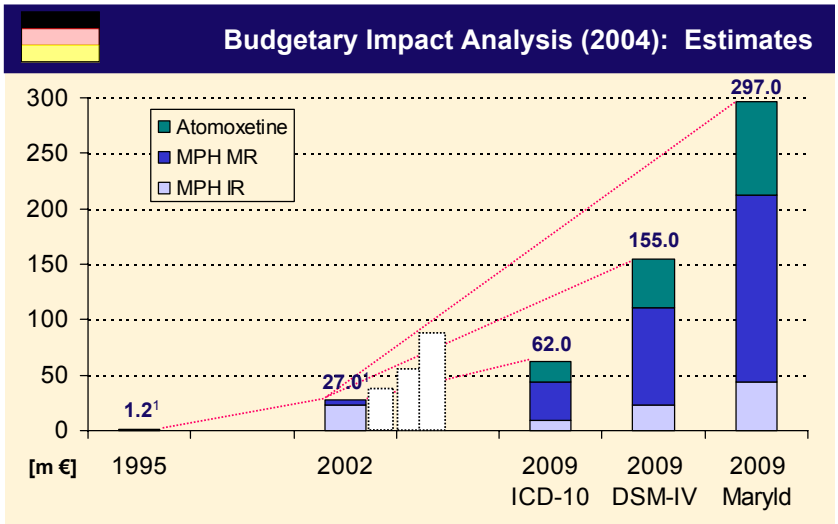
During the last decade, methylphenidate prescriptions have grown by a factor of ~37.



[1]Source: U. Schwabe, D. Paffrath 1993 – 2004; note change of database for year 2001/2002; all data on "public" spending refer to statutory sick funds (GKV); without parallel imports

AN ECONOMIC PERSPECTIVE

An earlier estimate of the future impact of ADHD on pharmaceutical spending (perspective of the Statutory Health Insurance, SHI [GKV])



[1]Data source: Schwabe und Paffrath (1996, 2003); GEK (2004); MPH sales data adjusted by excluding 5% share of indications other than ADHD in children and adolescent; year 2002 data include an estimated revenue of 4.6m€ MPH MR reimports; cf. 2003 (AVR 2004): 36.7m€ 2004 (AVR 2005): 51.6m€ (excl. imports) Source: Schlander (2004)

Explaining the profound increase in expected prescription drug spending

Reasons for Increased Spending on ADHD Treatment

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 cognitive-behavioral therapy) are likely to increase as well.

Schlander (2004)

Acquisition costs of important drugs licensed for treatment of ADHD

Prescription Drug Spending: Acquisition Costs[1]

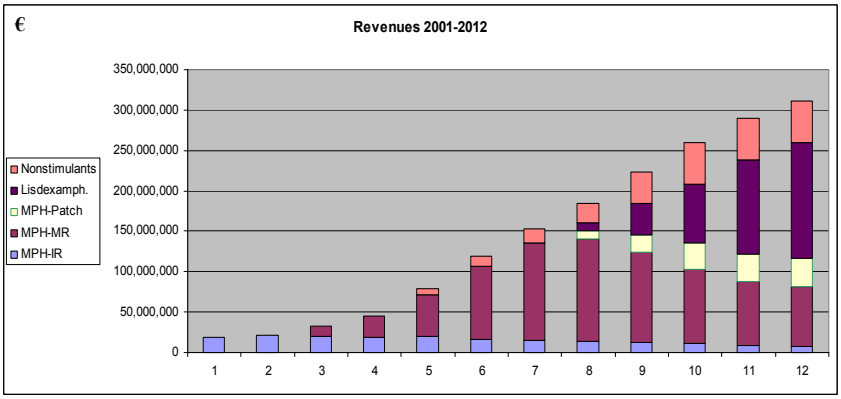
Trade name	Active ingredient	Abbreviation; DDD	Manufacturer / Distributor	Cost / DDD	Cost / DDD
Dexedrine®	Dexampheta-mine sulphate	**DEX** 20mg/d	UCB Pharma (UK)	./.	£ 0.42
Ritalin®	Methylphenidate hydrochloride	**MPH-IR** 30mg (t.i.d.)	Cephalon UK / Novartis	€ 1.58	£ 0.56
Equasym®	Methylphenidate hydrochloride	**MPH-IR** 30mg (t.i.d.)	UCB Pharma (UK, D)	€ 1.41	£ 0.56
MPH Generics	Methylphenidate hydrochloride	**MPH-IR** 30mg (t.i.d.)	TAD (D) (et al.!)	€ 1.13	<< £ 0.56
Equasym® XL Medikinet® ret.	Methylphenidate hydrochloride	**MPH-MR08** 30mg(o.a.d.[?])	UCB Pharma Medice (D only)	n.a. € 2.83	£ 1.17 ./.
Concerta® XL	Methylphenidate hydrochloride	**MPH-MR12** 36mg (o.a.d.)	Janssen-Cilag Ltd.	€ 2.84	£ 1.23
Strattera®	Atomoxetine hydrochloride	**ATX** (o.a.d.) [?]	E. Lilly & Company Ltd.	€ 3.69 (o.a.d.) / € 7.38 (b.i.d.)	£ 1.95 (o.a.d.) / £ 3.80 (b.i.d.)

[1]2005; data sources: UK: British National Formulary (BNF), March 2005 (Equasym XL: September 2005); Germany: Gelbe Liste, September 2005 (N2)

INCREASING RELEVANCE

The Example of Prescription Drug Spending – Updated Projections (2006)

Projected Spending for Child and Adolescent ADHD Drug Treatment (SHI Germany)[1]

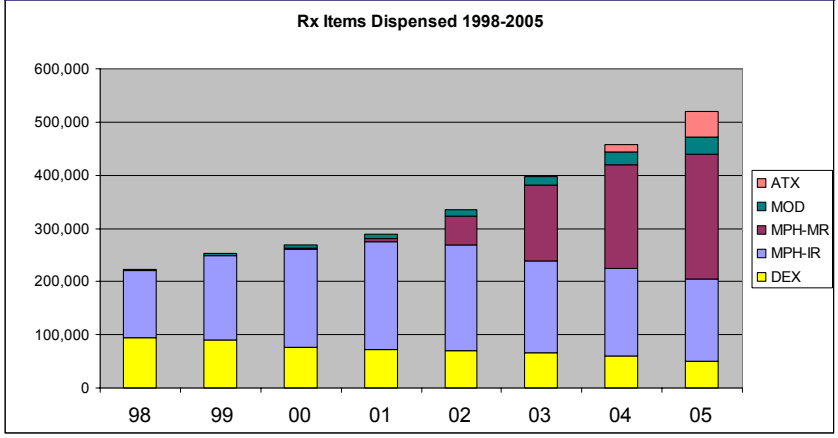


[1]Total (cumulated) expenditures p.a.; MPH: methylphenidate; IR: immediate-release formulations (Ritalin^{R}, branded generics [Equasym, Medikinet], generics; Focalin^{R}); MR: modified-release formulations (Concerta^{R} XL, Equasym^{R} XL, Medikinet^{R} retard, Focalin^{R} XR; MPH-Patch: transdermal system (Daytrana^{R}); LisDEX: lisdexamphetamine (NRP104); Nonstimulants: atomoxetine (Strattera^{R}), modafinil (Sparlon^{R}); SHI: statutory health insurance (Germany)

INCREASING RELEVANCE

The Example of Prescription Drug Spending

ADHD-Related Prescriptions (NHS England)[1]

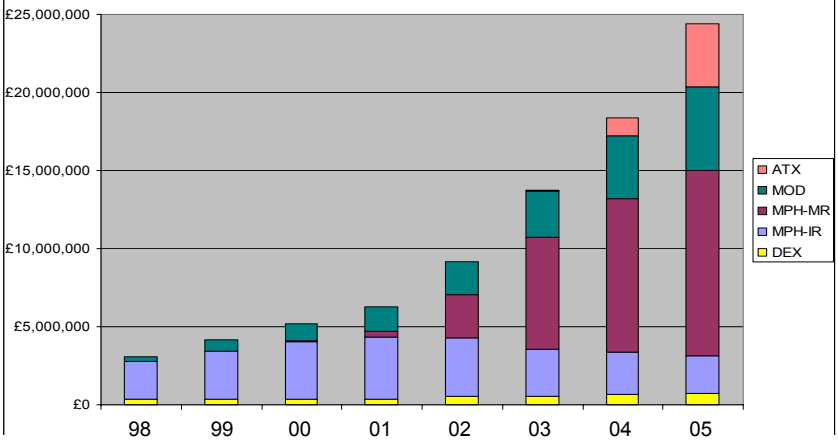


[1]Prescription items dispensed in the community p.a.; DEX: dexamphetamine (Dexedrine^{R} and others); MPH: methylphenidate; IR: immediate-release formulations (Ritalin^{R} and generics); MR: modified-release formulations (Concerta^{R} XL, Equasym^{R} XL; Ritalin^{R} SR imports); MOD: modafinil (Provigil^{R},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

INCREASING RELEVANCE

The Example of Prescription Drug Spending

ADHD-Related Expenditures (NHS England)[1]

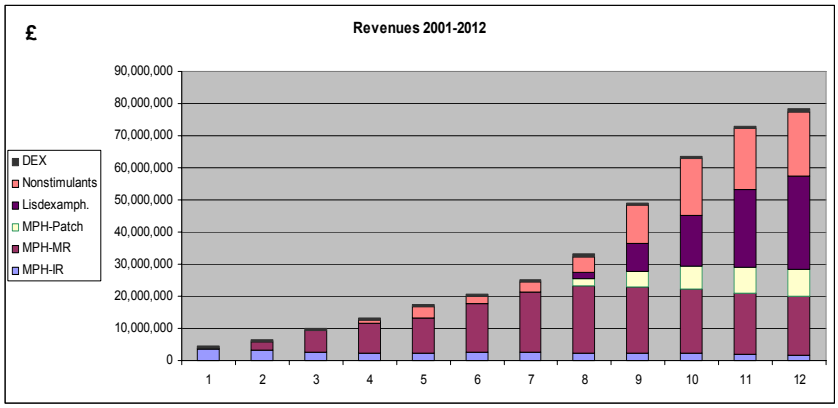


[1]Expenditures by category p.a.; DEX: dexamphetamine (Dexedrine® and others); MPH: methylphenidate; IR: immediate-release formulations (Ritalin® and generics); MR: modified-release formulations (Concerta® XL, Equasym® XL; Ritalin® SR imports); MOD: modafinil (Provigil®, licensed for daytime sleepiness);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

INCREASING RELEVANCE

The Example of Prescription Drug Spending

Projected Spending for Child and Adolescent ADHD Drug Treatment (NHS England)[1]



[1]Total (cumulated) expenditures p.a.; MPH: methylphenidate; IR: immediate-release formulations (Ritalin®, branded generics [Equasym, Medikinet], 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®), modafinil (Sparlon®); DEX: dexamphetamine (England only).

Source: Schlander (2006)

WHAT HAVE WE LEARNT?

- Principles of Economic Thinking
- Increasing Relevance
- Critical Review
  - Early HTAs
  - MTA-Based Cost-Effectiveness Analyses
  - NICE Technology Appraisal 2006
  - Further Data
- What Have We Learnt?
- An Emerging Pattern?
- Research Needs

CRITICAL REVIEW

ADHD

Treatment Options[1]

- **Evidence-Based Treatment** (supported by Clinical Guidelines)
  - "Multimodal" Treatment Strategy, usually including:
  - Pharmacotherapy
  - Psychosocial Treatment (Behavioral Therapy)
- **Other Interventions** (e.g., interventions within the school setting)

- **Less-Proven, Complementary and Alternative Medicine**
  - Physical exercises
  - Neurofeedback
  - Chelation therapy
  - Systemic antifungal treatment
  - Various diets (elimination diets, dietary supplements, vitamins)
  - Homeopathy, acupuncture, herbal regimens

[1]M.D. Rappley, 2005; R. Bussing et al., 2002;
L.E. Arnold, *Review* in Ann. N.Y. Acad. Sci., 2001

Overview of Cost-Effectiveness Studies of ADHD Treatment Strategies

- **Comparative Studies Only**
  - Providing data on costs and effects of at least two alternative treatment strategies, including incremental evaluation
  - Health Technology Assessments (HTAs) including economic evaluation
  - Cost-Effectiveness, Cost-Utility, Cost-Benefit Evaluations
- **Search Strategy**
  - MEDLINE, ebsco, OHE HEED databases
  - Major international scientific meetings (abstracts / presentations)
    a) psychiatry, child and adolescent psychiatry
    b) health economics and outcomes research, medical decision-making

Type	Basis	Agency / Authors	Juris-diction	Comparison	Effectiveness Measure
HTAs	Literature review and decision model	CCOHTA, December 1998 (Zupancic et al., 1998)	CAN	MPH-IR, DEX, PEM; BEH, Comb, NoTx	CTRS (Effect Size / WMD)
		NICE, July 2000 (Lord and Paisley, 2000)	UK	MPH-IR, NoTx	QALYs; (also CTRS points)
		NICE, March 2006 (King et al., 2004, 2006)	UK	DEX, MPH (-IR, -MR08, -MR12), ATX	QALYs based on synth'd. response rates
CEAs	NIMH MTA* Study (1999)	Jensen et al., 2004, 2005	US	CC, BEH, MedMgt, Comb	SNAP-IV Normalization Rates
		Foster et al., 2005, 2006	US	CC, BEH, MedMgt, Comb	Columbia Impairment Scale (CIS)
		Schlander et al., 2004, 2005	US, D	CC, BEH, MedMgt, Comb	SNAP-IV Normalization Rates
	Literature review, model	Narayan and Hay, 2004	US	MPH-IR, MAS[1], NoTx	QALYs based on response rates
	Literature, expert opinion	Iskedijan et al., 2003	CAN	MPH-IR, ATX	SFDs – symptom free days
	CCOHTA model (ext'd.)	Annemans and Ingham, 2002	CAN	MPH-MR12, MPH-IR (w/ or w/o NDT?)	CPRS (Effect Size)
	Meta-analysis and model	Donnelly et al., 2004	AUS	MPH-IR, DEX	YLD[2]; DALYs (averted)
	Literature review	Wessex DEC Report 1998, (Gilmore and Milne, 2001)	UK	MPH-IR, Plac.	QALYs based on response rates
	Meta-analysis and decision analytic model (CCOHTA ext'd.)	Schlander et al., 2004	UK	MPH-MR12, MPH-IR (w/ NDT)	CTRS (Effect Size)
		Schlander et al., 2004	D	MPH-MR12, MPH-IR (w/ NDT)	CTRS (Effect Size)

[2]MAS: mixed amphetmaine salts

[2]YLD: years lived with disability

Early HTAs of ADHD Treatment Strategies

- **CCOHTA (Canada, 1998)**[1]
  - Assumed daily dose MPH IR: 2 x 10mg
  - MPH IR dominated its alternatives
  - **ICER** (versus a hypothetical "Do Nothing" alternative):

    CAN-$ 498 / ES (basis CTRS, WMD)
  - Few data on behavioral therapy[3].

- **NICE (England and Wales, 2000)**[2]
  - Assumed daily dose MPH IR: 3 x 10mg
  - **Cost / QALY** estimated at **£ 9,200 – £ 14,600**

[1]J. Zupancic et al. (1998): a six-point or one standard deviation (weighted mean) difference was considered clinically relevant, CAN-$ (1997); [2]J. Lord & S. Paisley (2000; cf. also A. Gilmore & R. Milne (2001): NHS perspective, one-year time horizon, £ (1997); [3]fewer than 20 patients each for the BEH and COMB strategies.

The NIMH MTA Study[1]

- **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

[1]MTA Cooperative Group 1999a, 1999b

Effectiveness Data

- **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

[1]J. Swanson et al. 2001; [2]Lord, S. Paisley 2000; [3]D. Coghill et al. 2004

Cost-Effectiveness and Sensitivity Analyses

- **Incremental Cost-Effectiveness Ratios (ICERs)**

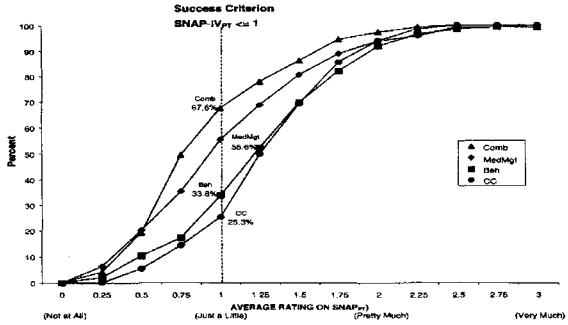
$$\text{ICER} = \frac{C_B - C_A}{U_B - U_A}$$

- **One- and Two-Way Deterministic Sensitivity Analyses** …
  - … for various cost assumptions did not change overall results
  - Details available on request (contact Peter Jensen at Columbia U)
- **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

CRITICAL REVIEW

MTA based economic evaluation of ADHD treatment strategies: primary analysis

Clinical Effectiveness[1]



n = 579

Costs per Patient[2]

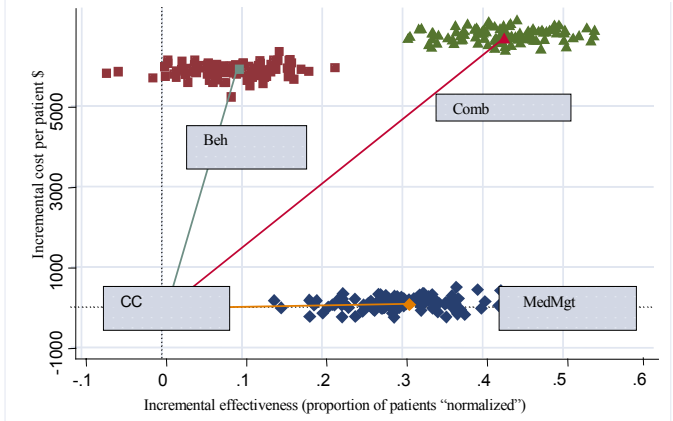
		CC	MedMgt	Beh	Comb
Components of Costs	Costs of Medication	$222	$624	$104	$538
	Medication Visit Costs	$91	$393	$34	$408
	Psychosocial Costs	$757	$163	$6,840	$6,881
	Total Costs	$1,071	$1,180	$6,988	$7,827

[1]J.M. Swanson et al. 2001; [2]P.S. Jensen et al. 2005

CRITICAL REVIEW

MTA based economic evaluation of ADHD treatment strategies: primary analysis[1]

Cost-Effectiveness Analysis

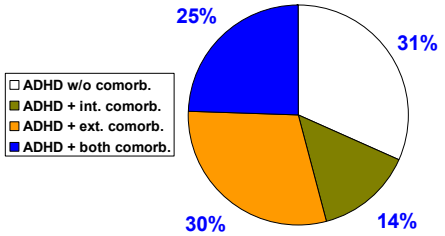


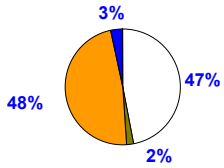
[1]P.S. Jensen et al. 2005

MTA based economic evaluation of ADHD treatment strategies

Study Population

	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	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





MTA based economic evaluation of ADHD treatment strategies

Primary Cost-Effectiveness Analysis

Cost per Patient "Normalized" [US-$]

Diagnosis		DSM-IV				ICD-10
Comorbidity	MTA overall	ADHD only	ADHD+intern.	ADHD+extern.	ADHD+both	HKD/HKCD
Comparison						
MedMgt vs. CC	**352**	**dominant**	**869**	**137**	**1,000**	**124**
COMB vs. MedMgt	**55,392**	**48,915**	**inferior**	**75,978**	**29,439**	**31,445**
BEH vs. CC	65,744	47,749	27,245	inferior	22,737	113,462
COMB vs. CC	15,712	14,071	12,062	15,319	13,020	14,350
COMB vs. BEH	2,468	936	4,831	2,090	4,235	2,535
BEH vs. MedMgt	inferior	inferior	inferior	inferior	inferior	inferior

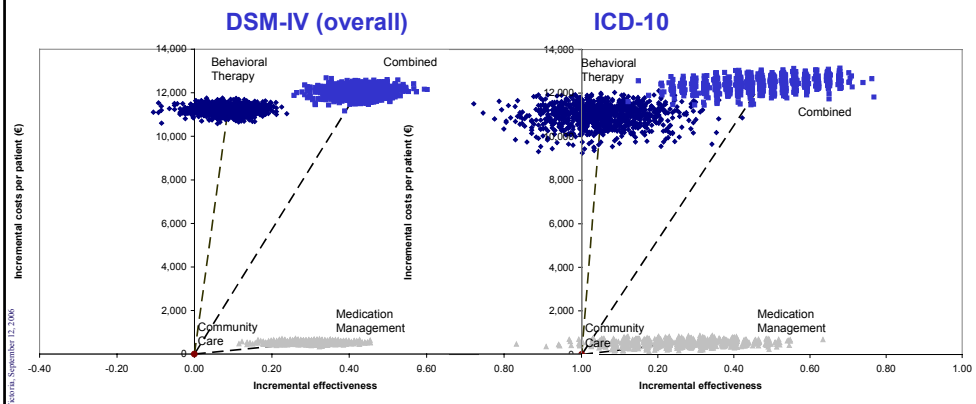
Cost per QALY Gained [US-$]

(a) Best Case:			**n.a.**	**n.a.**	**n.a.**	
MedMgt vs. CC	**3,009**	**dominant**	**n.a.**	**n.a.**	**n.a.**	**1,060**
COMB vs. MedMgt	**473,436**	**418,077**	**n.a.**	**n.a.**	**n.a.**	**268,761**
BEH vs. CC	561,915	408,111	n.a.	n.a.	n.a.	969,761
COMB vs. BEH	21,094	8,000	n.a.	n.a.	n.a.	21,667
(b) Base Case:						
MedMgt vs. CC	**5,500**	**dominant**	**n.a.**	**n.a.**	**n.a.**	**1,938**
COMB vs. MedMgt	**865,500**	**764,297**	**n.a.**	**n.a.**	**n.a.**	**491,328**
BEH vs. CC	1,027,250	746,078	n.a.	n.a.	n.a.	1,772,844
COMB vs. BEH	38,563	14,625	n.a.	n.a.	n.a.	39,609

CRITICAL REVIEW

German Cost-Effectiveness Analysis based on NIMH MTA Trial by Symptomatic Normalization of Patients

Incremental Cost-Effectiveness[1]

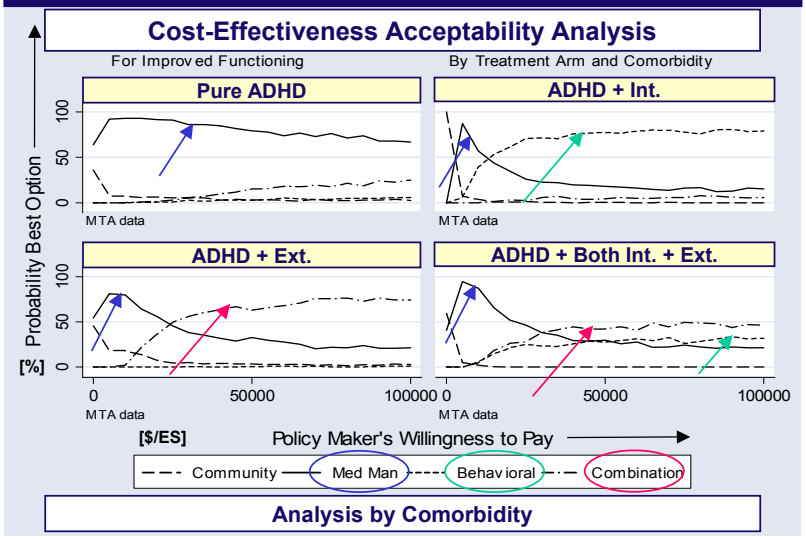


[1]M. Schlander et al. 2005

RESULTS

MTA based economic evaluation of ADHD treatment strategies

Secondary Cost-Effectiveness Analysis (CIS)



Foster, Schlander, Jensen, et al. (2005)

RESULTS

MTA based economic evaluation of ADHD treatment strategies

Key Observations

- A carefully monitored, intense **medication management** strategy as defined by the MTA protocol is clearly cost-effective[1].
- This observation holds **across all subgroups** analyzed (by comorbidity and diagnostic criteria) as well as by all measures of effectiveness studied.
- **Cost/QALY** estimates[2] are **US-$ 3,000 – 5,500** for all patients (n=579) and US-$ 1,000 – <2,000 for patients with hyperkinetic disorder (HKD/HKCD; n=145).
- Compared to "all" patients and those with "pure" ADHD, **behavioral interventions** are relatively more cost-effective in terms of achieving improved functioning in patients with more complex comorbidities (both internalizing and externalizing) .

Some Limitations

- Cost-effectiveness of less intense and/or better targeted behavioral interventions?
- Longer time horizons than employed in our present analyses may modify conclusions, particularly re. the cost-effectiveness of behavioral interventions.
- Normative premises of cost-effectiveness and cost-utility analyses should be kept in mind when interpreting these findings.

[1]compared to all other interventions tested; 2compared to community treatment; the least attractive cost per QALY estimate may be derived from the subgroup with both comorbidities, at an estimated US-$/QALY ranging from 8,550 to 15,600 which by current standards would reflect acceptability; however, cost/QALY estimates in the presence of comorbidity are difficult to interpret and have, therefore, not been presented.

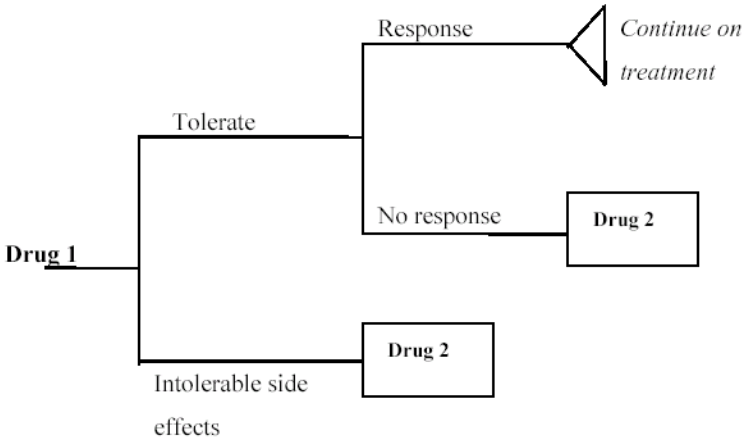
CRITICAL REVIEW

Technology Appraisal of Methylphenidate, Dexamphetamine and Atomoxetine (NICE 2006)

NICE Technology Appraisal Process

- **Three (to four) phases**
  - Scoping
  - Assessment
  - Appraisal
  - Appeal (if lodged by one or more consultees)
- **General features**
  - Relatively high degree of transparency
  - Multiple opportunities for stakeholders to provide input
  - Highly standardized ("reference case analysis")
  - Highly predictable nature of process

NICE 2006: Economic Model Structure[1]



[2]Assessment report, p. 223; King et al., 2004

CRITICAL REVIEW

Technology Appraisal of Methylphenidate, Dexamphetamine and Atomoxetine (NICE 2006)

NICE 2006: Clinical Evidence Informing Economic Model

Evidence base

Literature search: 2,908 publication titles identified and screened (AR, p. 52)
AHRQ Review (Jadad et al., Nov. 1999): 78 trials (77 RCTs) selected
CCOHTA Review (Miller et al., Dec. 1998): 26 trials selected (n~1,000)
Schachar et al. (2002): 14 trials (≥ 12 weeks) selected (n=1,379)
MTA Cooperative Study Group (1999): 4 groups, 2 years, n=579
Klein et al. (2004), **Abikoff** et al. (2004): 3 groups, 2 years, n=103

Filter 1

RCTs examining MPH, DEX, or ATX,
alone or in combination, with or without NDT;
patients age <18y; "≥3 weeks treatment duration";
reporting core symptoms, quality of life,
adverse effects, or educational performance

Effectiveness review
Focus on hyperactivity ratings

64 randomized clinical studies (n~7,000)
plus
NIMH MTA Study (n= 435 out of n=579)

CRITICAL REVIEW

Technology Appraisal of Methylphenidate, Dexamphetamine and Atomoxetine (NICE 2006)

NICE 2006: Clinical Evidence Informing Economic Model

Effectiveness review
Focus on hyperactivity ratings

64 randomized clinical studies (n~7,000)
(hereof, >1/3 short-term cross-over trials
with <3 weeks observation period per treatment arm)
plus
NIMH MTA Study (n= 435 out of n=579)

Filter 2

Availability
of
CGI-I scores
(subscale)

Economic model
Focus on CGI-I scores

5 clinical studies (n= 1,926), treatment duration 3–8 weeks,
hereof 1 study with n=1,323 (Kemner et al., 2004)
and 1 study "CIC";
plus
1 cross-over study previously excluded, n=32 (Sharp et al., 1999)

CRITICAL REVIEW

Technology Appraisal of Methylphenidate, Dexamphetamine and Atomoxetine (NICE 2006)

NICE 2006: Clinical Evidence Informing Economic Model

Economic model
Focus on CGI-I scores

5 clinical studies (n= 1,926), treatment duration 3–8 weeks,
hereof 1 study with n=1,323 (Kemner et al., 2004)
and 1 study "CIC";
plus
1 cross-over study previously excluded, n=32 (Sharp et al., 1999)

Secondary extensions

Availability
of **CGI-S**
or **ADHD-RS**
or **SNAP-IV**

Extended economic model
Focus on "response rates"
defined by four different scales

13 clinical studies (n≥2,768); 4 studies "CIC",
one "CIC" study could not be identified
plus
3 arms of NIMH MTA Study (n=435 out of n=579)

NICE 2006: Economic Model[1]

Studies used in the base case analysis

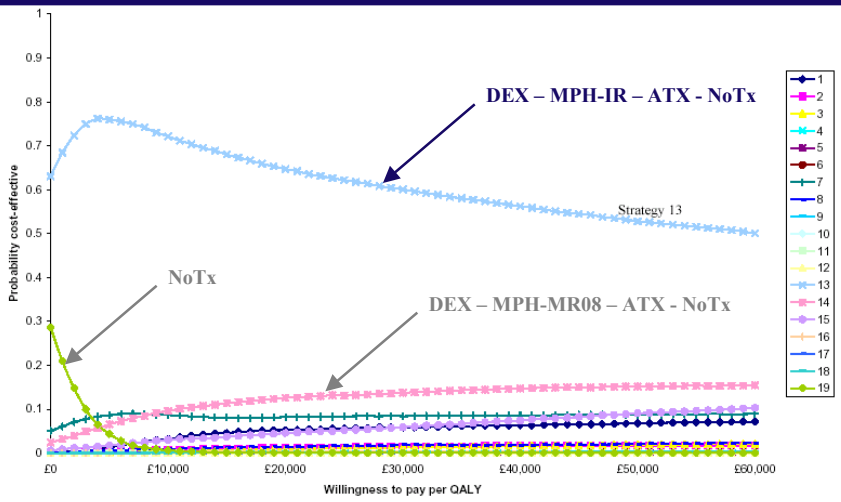
Study	Comp-arators	Study Design	Study Patients	Endpoints used	Notes
Sharp et al., 1999	MPH-IR DEX Plac.	RCT double-blind 3x crossover (3x3 weeks)	n=32 (girls only)	CGI-I	Excluded from effectiveness review (for "inadequate data presentation"); no data provided in AR; inclusion "initially" based on DSM-IIIR, "later" DSM-IV, combined type
Greenhill et al., 2002 (32 sites)	MPH-MR08 Plac.	RCT PG (1:1) double-blind 3 weeks	n=314 (82% male)	CGI-I CGI-S	Primary endpoint: Conners' Teacher Global Index; study listed among MPH-ER medium dose group in AR (average dose 40.7mg/d)
Kemner et al., 2004 ("multiple sites")	ATX MPH-MR12	RCT PG (2:1) open-label 3 weeks	n=1,323 (74% male)	CGI-I ADHS-RS	"CIC" (no data provided in AR);primary endpoint: ADHD-RS improvement (change in mean score): MPH-MR12 superior to ATX (but included also patients with prior stimulant treatment)
Steele et al., 2004, 2006	MPH-IR MPH-MR12	RCT, PG (1:1) open-label, "real-world" design	n=145 (83% male)	CGI-I CGI-S? SNAP-IV	"CIC" (no data provided in AR); primary endpoint: SNAP-IV (18/26 items, parent ratings); real-world effectiveness trial; MPH-MR12 superior to MPH-IR
Pliszka et al., 2000 ;	MPH-IR MAS Plac.	RCT double-blind PG (1:1:1) 3 weeks	n=58 (% males ?)	CGI-I	Primary endpoint: IOWA Conners' ratings
Klein and Abikoff, 1997	MPH-IR (w/ and w/o NDT) Plac.	RCT double-blind PG (1:1:1) 8 weeks	n=86 (94% male)	CGI-I	Primary endpoints: CTRS, CPRS; multiple further assessments

NICE 2006: Base Case Results of the Economic Model[1]

Strategy	Order of treatments received	Cost	QALYs
1	IR-MPH – ATX – DEX - No treatment	£1,233	0.8279
2	ER-MPH8 – ATX – DEX - No treatment	£1,470	0.8273
3	ER-MPH12 – ATX – DEX - No treatment	£1,479	0.8278
4	ATX – IR-MPH – DEX – No treatment	£1,480	0.8278
5	ATX – ER-MPH8 – DEX – No treatment	£1,550	0.8277
6	ATX – ER-MPH12 – DEX – No treatment	£1,563	0.8274
7	IR-MPH – DEX - ATX - No treatment	£1,140	0.8283
8	ER-MPH8 – DEX - ATX - No treatment	£1,336	0.8277
9	ER-MPH12 – DEX - ATX - No treatment	£1,410	0.8284
10	ATX – DEX – IR-MPH– No treatment	£1,466	0.8281
11	ATX – DEX – ER-MPH8 –No treatment	£1,485	0.8281
12	ATX – DEX – ER-MPH12– No treatment	£1,488	0.8278
13	**DEX – IR-MPH – ATX – No treatment**	**£1,098**	**0.8289**
14	DEX – ER-MPH8 – ATX – No treatment	£1,157	0.8287
15	DEX – ER-MPH12 – ATX – No treatment	£1,159	0.8287
16	DEX – ATX – IR-MPH– No treatment	£1,158	0.8288
17	DEX– ATX – ER-MPH8 –No treatment	£1,177	0.8288
18	DEX– ATX – ER-MPH12 –No treatment	£1,180	0.8285
19	No treatment	£1,223	0.7727

[2]Assessment report, p. 237; King et al., 2004

NICE 2006: Base Case Cost-Effectiveness Acceptability Curves[1]



[2]Assessment report, p. 238; King et al., 2004

NICE 2006: Main Conclusions of Assessment[1]

- Drug therapy seems to be superior to no drug therapy.
- No significant differences between the various drugs in terms of efficacy or side effects were found – mainly due to lack of evidence.
- The additional benefits from behavioral therapy (in combination with drug therapy) are uncertain".
- "Given the lack of evidence for any differences in effectiveness between the drugs, the [economic] model tends to be driven by drug cost, which differ considerably"[1].
- "For a decision taken now, with current available data, the results of the economic model clearly identify an optimal treatment strategy"[2] and "this analysis showed that a treatment strategy of 1st line dexamphetamine, followed by 2nd line methylphenidate immediate-release for treatment failures, followed by 3rd line atomoxetine for repeat treatment failures was optimal."

[2]Assessment report, p. 20; King et al., 2004; [2]AR, p.261

CRITICAL REVIEW

Technology Appraisal of Methylphenidate, Dexamphetamine and Atomoxetine (NICE 2006)

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[2]Assessment report, p. 237; King et al., 2004

NICE 2006: Appraisal Summary

- Where drug treatment is considered appropriate, methylphenidate, atomoxetine, and dexamphetamine are recommended within their licensed indications.
- There are no significant differences between individual drugs in terms of efficacy or side effects – a conclusion derived as a consequence of paucity of evidence used for assessment.
- Given the limited data used to inform response and withdrawal rates, it is not possible to distinguish between the different strategies on the grounds of cost-effectiveness.
- If there is a choice of more than one appropriate drug, the product with the lowest cost should be prescribed.

NICE 2006: Appraisal Recommendations

- The decision about choice of intervention should be based on
  - The presence of comorbid conditions (e.g., tic disorders, Tourette's syndrome, epilepsy).
  - The adverse event profile.
  - Compliance issues (e.g., the need to administer a mid-day dose at school, and its associated implications).
  - The individual preferences of the patient and/or parent/guardian.

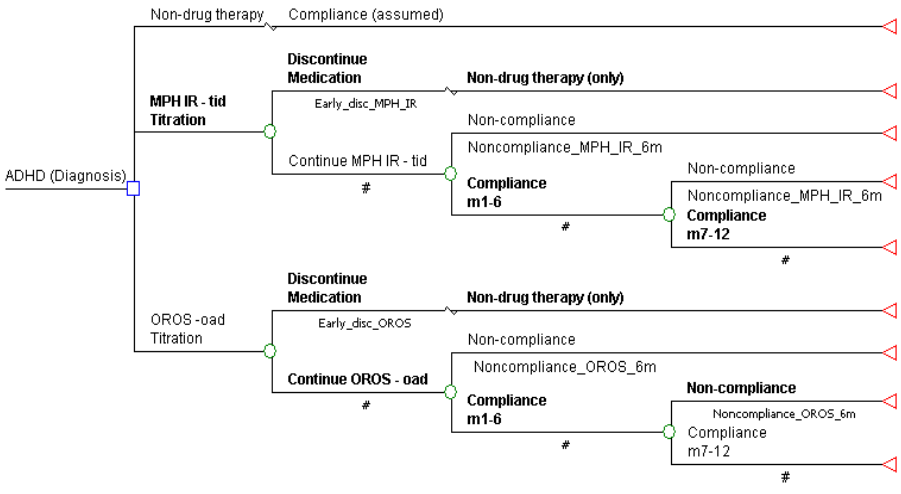
Factors affecting treatment compliance in children with ADHD

Noncompliance with ADHD Treatment[1]

- **Reluctance to take medication**
  - Inconvenience of multiple daily dosing
  - Social stigma associated with taking medication
  - Concerns over safety and long-term effects of treatment
  - Unpleasant effects associated with treatment
  - Difficulty in swallowing medication
  - Individual and/or parental attitudes to medication
- **Inadequate supervision**
- **Disease-related factors**
  - Oppositional and defiant behavior
  - Easy distractibility
  - Poor self-regulation

[1]Source: J. Swanson (2003)

Economic Evaluation: Compliance Model[1]



[1]Decision Analysis Software: TreeAge DATA Pro (2002)

Economic evaluation from the perspective of the UK National Health Service (NHS)

Cost-Effectiveness [£ / ES x Year]

IOWA Conners Inattention / Overactivity (I/O) Scale

	Base Case[1]		"ADHD" Case[2]	
Rating	**Teacher**	**Parent**	**Teacher**	**Parent**
MPH IR vs. Non-Drug Treatment Only	**1,120**	**1,065**	**1,208**	**1,148**
MPH MR12 vs. Non-Drug Treatment Only	**1,161**	**1,041**	**1,161**	**1,041**
MPH MR12 vs. MPH IR	**1,345**	**962[3]**	**1,041[3]**	**816[3]**

[1]Assumptions for base case analysis derived from A.M. Claxton et al. (2001);
[2]for ADHD case, assuming reduced compliance for MPH IR (according to P. Firestone, 1982);
[3]extended dominance MPH OROS over MPH IR

Impact of Treatment Compliance (Persistence)

- **Methylphenidate (MPH) IR t.i.d.**
  - alone or in combination with cognitive-behavioral therapy, has been shown to be an effective and cost-effective treatment for ADHD in children, with an estimated ICER of ~ £ 9,200 / QALY (from the UK NHS perspective[1]);
  - effectiveness is likely to be impaired by the negative impact of multiple daily dosing, combined with ADHD-specific factors, on treatment adherence.
- **Methylphenidate MR12 o.a.d.**
  - may be expected to improve treatment compliance, resulting in …
  - improved clinical effectiveness, translating into …
  - an acceptable incremental cost-effectiveness ratio (comparable to MPH IR t.i.d., with …
  - extended dominance over MPH IR t.i.d. under a broad range of assumptions).
- **Data from modeling studies suggest that MPH-MR12 will play an important role in the effective and cost-effective management of ADHD[2].**

[1]NICE assessment, J. Lord & S. Paisley (2000), and A. Gilmore & R. Milne (2001). For comparison, most recent estimates based on the MTA Study indicate an ICER of ~ US-$ 21,000 / QALY from the U.S. societal perspective, for MPH OROS o.a.d. compared to MPH IR t.i.d., both in combination with cognitive-behavioral therapy; cf. P. Jensen et al. (2004), M. Schlander et al. 2004).
[2]Note that limitations of the present analysis include the use of DSM-IV diagnostic criteria, the comparison with MPH IR administered t.i.d. only, and the absence of direct cost/QALY calculations. Real-world data will have to confirm these estimates.

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 corresponding effectiveness advantages[1]
  - **ATX supported by less compelling data**
    - Controversial cost-effectiveness
    - Most likely economically inferior to MPH-MR

Data from

- **USA, UK, CAN, AUS**
- **Product availability and unit costs**
- **CAN, UK, D**
- Suggestive US data[1]
- **CAN?**
- England +?; Scotland (SMC), AUS (PBAC) -?

[1]Currently available data restricted to MPH-MR12

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 urgently needed**
      - on better targeted psychosocial interventions
      - on impact on long-term outcomes

Research Needs

- **Currently, still no data for many jurisdictions**
  - Assess transferability of existing economic data
  - Determine relative cost-effectiveness of atomoxetine
- **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-type strategies)

"It may well bring about immortality

–

but it will take forever to test it."