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Cost-Effectiveness of ADHD Treatment Strategies

What We Do Know ... and What We Do Not Know ...

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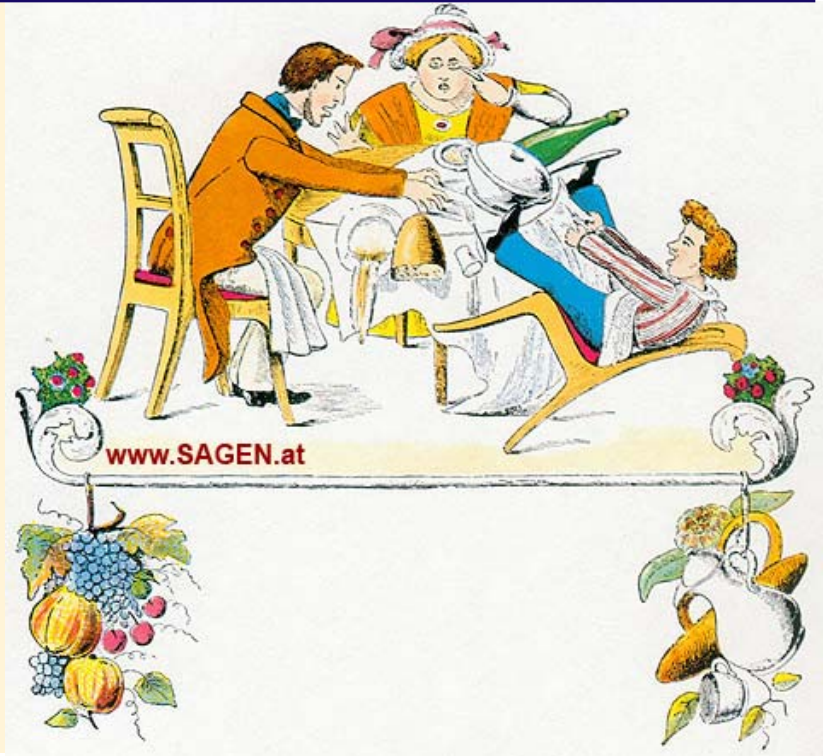


Attention-Deficit/Hyperactivity Disorder (ADHD)

▭ Cores Symptoms ...

- ▭ Inattention
- ▭ Impulsivity
- ▭ Hyperactivity

▭ ... and beyond?



Need for a broader perspective



ADHD: Burden of Disease (Overview)¹

▮ 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

¹multiple references

Key Questions Addressed

1.

Safety



- ▭ Does it harm?
(controlled conditions)

2.

Efficacy



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



EBM *“How sure are we?”*

3.

Effectiveness



- ▭ **Does** it work¹ and is it safe?
(normal practice)



4.

Efficiency

- ▭ *usually: “Is it cost-effective?”*

¹cf. D. Schwartz & J. Lellouch 1967

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

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)

Acquisition costs of important drugs licensed for treatment of ADHD

Prescription Drug Spending: Acquisition Costs¹



Trade Name	Active Ingredient	Cost / Daily Dose ³	Assumed Average Daily Dose ²	Daily Dosage Schedule ²
Dexedrine ^R	Dexamphetamine sulphate	£ 0.42	20mg/d	2 times
Ritalin ^R	Methylphenidate hydrochloride	£ 0.56	30mg/d	3 times
Equasym ^R	Methylphenidate hydrochloride	£ 0.56	30mg	3 times
MPH Generics	Methylphenidate hydrochloride	<£ 0.56	30mg	3 times
Equasym ^R XL	Methylphenidate hydrochloride	£ 1.17	30mg	1 time
Concerta ^R XL	Methylphenidate hydrochloride	£ 1.23	36mg	1 time
Strattera ^R	Atomoxetine hydrochloride	£ 1.95 (to £ 3.80)	Irrelevant due to flat pricing	1 (to 2) times

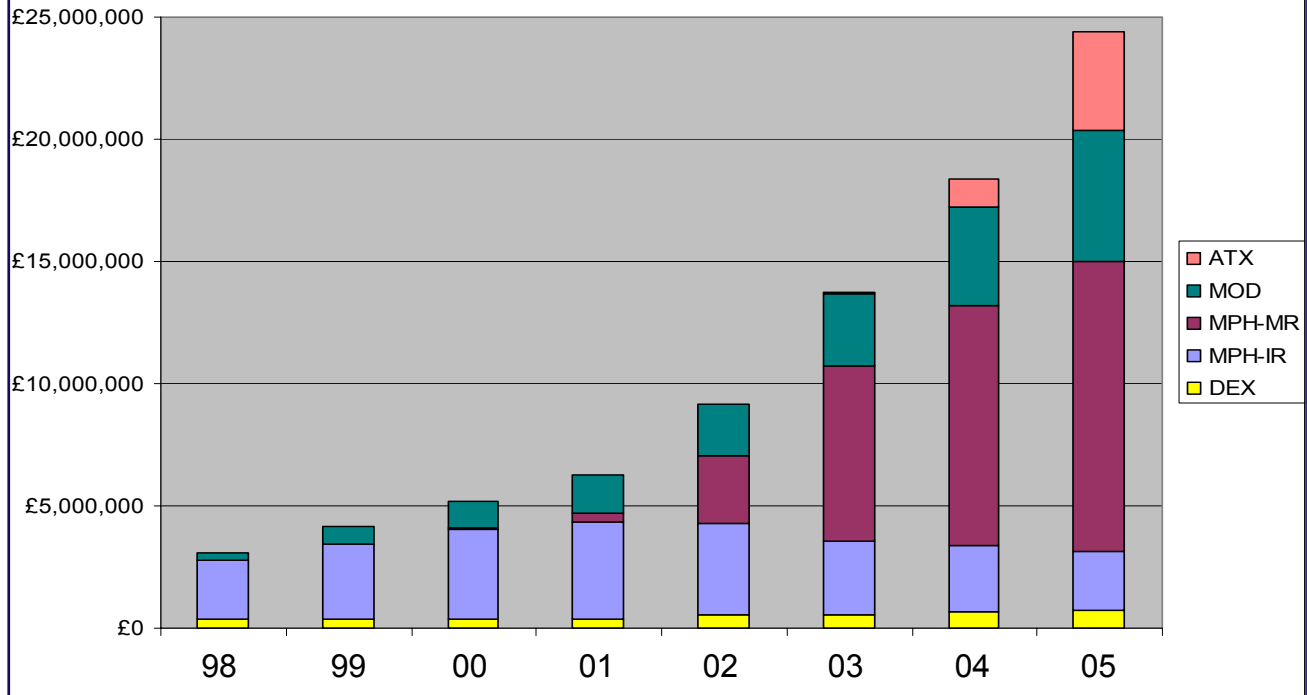
¹2005; data sources: UK: British National Formulary (BNF), March 2005 (Equasym XL: September 2005);

²assumptions underlying cost data provided here, not to be construed as treatment recommendations since ADHD medication require individual titration;

³note that individual doses and hence costs may vary.

Prescription drug spending has been predicted to rise beyond £ 75 million by 2012¹

ADHD-Related Expenditures (NHS England)²



¹Schlnder (2007); ²Expenditures 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.



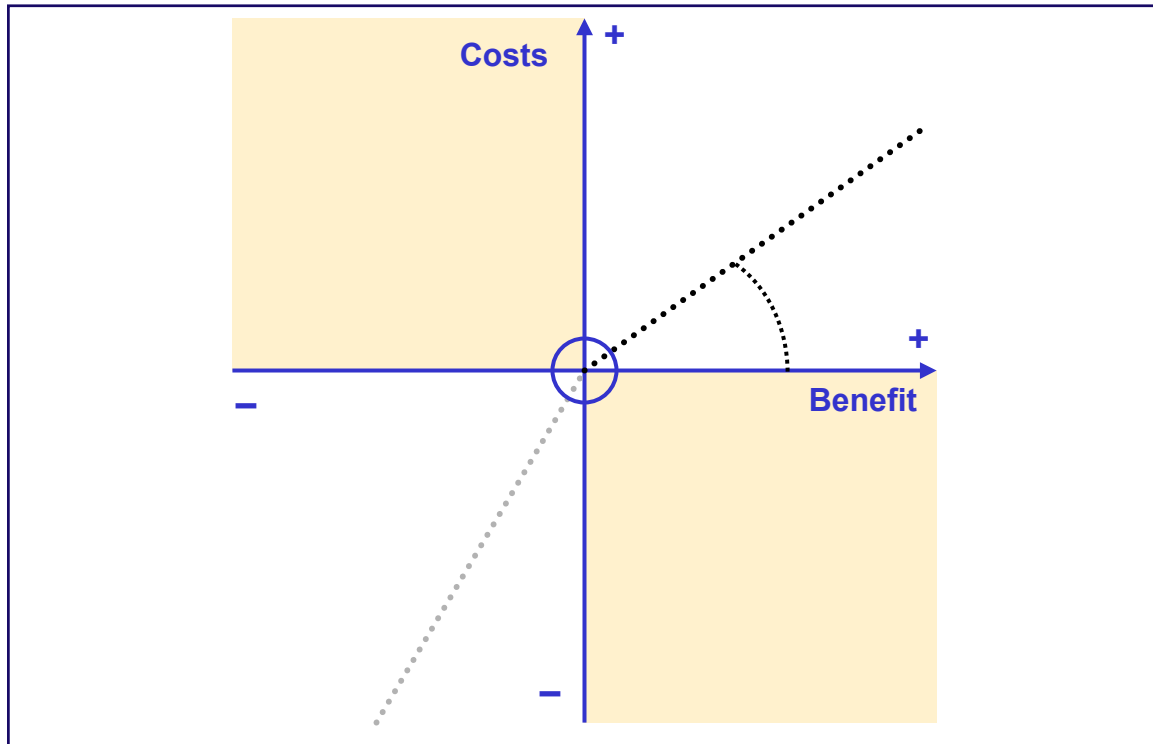
Cost-Effectiveness

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

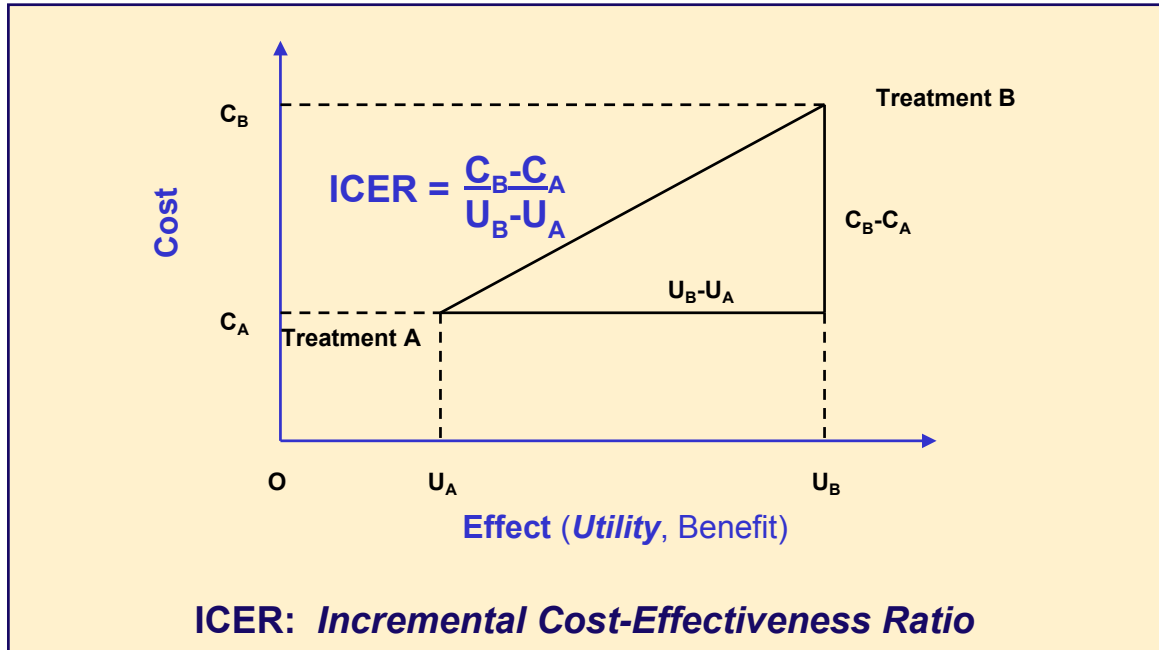
¹Chart courtesy of G. Kobelt (2002)

The Cost-Effectiveness Plane¹



¹W.C. Black (1990)

Incremental Analysis



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 therapy³.

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

¹J. Zupancic et al. (1998): a six-point or one standard deviation (weighted mean) difference was considered clinically relevant, CAN-\$ (1997);

²J. Lord & S. Paisley (2000); cf. also A. Gilmore & R. Milne (2001): NHS perspective, one-year time horizon, £ (1997); ³fewer than 20 patients each for the BEH and COMB strategies.

The NIMH MTA Study¹

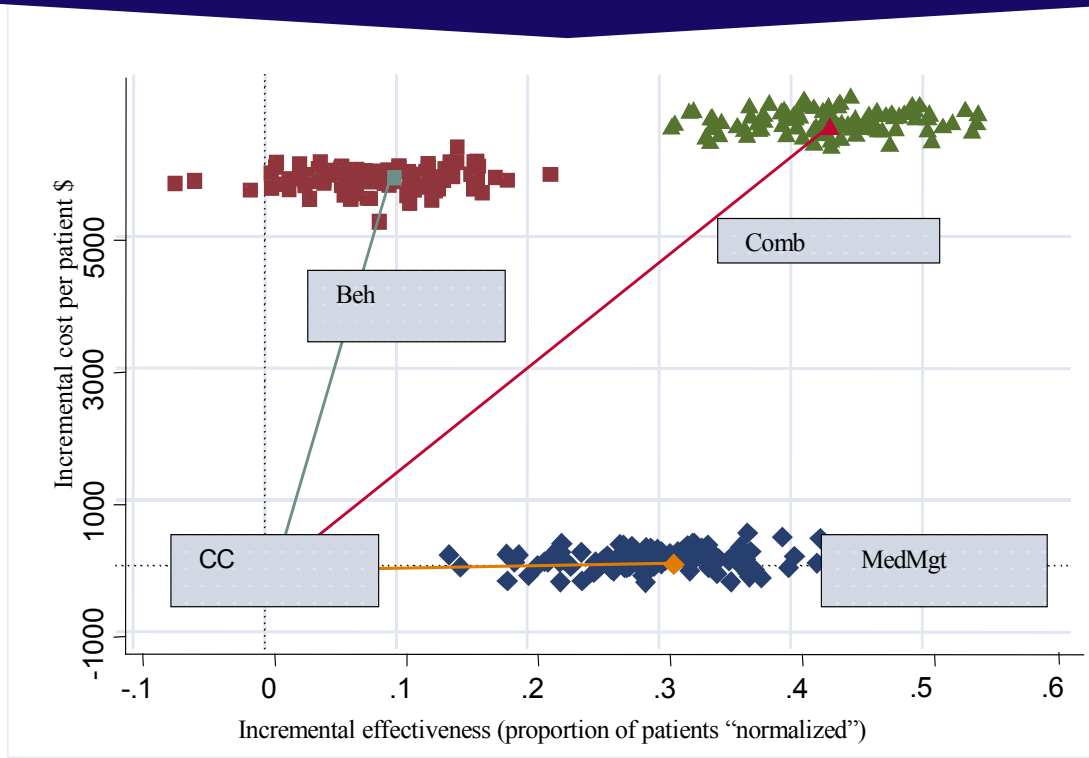
- ↪ **Randomized Clinical Trial of Treatment Strategies**
 - ↪ Psychosocial Treatment Alone [BEH]
 - ↪ Pharmacological Treatment Alone [MM]
 - ↪ Combined Psychosocial and Pharmacological Treatment [COMB]
 - ↪ Community Comparison Group [CC]
- ↪ **579 subjects**
 - ↪ entered between January and May of 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



MTA based economic evaluation of ADHD treatment strategies

Primary Cost-Effectiveness Analysis¹



Economic evaluation of ADHD treatment strategies: a European perspective



Evaluation Strategies¹



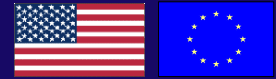
- ↪ **Preferred diagnostic criteria vary between jurisdictions**
 - ↪ Analyzing subgroups with hyperkinetic disorder (with and without comorbidity)
- ↪ **Standards of care / treatment preferences vary between jurisdictions**
 - ↪ Adding a hypothetical “Do Nothing” alternative for modeling
- ↪ **Unit costs vary between jurisdictions (and by perspective)**
 - ↪ Costing by country (D, NL, S, UK, USA) and by perspective; sensitivity analyses
- ↪ **Psychiatric comorbidity is common and known to moderate treatment effectiveness**
 - ↪ Analyzing subgroups with and without 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



ADHD treatment strategies: Key economic evaluation results

Some Conclusions



- ↪ A carefully monitored, **intense medication management** strategy as defined by the MTA protocol is clearly cost-effective¹.
- ↪ This observation holds **across all subgroups** analyzed (by comorbidity and diagnostic criteria) as well as by all measures of effectiveness studied.
- ↪ 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 (primarily **internalizing**, also both internalizing and externalizing) .

Some Limitations

- ↪ Cost-effectiveness of **less intense and/or better targeted behavioral interventions?**
- ↪ **Longer time horizons** than employed in our analyses may improve cost-effectiveness results, particularly concerning behavioral interventions².

¹compared to all other interventions tested; ²the same is true for medication management, although (most likely) to a lesser extent;

³note however a number of assumptions made favoring behavioral interventions in these analyses (Schlander et al., 2006a,b,c; Jensen et al., 2005; Foster et al., 2007).

Economic evaluation of ADHD treatment strategies (NICE 2006): An incomplete assessment of pharmacotherapy only

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.” => Limitations =>

INNOVATION AND VALUATION IN HEALTH CARE

Michael Schlander

Health Technology
Assessments by the
National Institute for Health
and Clinical Excellence

A Qualitative Study

 Springer

Update of European ADHD Treatment guidelines by a European group of clinical experts: EUNETHYDIS (2004 / 2006)

EUNETHYDIS 2006¹: Clinical Recommendations

- ▭ Long-acting preparations should be available and used.
- ▭ They should not replace short-acting drugs (which will be the initial treatment for many children for **reasons of cost** and flexibility of dosing).
- ▭ Both ATX and extended-release preparations of stimulants should be available.
- ▭ The choice will depend upon the (clinical) circumstances.
- ▭ **No formal economic evaluation informing these recommendations.**

¹Banaschewski et al. (2006)

Noncompliance with ADHD Treatment¹

- ▭ **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

¹Source: J. Swanson (2003)

Treatment compliance and cost-effectiveness¹

“Great efforts are typically made in the conduct of a clinical trial to ensure that patients consume their prescribed medications.”¹

Intent-to-treat evaluation strategies may further obscure the effects of noncompliance, since the practice of preserving data in a typical “last-observation-carried-forward” analysis cannot be expected to reflect the situation of non-compliant patient (who discontinued treatment) at the time when the study was completed.²

Proposed Solutions:

- 1. Modeling studies**
including appropriate sensitivity analyses¹⁻³
- 2. Randomized pragmatic trials**
capturing the “real-world” situation of routine care¹⁻³
- 3. Retrospective database analyses**
which may provide information on treatment pathways and resource utilization but may be prone to confounding effects³

¹M.F. Drummond et al. (2005); ²D.A. Hughes et al. (2001); ³M. Schlander (2007)

Treatment compliance and cost-effectiveness¹

- ↪ **Disorder-specific factors and core symptoms of ADHD**
may increase the risk of non-adherence
- ↪ **Clinical studies consistently report low persistence rates**
with stimulant treatment in natural setting
- ↪ **PK/PD properties of stimulants**
making them prototypical “unforgiving compounds” (re. missed doses)
- ↪ **Modeling studies (Canada, England, Germany)**
suggestive of comparable cost-effectiveness
of MPH-MR12 and MPH-IR t.i.d., even under conservative assumptions
- ↪ **A Canadian randomized pragmatic trial**
reporting superior effectiveness of MPH-MR12 over MPH-IR t.i.d.²
- ↪ **Three U.S. retrospective administrative database analyses**
consistently showing significant differences in treatment persistence
between short-acting and long-acting medications

¹Schlender (2007); ²consistent with the observation of adherence as a moderator of effectiveness in the NIMH MTA Study (1999)

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
- USA¹
- (CAN?)
- England +?;
Scotland (SMC) -?
AUS (PBAC) -?

¹Data available for MPH-MR12 (Steele, 2006) and MPH-IR (MTA Cooperative Group 1999)

Currently Available Evidence (2)

▭ Psychosocial Interventions

▭ Few data available¹

- ▭ Mostly disappointing (and sometimes disastrous) 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

¹Note that absence of evidence for cost-effectiveness based on the MTA-based evaluations should *not* be equated with evidence of absence.

Towards a More Complete Analysis

- ↪ **To date, most evaluations have been based on treatment effects on core symptoms**
 - ↪ Confirm transferability of existing economic data across jurisdictions
 - ↪ Better understand 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 protocol)
- ↪ Need analyses from the **perspectives** of individuals (patients), families (caregivers), the economy and society as a whole