The Pharmaceutical Economics of Child Psychiatric Drug Treatment

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Abstract: Over the last decade, the number of health economic evaluations has increased substantially in the field of child psychiatry. The objective of the present paper is to offer an overview of economic evaluations of child psychiatric drug treatment. Major electronic databases, as well as abstract booklets from international clinical and health economics conferences with an external peer review process, were examined to search for comparative economic evaluations of child and adolescent psychiatric drug treatment. Most studies of pharmacotreatment were cost effectiveness analyses (CEAs) concerned with attention-deficit/hyperactivity disorder (ADHD). Three evaluations were done by or on behalf of agencies as part of ADHD-related health technology assessments. A number of economic studies used patient-level data from specific randomized clinical trials, especially the NIMH-initiated MTA (in childhood ADHD) and TADS (in adolescent major depression) studies. Almost all studies relied on narrow scale symptom scales to assess effects of treatment, even when quality-adjusted life years (QALYs) were reported. In many cases, effectiveness data came from short-term studies, and extrapolation to a one-year time horizon was usually based on assumptions. Even those evaluations attempting to address longer time horizons by way of modeling did not include the impact of treatment on long-term sequelae of the conditions studied, mainly due to a paucity of robust clinical data. Nevertheless, currently available health economic evaluations broadly suggest an acceptable to attractive cost effectiveness of medication management of ADHD, whereas there is no such evidence for child psychiatric disorders other than ADHD.

Keywords: Economic evaluation, cost effectiveness analysis, cost utility analysis, quality-adjusted life year (QALY), cost benefit analysis, health technology assessment, attention deficit hyperactivity disorder (ADHD), depression, pharmacoeconomics.

INTRODUCTION

To date, the economic implications of child and adolescent psychiatric disorders and related interventions at the individual level have received considerably less attention than the impacts on symptoms, functioning, health-related quality of life (HRQoL) and other patient-reported outcomes (PROs). This is particularly true for comparative evaluations of the cost effectiveness of treatment options in child and adolescent psychiatry. In their review of the subject covering the period before September 2003, Renée Romeo and colleagues concluded in 2005, "economic evaluations in the field […] are few in number and generally poor in quality, although the number of studies undertaken appears to be rising" [1]. Many reports identified by these authors addressed questions of relative effectiveness but had little if anything to say about the value for money provided by the interventions undergoing evaluation. Other studies were descriptive cost studies only, i.e., they investigated costs or cost offsets but did not measure treatment outcomes [1].

Across all types of study (cf. Table **1**) [2-4] and irrespective of methodological quality, the total number of reports identified by Romeo *et al.* (2005) was 21; of those, 14 measured both costs and benefits of at least two interventions. One study assessed a pharmacological treatment option, methylphenidate [5]. These observations are remarkable on several accounts. First, this very small number constitutes a striking contrast to other therapeutic areas, which have experienced an exponential growth in the number of published economic evaluations. Second, in other clinical areas pharmaceuticals feature prominently among technologies subjected to economic analysis [6]. Third, following the early examples of Australia (in 1992) and Canada (in 1994), many jurisdictions have adopted Health Technology Assessments (HTAs) including formal economic evaluation to guide pricing and reimbursement decision-making, again frequently focusing on pharmaceutical treatments [7,8]. Fourth, with the emergence of novel pharmacological treatment options, the budget impact of drug treatment in child and adolescent psychiatry either has grown substantially (like in the United States), or is set to grow dramatically, with the implication of the field losing its status as a relatively small pharmaceutical market niche and the inevitable consequence of an increasing relevance of health economic evaluations [9].

Put in the broader context of the enormous public health burden caused by child and adolescent psychiatric problems [10,11], the conspicuous paucity of comparative evaluations of treatments can only surprise, despite or - perhaps somewhat paradoxically from an economic perspective - because of the wide-held belief that "children [are] our most valuable resource" [12]. *But what value do we attach effective treatment of behavioral problems of our children?*

The intended readers of the present paper are primarily clinicians - both clinical researchers and practitioners with an interest in health economics. The goal of the paper is to offer an overview and critical appraisal of economic evaluations of drug treatment in child and adolescent psychiatry, portraying both decision-analytic modeling approaches and prospective cost effectiveness studies.

ECONOMIC EVALUATION OF DRUG TREATMENT IN CHILD PSYCHIATRY: RECENT DEVELOPMENTS

Recent pharmacoepidemiological research indicates an enormous international variability in the use of medication for children and adolescents [13]. This variability, which appears particularly striking with respect to treatment of mental disorders, cannot be explained on grounds of differences in the prevalence rates of disorders [14]. For example, the United States (US) alone account for more than four fifth of the worldwide use of psychostimulants [15]. Another example concerns the use of antidepressants in children and adolescents, which is also much greater in the US compared to European countries [16,17]. Also within Europe, there are substantial differences between countries - to mention just one example, herbal products appear to be particularly popular in Germany, with the consequence that about 80% of antidepressant consumption by children and adolescents in Germany was accounted for by St John's wort extracts in 2003 [18]. Accordingly, expenditures for

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1381-6128/10 $55.00+.00

Table 1. Health Economic Evaluation Types

Type of Analysis	Measurement and Valuation of Costs	Measurement of Consequences (Effects)	Valuation of Consequences (Effects)	Theoretical Foundation (Standard)
CMA: cost minimization analysis	Monetary units (usually from a "decision maker's perspective")	None	None	Costing theory
CEA: cost effectiveness analysis	Monetary units (usually from a "decision maker's perspective")	Single effect measure of interest, common to alternatives evaluated, but achieved to different degrees	Natural units (e.g., life years gained, response rates, etc.)	Decision analysis and operations research; goal: technical efficiency
CUA: cost utility analysis	Monetary units (in theory, often recommended to be determined from a "societal perspective"; in practice, often from a "health care policy maker's perspective"	Single or multiple effects, not necessarily common to alternatives evaluated	Health-adjusted life years (usually QALYs)	"Extrawelfarism" - maximizing total health gains under a resource constraint; goal can be technical or allocative efficiency (usually applying a cost/QALY benchmark)
CBA: cost benefit analysis	Monetary units (from a "societal perspective", i.e., ignoring transfer payments)	Single or multiple effects, not necessarily common to alternatives evaluated	Monetary units (usually WTP)	Economic welfare theory - maximizing the impact of health care on overall well-being; goal: allocative efficiency

Similarities and Differences of Commonly Used Techniques for the Comparative Economic Evaluation of Health Care Programs [2-4].

child psychiatric drug treatment, with budgetary impact being the product of number of prescriptions and average unit costs, also varies greatly between jurisdictions [9,15].

There is a host of underlying reasons, ranging from international differences in diagnosis rates under conditions of routine care, diagnostic criteria (e.g., ICD-10 versus DSM-IV), to different treatment preferences, but also related to the very availability of treatment options [9]. For example, amphetamine products are widely prescribed for ADHD in countries such as the US and the UK, but are not available in Germany, Italy, and some other European countries. International heterogeneity is further exacerbated by regulatory differences related to available products, with many compounds being used off-label, i.e., without being officially approved for pediatric use. Of course, different utilization patterns are highly relevant for the choice of appropriate comparators in economic evaluations.

Among the most commonly diagnosed child psychiatric disorders, ADHD, conduct disorder, and anxiety and depressive disorders consistently rank highest in studies [10,19-21]. Of these ADHD arguably represents the most well-researched condition. Correspondingly, the vast majority of comparative economic evaluations of drug treatment concern this disorder.

ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)

ADHD is a chronic psychosocially impairing condition frequently persisting into adulthood [22,23]. Beyond its direct costs [24,25] and the burden placed on parents and other family members [25,26], the disorder has been linked to serious long-term sequelae. These include poor driving abilities [27], higher risks of accidents and injuries [28-30], increased rates of tobacco, alcohol and other substance use disorders [31], more frequent antisocial behaviors [32-34] and encounters with the criminal justice system [35-38] across the lifespan, as well as relatively poor educational outcomes and lower-ranking occupational positions than controls [33,39-42]. Despite important gaps in our understanding of the economic implications of these sequelae, the annual societal cost for ADHD in childhood and adolescence has been estimated to exceed $40 billion in the US alone [43]. Only a fraction of these costs - between 10 percent according to UK data for conduct disorder and up to 20 percent for ADHD in the US - fall into the health sector [11,43,44]. For Germany, direct medical costs borne by statutory health insurance (SHI) attributable to ADHD - i.e., excess costs of health care compared to a control group matched by age, gender, and type of SHI - were estimated at €260 million in year 2003, and have continued to increase at a fast pace since [45,46]. The German data did neither include other social costs nor the productivity loss attributable to ADHD [45].

Coexistence of other child psychiatric conditions is common in children with ADHD [47-50]. Actually, "pure" ADHD appears to be rather the exception than the rule, and some scholars even suggested the use of distinct comorbid subtypes of ADHD [51]. It seems both plausible and likely that coexisting conditions should increase direct costs [25,43,52]. Yet many cost of illness studies did not reveal a noticeable impact of specific coexisting conditions on the cost of mental health services for patients with ADHD, and this is mostly due to study design and sometimes small sample sizes [25,43]. In-depth analyses are available for Germany and the US, and these studies concur in indicating higher costs of care in the presence of conduct and personality disorders, mood and affective disorders, as well as adjustment disorders, but not learning disabilities and specific development disorders [53-55]. Furthermore, some coexisting conditions might represent an independent predictor [56] and moderator [57] of long-term treatment outcomes, although data available to date are limited and somewhat contradictory [58].

As a consequence, one might expect attractive cost effectiveness ratios for clinically proven therapeutic strategies for ADHD, providing, of course, a positive impact on some of the sequelae associated with the disorder can be demonstrated. At the same time, valid economic analyses need to address a variety of issues, which adds substantial complexity - such as the role of diagnostic criteria (DSM-IV versus ICD-10) [59-62], the presence of coexisting conditions [47-50], and the broad variety of instruments used to measure clinical outcomes in ADHD [63,64]. Further to this, international differences deserve attention, for example concerning utilization patterns, treatment patterns, and unit costs [65,66].

TREATMENT OF ADHD

The principal evidence-based treatment options for ADHD are psychosocial interventions and drug therapy, as well as the combination of both. International clinical guidelines generally provide support for both options but have not been informed by economic assessments [67-71]. While there are limited data available on the economic attractiveness of psychosocial interventions, a substantial number of cost effectiveness studies of drug treatment for ADHD have become available since the earlier reviews by Knapp (1997) [72] and Romeo *et al*. (2005) [1]. Following the editors' request, the present review will focus on economic evaluations of pharmacotherapy.

From the 1960s through the 1990s, pharmacotherapy for the treatment of ADHD consisted of short-acting stimulant medications with a duration of action of about three to four hours (hence requiring twice ["b.i.d."] or thrice ["t.i.d."] daily administration to achieve full-day symptom control), most notably methylphenidate (MPH). MPH, like the other stimulants used in ADHD (primarily, dexamphetamine [DEX] and mixed amphetamine salts [MAS]), is thought to act primarily by increasing dopamine at the synapse [73-75]. Another stimulant drug, pemoline (PEM), had to be withdrawn from market due to an unacceptable risk of liver toxicity [76]. During the last two decades, not only the number of chemical entities grew, but also new longer-acting formulations of psychostimulants became available, which often need to be administered once-daily ("q.d.") only [69,77,78]. Also a nonstimulant alternative, atomoxetine (ATX), is now available. ATX is thought to exert its effects primarily by selectively inhibiting presynaptic norepinephrine reuptake in the prefrontal cortex, ie. through the noradrenergic pathway [79]. Finally, there are some other drugs less frequently prescribed for treatment of ADHD, which have not been approved for this use (for example, alpha receptor agonists such as clonidine and guanfacine, the antidepressant bupropion, and the stimulant modafinil) [78,79].

All drugs are effective in reducing the core symptoms of ADHD, with reported effect sizes of around 0.9 to 1.0 for stimulants and about 0.6 to 0.7 for the nonstimulant atomoxetine [71]. Furthermore, unlike the stimulant compounds that exhibit a very close correlation of pharmacokinetics and pharmacodynamic effects, the initial onset of therapeutic effects of atomoxetine builds up gradually over a period of two to six weeks [80]. Of note, most economic evaluations conducted to date have used some measure of symptom improvement either directly as the clinical outcome of interest, or indirectly as a basis to estimate quality-adjusted life year (QALY) gains.

QALYs combine, by means of multiplication, length of life with health-related quality of life in one single metric. Quality of life is represented by an index, which is assumed to represent the expected utility of a given health state and can vary between 1 for "perfect health" and 0 for "dead" (Fig. **1**). Rankings of interventions on the basis of their incremental cost per QALY gained, assumed by many economists to reflect an increasing social desirability with decreasing incremental cost effectiveness ratios (ICERs; Fig. **2**), are often referred to as cost effectiveness league tables [2-4,81].

Acquisition costs vary between products and by jurisdiction. As a general rule, it can be said that short-acting stimulant drugs (including amphetamine, mixed amphetamine salts, dexamphetamine, and methylphenidate preparations). are available as relatively low-priced generic versions, whereas stimulant preparations with a longer duration of action (modified-release formulations for oral use or patch for transdermal administration) are more expensive, and the acquisition cost of atomoxetine tends to be either comparable to the upper end of the range for long-acting stimulants (US) or considerably higher (D, UK) [82-84].

Many scientific contributions to the economics of child psychiatric drug treatment have not yet become available as full-text articles. In order to provide an up-to-date overview of the field, the search strategy included papers presented at international health economics meetings with an established peer review process. Abstracts were included if the information provided appeared sufficient in relation to the conclusions offered. It needs to be recognized that search results for meeting presentations might be incomplete, because conference abstracts and presentations are notoriously difficult to locate as they are poorly (or not) indexed in standard bibliographical databases. In addition, overall quality of re-

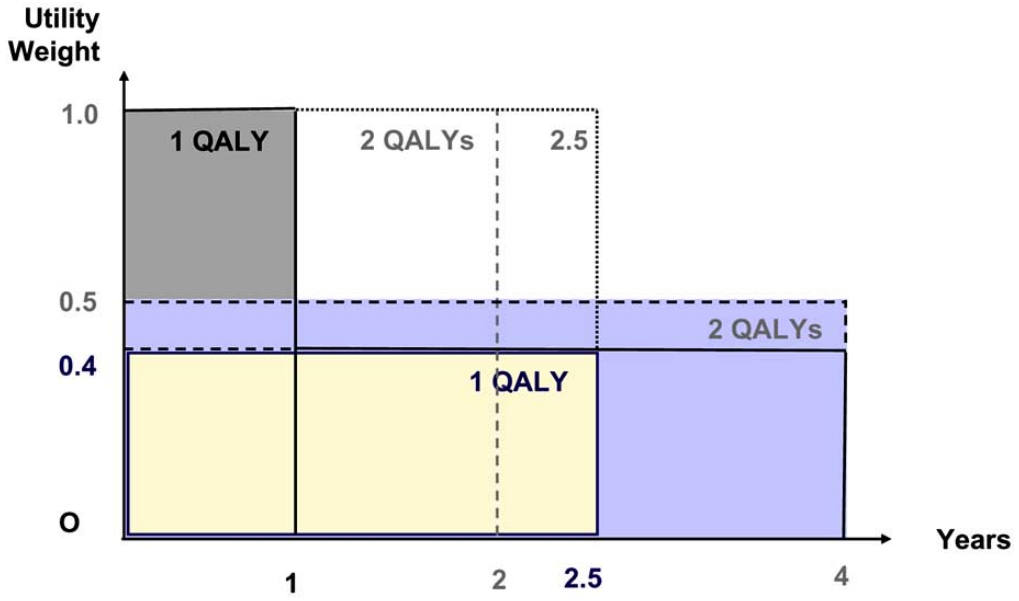

Fig. (1). The quality-adjusted life year (QALY) concept
Length (horizontal axis) and quality (vertical axis) of life determine the number of quality-adjusted life years (QALYs). The quality (or utility) weights should be based on actual preferences and measured on a cardinal scale to enable a meaningful computation of sums and differences (cf. Figs. **3** and **4**). For example, four life years spent in a health state with a utility of 0.5, such as blindness according to some studies, give 0.5 x 4 = 2 QALYs, equivalent to 2 years spent in full health. For a sequence of health states, the area under the curve (AUC) is the number of QALYs corresponding to this trajectory [3].

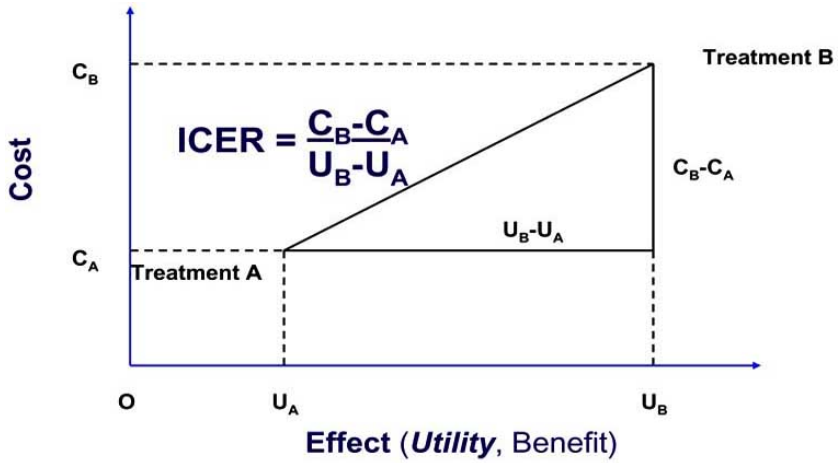

Fig. (2). Incremental cost effectiveness ratios (ICERs)
Results of cost effectiveness analyses are usually reported as incremental cost effectiveness ratios, ICERs. This is intuitively appealing as efficiency can be interpreted as the ratio of (incremental) inputs to (incremental) outputs [3,4]. As a ratio of two absolute differences, the ICER possesses weird statistical properties, complicating probabilistic sensitivity analyses (capturing parameter uncertainty) and the computation of ICER confidence intervals. It also does not provide any information about the size of its numerator and its denominator and, therefore, the budgetary impact of adopting an intervention [2-4,81].

porting in abstracts may be inadequate, data might be incomplete, and may on occasion even be inconsistent with those reported in subsequent full publications [85].

HEALTH TECHNOLOGY ASSESSMENTS (HTAs) INCLUDING ECONOMIC EVALUATION

One might reasonably expect HTAs including economic evaluation to provide the most comprehensive information on the clinical and cost effectiveness of medical interventions. Inter alia, HTAs attempt to provide evidence-based insights whether a medical "technology" (drug, device, procedure, etc.) is effective, for whom it works, what costs are entailed in its use, and how it compares with available alternatives [7,8,86,87]. A typical contemporary HTA includes a systematic review of the available information, a quantitative synthesis of clinical data, and increasingly also an economic assessment of relevant alternatives. In the field of ADHD, formal HTAs have been presented by the Canadian Coordinating Office for Health Technology Assessment (CCOHTA; now known as the Canadian Agency for Drugs and Technologies in Health, CADTH) in Ottawa, Ontario, and by the National Institute for [Health and] Clinical Excellence (NICE) in London.

HTAs (1): CCOHTA 1998

The CCOHTA review of therapies for ADHD comprised three parts, an overview of the use of methylphenidate (MPH) for ADHD, a systematic review and meta-analysis of medical and other therapies for ADHD, and an economic evaluation of pharmaceutical and psychological/behavioral therapies [88-90]. 26 treatment studies were selected for meta-analysis. Of these, 24 studies involved the use of medication - MPH, dexamphetamine (DEX), and/or pemoline (PEM), three of them assessing the combination of drug treatment with psychological / behavioral interventions, and two studies reported results of psychosocial interventions. Observation periods in studies of drug treatment were limited to 28 days or less, except for one study that reported outcomes after 120 days, whereas the studies involving psychological/behavioral interventions had follow-up periods of several months, in one study up to 24 months [91].

Efficacy was determined as symptom improvement reported by teachers or parents, most frequently by means of Conners Rating Scale (CRS) scores [64,89], and was expressed as effect sizes (or standardized mean differences). Teacher ratings were subsequently used for cost effectiveness analysis because they were most widely available and believed to best reflect the therapeutic objective to improve classroom behavior. For economic evaluation, the CCOHTA team adopted the perspective of Canadian provincial ministries of health and their associated drug benefit plans, and a one-year time horizon. Based on survey data from British Columbia on the average duration of MPH treatment in ADHD [89,92], which were supported by expert input and medication attrition data over 10 months from one clinical study [93], "non-compliance" (or more accurately, nonpersistence) was modeled over six month intervals (cf. Fig. **3**). A series of sensitivity analyses for both costs and outcomes but no subgroup analyses were performed. In this Canadian evaluation, MPH turned out to be dominating DEX, PEM, and non-drug treatment (NDT), with an estimated ICER of $64 to $83 versus "no treatment" for each point difference in the Conner Teacher Ratings Scale (CTRS) score sustained over one year. This translated into an estimate of $384 to $498 for a 6-point or one standard deviation difference versus no treatment, which was considered to represent a clinically significant improvement [89]. Two aspects of this study appear noteworthy. First, this study evaluated immediate-release MPH given twice daily only (long acting formulations and atomoxetine had not yet been available). Second, the use of rating scale scores as an outcomes metric implicitly assumes that differences across the scale are valued equally, irrespective of their size and where they occur, and as a typical cost effectiveness analysis (CEA; cf. Table **1**) using a clinical measure of treatment benefit, this approach precludes any comparison with interventions in other therapeutic areas.

After careful consideration of the limitations of this early HTA, CCOHTA concluded, "that MPH is the most cost-effective alternative for the management of ADHD" in Canada [94]. More recent Canadian HTAs including economic evaluation are not available; but CADTH has initiated an assessment of long versus short acting drugs for ADHD, which is still ongoing at the time of writing [95].

HTAs (2): NICE 2000

In 2000, NICE addressed the clinical and cost effectiveness of ADHD treatment for the first time [96]. The evaluation was limited to the use of MPH and relied heavily on the previous systematic reviews by Jadad *et al*. (1999) from McMaster University in Hamilton, Ontario, on behalf of the U.S. Agency for Healthcare Research and Quality (AHRQ) [97] and by CCOHTA [88,89]. It was further

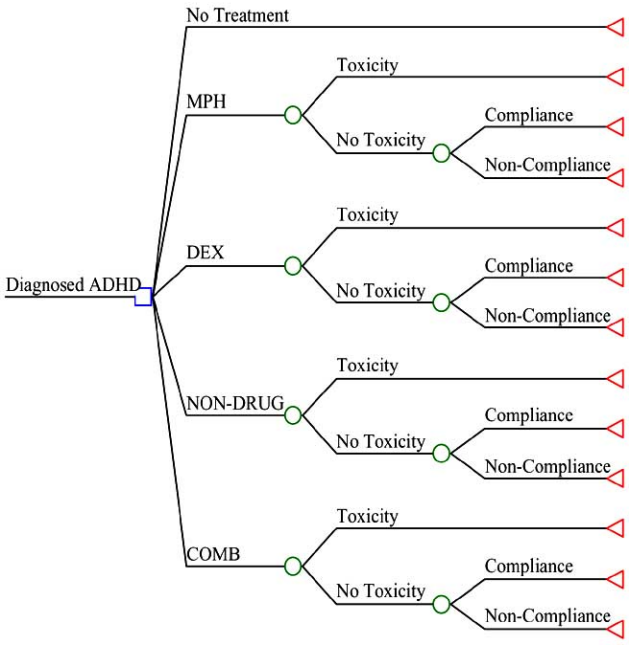

Fig. (3). Model used by the Canadian Coordinating Office for Health Technology Assessment (CCOHTA) 1998

Decision analysis tree diagram (pemoline excluded) used by CCOHTA to evaluate the cost effectiveness of ADHD treatment options. MPH, methylphenidate (10mg/dose b.i.d.); DEX, dextroamphetamine (15mg/day, 10mg in the morning and 5mg in the evening); NON-DRUG, psychological/behavioral therapy; COMB, a combination of methylphenidate (10mg/dose b.i.d.) and psychological/behavioral treatment (from Zupancic *et al*., 1998, p 34) [89].

informed by two company submissions and by a report published by the Wessex Institute for Health Research and Development [5,98], which had already been discussed by Romeo *et al*. (2005) in their review mentioned earlier [1,5]. The primary clinical findings of the NIMH MTA Study (see below) were considered as well [99,100].

The authors of the first NICE assessment did not attempt a quantitative synthesis of effectiveness data. The economic evaluation was also confined to a qualitative appraisal of the existing information base and concluded that the cost per QALY gained, from the perspective of the NHS and with a one year time horizon, would most likely fall between £9,200 (sensitivity analysis: from £4,700 to £28,200) and £14,600 (£5,600 to £17,500). For QALY computation, response rates had been linked to utility estimates based on expert assumptions on the differences in health-related quality of life between treatment responders and nonresponders.

HTAs (3): NICE 2004

In 2004, NICE again addressed ADHD treatment options [7,101-107]. A broader scope, including dexamphetamine (DEX), atomoxetine (ATX), and long-acting formulations of methylphenidate with an average duration of action of eight (MPH-MR08) or ten to twelve hours (MPH-MR12) [101], came in parallel with the implementation of more ambitious evaluation methods by NICE earlier in the same year [108,109]. Comparators should include placebo and usual care, and treatment outcomes to be included in the analysis were incidence and severity of core symptoms, of coexisting problems, measure of depression and/or anxiety, adverse events, and quality of life. Consideration should also be given to comorbid disorders [103].

The final assessment report included a systematic review of clinical studies, statistical data synthesis using mixed treatment comparison (MTC) techniques, a review of submissions by manufacturers, and an economic evaluation model developed *de novo* by the assessment group. Whereas the clinical effectiveness review focused primarily on measures of hyperactivity and included 64 randomized clinical trials (RCTs), the economic model was informed by six short-term studies only (including one that had been excluded from the effectiveness review for quality concerns), which provided CGI-I scores believed by the NICE team to enable response definition and subsequent QALY calculation. Utility weights came from a study using parent proxy ratings [108].

On the basis of six RCTs with treatment durations between three and eight weeks, 19 treatment sequences (taking account of concomitant non-drug treatment, the original model featured even 37 different treatment strategies) were simulated, and incremental cost per QALY was calculated for each from the perspective of the NHS over a one year time horizon. Secondary extensions added response rates from studies reporting other clinical endpoints and increased the time horizon to twelve years - however, without considering any of the long-term sequelae associated with the disorder. Given that the so projected differences in QALY outcomes between the various active treatment strategies were generally limited to the third or fourth decimal place only, and that differences in treatment compliance between short and long acting medications had been ignored (all responders were assumed by the NICE team to remain on treatment for the full one-year period of the primary model), the assessment failed to reveal any effectiveness differences between the various options and sequences evaluated. Thus the economic model was entirely driven by differences in drug acquisition costs, and the assessment group concluded that "the results of the economic model clearly identify an optimal treatment strategy" [104], namely to begin drug treatment with dexamphetamine. The conclusion was based on clinical evidence from one particular study only that had previously been excluded from the effectiveness review on grounds of "inadequate data presentation" (cf. above); this study had compared DEX with MPH-IR and placebo in 32 girls following a threefold cross-over design [109].

A critical appraisal of the NICE assessment revealed a range of further problems, including but not limited to issues related to data selection, the distinction between efficacy and effectiveness data, and several violations of the assessment protocol [7,110]. Hence this HTA by NICE should be interpreted with great caution. Indeed, also the NICE appraisal committee did not follow the "clear" conclusions of the assessment and in effect recommended all options investigated, based on an estimated cost per QALY below £7,000 compared to no treatment [105] - well below its usual benchmark of £20,000 to £30,000 per QALY gained [108,111,112].

In conclusion, it can be said that economic evaluations as part HTAs of ADHD treatment strategies have been of limited value to date. While in agreement regarding the acceptable to attractive cost effectiveness of the medication strategies evaluated, they have offered little to nothing in terms of the desirable differentiation of the various drug regimens available.

COST EFFECTIVENESS ANALYSES (CEAS) BASED UPON THE NIMH MTA STUDY

In the field of clinical ADHD research, it is widely acknowledged that the Multimodal Treatment Study (MTA), initiated by the National Institute of Mental Health (NIMH), represents a landmark or "mega-trial" [97,99,100,113-115]. The complete set of patient-level data from this study was available for health economic evaluations, which have provided insights into the cost effectiveness of ADHD treatment strategies beyond the United States.

The NIMH MTA Study enrolled 579 children, aged 7 to 9.9 years, at six North American centers and adhered to a parallel group

design. For an interpretation of its key findings, it is necessary to appreciate that it was an extensively standardized, highly manualized comparison of three treatment strategies and routine community care in the United States and Canada. All four approaches tested were highly effective and showed substantial improvement (from baseline at study entry) by the end of the controlled study after 14 months [99]. Two thirds of the children in the community comparison group received medication, principally MPH (average daily dose at study completion 22.6mg, administered, on average, as 2.3 divided daily doses). Emphasis on subject rapport, extensive use of manuals, and regular supervision of therapists by skilled clinician investigators, together with robust monitoring measures, ensured a high degree of protocol adherence for the active three treatment strategies investigated [99]. Psychosocial interventions in the MTA Study involved three major integrated components, comprising parent training, school intervention, and summer treatment program, and were designed to maximize the opportunity to demonstrate treatment effects [116,117], not cost effectiveness. Medication management in the MTA consisted of a structured set of algorithms (starting with a double-blind, daily-switch titration protocol for MPH, followed sequentially by DEX, PEM, and imipramine, until a satisfactory response was obtained) rather than a single medication, which like the behavioral interventions were accompanied by extensive measures to ensure protocol fidelity. Of 289 children randomized to one of the medication management arms, 256 adhered to and completed the full titration protocol. Of those 77% (198 out of 256) responded to one of the MPH titration doses, and 88% (174 out of 198) were still taking MPH at the end of the maintenance phase at 14 months. Mean MPH doses at the end of 14 months were 31.1 mg per day for the combination management group and 38.1 mg per day for the medication management group ($p<0.001$); both groups received MPH-IR divided in three daily doses ("t.i.d.") [118-120].

A wide range of outcome measures, but not health-related quality of life, were assessed in the MTA Study, and complex relationships were observed between parameters [121]. The primary CEA based upon the MTA Study used response rates based on averaged parent and teacher ratings of ADHD and oppositional defiant disorder symptoms on the SNAP-IV scale [122]. Response rates after 14 months were 25% for the community comparison group, 34% for behavioral management, 56% for medication management, and 68% for the combination of both [122]. Follow-up of patients beyond the 14-months controlled study period was naturalistic, i.e., there was no study protocol stipulating specific interventions. At 10 months follow-up beyond the intensive treatment phase (i.e., 24 months after enrolment), the medication management strategy continued to show significant superiority over the behavioral management and community comparison groups, although effects were attenuated compared to the end of the 14 months controlled trial period [123]. However, 36 months after study initiations, differences between the four study groups had disappeared [124]. Likewise, analyses eight years after MTA Study enrolment indicated that treatment-related improvements were generally maintained, but no appreciable differences between the initial treatment groups could be identified [125]. These observations spurred an intense scientific debate, which highlighted the need for further research, in particular for a long-term (5-8 years) controlled study of medication versus nonmedication treatments for ADHD [126-130].

MTA-based CEAs available to date have been limited to a time horizon of one year, or 14 months including the initial titration period. Direct costs were determined combining utilization data from the study, excluding its research component, with unit costs being valued from a "societal perspective" (and, for the international analyses reported below, in some jurisdictions such as The Netherlands and Germany from a payer's perspective). These evaluations were enhanced by access to patient-level data and the resulting opportunity to conduct stochastic sensitivity analyses by means of nonparametric bootstrapping, a data resampling technique that enables analyses reflecting the underlying variance within the sample data, without making potentially incorrect distributional assumptions [131].

In the primary MTA-based CEA, ICERs for one additional patient with symptomatic "normalization" (according to SNAP-IV scores [122]) over a time horizon of 12 months were estimated at around US-$ 350 for medication management (versus community care) and US-$ 2,500 for combination treatment versus behavioral treatment only [132]. For pure ADHD (i.e., ADHD according to DSM-IV diagnostic criteria, without coexisting anxiety, depression, conduct of oppositional defiant disorder), medication management dominated (i.e., it was more effective and less costly than) community care, and combination treatment versus behavioral treatment was associated with an ICER of US-$ 940. This translated into estimated costs per QALY gained for medication management versus community care ranging between US-$ 3,000 and US-$ 5,500 for the overall DSM-IV-defined study population; in patients with pure ADHD (i.e., without coexisting internalizing or externalizing psychiatric morbidity), medication management again dominated community care. Accordingly, estimated costs per QALY for the comparison between combined treatment and behavioral management (i.e., for adding the MTA medication management algorithm to the psychosocial intervention protocol) ranged between US-$ 20,000 and US-$ 40,000 for the overall study population, and US-$ 8,000 to US-$ 15,000 for pure ADHD [132].

Although comorbidity had been identified as an important moderator of treatment response [57], these principal observations held across comorbid subgroups [132]. Secondary CEAs used functional impairment as measured by Columbia Impairment Scale (CIS) scores as the clinical endpoint of interest. The scale is completed by parents, captures four domains of impairment - interpersonal relations, psychopathology (such as depression, anxiety, behavior problems), schoolwork, and leisure time - and has been shown to have good internal consistency and construct validity [133-135]. The secondary CEAs revealed a somewhat more differentiated picture; while medication management was still the most cost effective option overall and across subpopulations, cost effectiveness for the behavioral treatment strategy as defined by the MTA study protocol was less disappointing in subgroups with more severe comorbidity, in particular in patients with coexisting internalizing signs and symptoms [136].

In an extension of the primary analysis, also cost per symptomatic responder and estimates per QALY gained were reported for the study subpopulation meeting criteria for hyperkinetic disorder [60,137], applying the same methodology [131]. On the basis of 145 patients eligible for this analysis, costs per QALY gained were estimated at below US$ 2,000 [138] - better than the estimate of up to US-$ 5,500 for the DSM-IV-defined study population and suggestive of an improved cost effectiveness of intense medication management in this presumably more severely impaired subgroup [61,62,138].

Subsequent international CEAs explored whether these observations can be transferred into a European context [139-142]. In order to assess the portability of US findings to an international context [65,66], a number of issues were addressed, such as different diagnostic criteria preferred in Europe ("hyperkinetic [conduct] disorder" - HK[C]D - according to ICD-10) [60,67], different treatment preferences and standards of care (raising questions regarding the relevance of the "community care" comparison arm of the study) [13-18], and of course different unit costs (varying by jurisdiction as well as by perspective, i.e., payers' *versus* societal) [65, 66].

International economic analyses based upon the NIMH MTA Study have been reported for Germany (D), The Netherlands (NL),

Sweden (S), and the United Kingdom (UK) [139-142]. Evaluation strategies included addressing subgroups (beyond the total study population with ADHD according to DSM-IV criteria) meeting criteria for hyperkinetic disorder [137] and by comorbidity (pure ADHD, internalizing, externalizing, or both comorbidities), modeling a hypothetical "Do Nothing" alternative (to account for the context-specific "community care" comparison arm of the MTA), using symptomatic "normalization" and functional impairment as efficacy endpoints, estimating cost per QALY gained based on response rates, applying parent proxy ratings [107,108] and expert estimates [96], using health care resource utilization data from the trial excluding its research component and substituting its initial double-blind titration protocol with a clinically proven algorithm which led to similar dosing regimens [143], and applying unit costs (for year 2005) for direct medical expenditures from a "societal perspective" (D, NL, S, UK, USA) and from a payers' perspective (D, NL). Patient-level data from the study were available for analysis, enabling probabilistic sensitivity analyses by means of non-parametric bootstrapping (cf. below; Fig. **4**).

Treatment response was again defined as normalization of core symptoms (SNAP IV teacher/parent scores $\leq$1) [122]. ICERs were determined for the total study population and subgroups with pure ADHD (without comorbidity, n=184), pure hyperkinetic disorder (HKD, n=77), and patients with hyperkinetic disorder with or without concomitant conduct disorder (HKD/HKCD, n=145). For all subgroups and across jurisdictions (D, NL, S, UK) and perspectives (societal, payers') studied, ICERs per additional patient "normalized" ranged from dominance to 4,200€ for medication management *versus* community care and from 21,000€ to 100,000€ for the combined treatment strategy versus medication management. Medication management dominated behavioral treatment and exhibited extended dominance over community care compared to the hypothetical "Do Nothing" alternative. Across comorbid subgroups, ICERs per responder for medication management versus community care ranged from €100 to €5,000, again across jurisdictions and perspectives [142]. Robustness of the results reported above was supported by a range of one-way and probabilistic sensitivity analyses (cf. also Fig. **4**).

Cost effectiveness was also assessed for the subgroup of patients meeting diagnostic criteria for hyperkinetic disorder (HKD), replicating the United States findings that medication management seemed relatively more efficient compared to community care in these children [138-140].

For medication management versus community care, reasonable estimates across jurisdictions and perspectives ranged from €4,500 (best case) to €52,000 (worst case) per QALY gained. For illustration, German data for medication management versus the "Do Nothing" alternative are provided below for the total study population, as well as for the subgroups without psychiatric comorbidity ("pure ADHD," n=184) and for study patients meeting ICD-10 criteria for hyperkinetic (conduct) disorder (HKD/HKCD, n=145), Table **2** [144].

For the secondary international economic evaluations, ICERs were again determined using Columbia Impairment Scale (CIS) effect size (Cohen's d) as clinical outcome criterion. Although incremental cost per CIS effect size gained is more difficult to interpret compared to cost per additional responder or cost per QALY, medication management (with ICERs versus "Do Nothing" ranging from €1,000/ES to 2,700/ES, and ICERs versus community care from dominance to €3,000/ES) appeared attractive on grounds of cost effectiveness for subgroups without psychiatric comorbidity, across jurisdictions and perspectives studied [141].

This observation held for patient subgroups with psychiatric comorbidity as well. Behavioral interventions, however, appeared relatively less disappointing in patients with more severe comorbidity, as cost effectiveness acceptability analyses revealed potentially more acceptable cost effectiveness at higher levels of willingness to pay for functional improvement [142]. Although these data do not lend themselves to a simplistic interpretation, it seems noteworthy

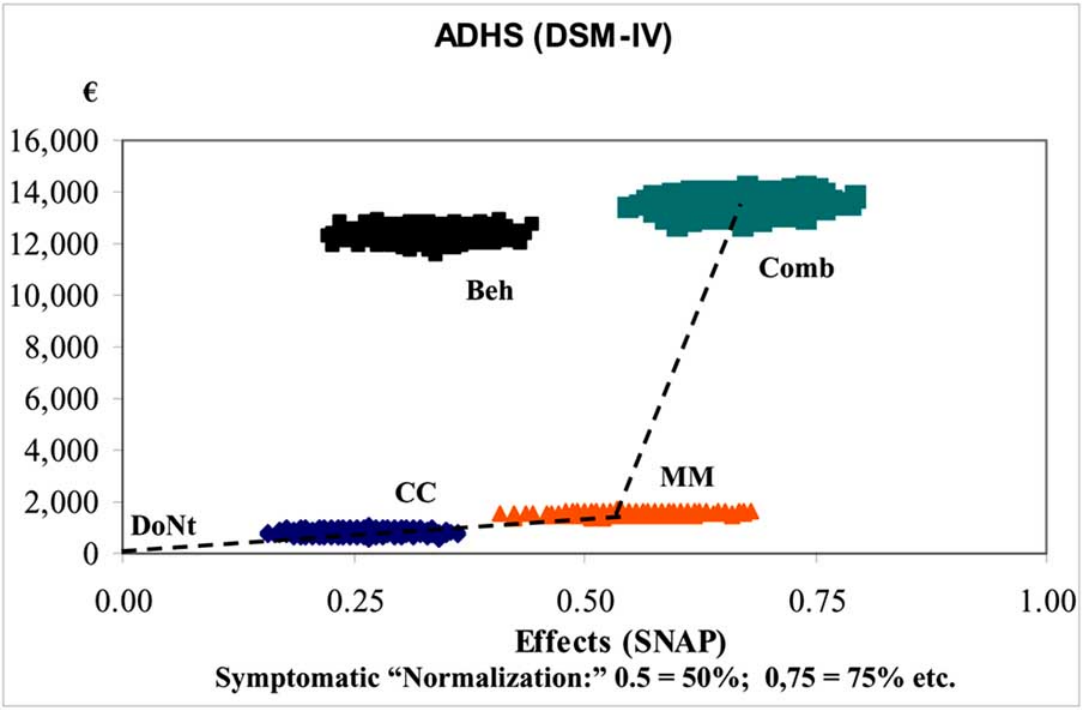

Fig. (4). International CEA of ADHD treatment strategies based on the NIMH MTA Study: Germany (2005) [139, 140, 144]
Decision uncertainty is represented by the ellipsoid scatter plots showing the joint distribution of costs and effects for each intervention. Effect measure is response rate in terms of symptom normalization as measured on the SNAP-IV scale [181]. Time horizon 14 months. Abbreviations: Beh, behavioral treatment arm; CC, community comparison arm; Comb, combined treatment arm; DoNt, (hypothetical "Do Nothing" alternative; MM, medication management arm. The dashed line joining DoNt, MM and Comb is the 'efficiency frontier'.

Table 2. Pharmacotherapy of Childhood ADHD: Cost Estimates per QALY Gained (Germany 2005) Based Upon the NIMH MTA Study [144]

	ADHD (DSM-IV) (total study population) n=579	Pure ADHD (DSM-IV) (without psychiatric comorbidity) n= 184	HKD/HKCD (ICD-10) (hyperkinetic disorder with or without concomitant conduct disorder) n=145
Medication management vs. "Do Nothing"	€ 20,100 - € 36,800	€ 19,000 - € 34,600	€ 22,600 - € 41,300
Combined vs. medication management	€ 731,800 - € 1,336,700	€ 637,100 - € 1,163,800	€ 422,600 - € 772,000

Note that Table Provides ICERs for Interventions on the Efficiency Frontier (cf. Fig. **4**) Only.

that these results (which were replicated consistently for Germany, Sweden, The Netherlands, and United Kingdom [140,141,144]) appear concordant with analyses reported for the United States [136].

Summing up, it can be concluded at this point that the main health economic insights derived from the NIMH MTA Study appear robust across jurisdictions. They provide strong support for an acceptable to attractive cost effectiveness of a carefully monitored intense medication strategy over a time horizon of 12 to 14 months, compared to less intense North American community care (which in the majority of patients included medication as well, albeit at lower doses on average) as well as in comparison to a hypothetical "Do Nothing" alternative. Accordingly, these analyses offer important insights regarding the cost effectiveness of a stimulant-based medication management strategy, even at the "intensity margin" (i.e., for increasingly intense intervention). Of course, by design the NIMH MTA Study does not allow any inferences regarding the relative value of alternative drugs, and it should be emphasized here that none of the relatively more expensive long-acting products had been available during the MTA study period. While medication-based strategies were clearly economically superior to behavioral interventions, the very poor cost effectiveness of psychosocial treatment (cf. Table **2**) should be interpreted more cautiously in light of the MTA study objectives and design choices.

COMPARATIVE ECONOMIC EVALUATIONS OF ADHD DRUG TREATMENT

In the United States, economic analyses comparing alternative drug regimens for treatment of ADHD in children and adolescents began to appear as late as 2001. Marchetti and colleagues (2001) [145] attempted to compare six different formulations of stimulants from a payer perspective over a time horizon of one year. In addition, in a remarkable departure from the payer perspective, the study included school-related costs "*based on results from a[n unspecified] stakeholder survey […] that indicated that payers were concerned with costs associated with dosing of medication at school*" [145]. Effectiveness estimates were reportedly derived from a meta-analysis, but results were presented only for three products. For these drugs, differences in response rates found these analysts were small (all at around 80%) and did not reach statistical significance. The economic evaluation compared expected total cost of treatment (presumably for year 2001) only, and did not provide ICER estimates. Therefore, this study may be classified as a cost minimization analysis (CMA).

Marchetti *et al.* (2001) [145] concluded that the total expected annual cost of pharmacologic ADHD treatment in the United States was lowest with long-acting formulations. However, this conclusion held only if costs associated with school-dosing were included - a procedure that necessarily obscured the perspective of the study, thereby greatly reducing its value.

CEAs of Short-Acting Stimulants

In a subsequent report U.S. study, Narayan and Hay (2004) [146] addressed the comparative cost effectiveness of immediate-release methylphenidate (MPH-IR, Ritalin®) and mixed amphetamine salts (MAS, Adderall®) for the first line treatment of school-aged children with ADHD. They constructed a decision tree model to capture, for three strategies (MPH-IR 10mg, presumably administered b.i.d., but not specified by the authors; MAS 10mg/d, divided in two doses; and a no treatment alternative) the impact of response and drop out rates that were taken from the metaanalysis reported by Marchetti *et al.* (2001) [145]. Based on ADHD core symptoms, response rates for MAS (82.7%) were slightly higher than those for MPH-IR (78.7%), a small difference that was later confirmed by meta-analyses reported by Faraone *et al.* (2002, 2010) [147,148]. Nonresponders to either drug were assumed to be treated with dexamphetamine (DEX) because the authors believed DEX would be used a second line treatment option only, owing to fears of illicit drug diversion and abuse. Modeling a one-year period from a "societal perspective" [146], which however encompassed only direct medical costs and assumed costs for school administration, these authors came up with an estimated cost per QALY gained of US-$ 21,957 for MAS versus no treatment (with costing done for year 2003). In their analysis, MPH-IR was dominated by MAS therapy. Nevertheless, the authors suggested that treatment with either MAS or MPH-IR was cost effective compared with no treatment [146].

The early study by Gilmore and Milne (1998, 2001) was already mentioned in the *Introduction* [5,98]. It had been incorporated in the first NICE Health Technology Assessment (2000) [96] and in the review by Romeo *et al.* (2005) [1]. In brief, these authors aimed to examine the cost effectiveness of methylphenidate (immediate release formulation, MPH-IR) compared to placebo in children with hyperkinetic disorder with or without externalizing comorbidity (conduct or oppositional defiant disorder), but not anxiety disorders. Based on a systematic literature review, they actually used studies in children with ADHD, estimating an average response rate of 70%. They assumed that benefits seen at four to six months would persist for a year, which was the time horizon of the study, and an assumed early drop out rate of six percent due to side effects. Costing was done from an NHS perspective (in £ for year 1997). This led to a calculated cost per QALY gained of £9,177, with a range from £5,965to £14,233 for the scenario considered most likely by the study authors, and a "most accurate estimate" of £7,446 to £9,177 when slight physical disability was assumed to add to the level of disability experienced by ADHD patients [5].

In an Australian analysis, Donnelly *et al.* (2004) [149] assessed the comparative cost effectiveness of dexamphetamine and methylphenidate over a time horizon of 12 months from the perspective of

patients and government (Australian NHS, year 2000). They calculated cost per disability-adjusted life year ("DALY" - another variant of the group of health-adjusted life years, in essence measuring quality-adjusted life expectancy lost [150]) averted, using disability weights (conceptually corresponding to the inverse of utility weights used for QALY computations, but adopting a social perspective for valuation) for mild and moderate-severe ADHD derived from a study with Dutch health care professionals [151]. The resulting differences on (dis)utility weights between responders and nonresponders were roughly in line with expert estimates from the UK [96], which had also been used for the (best case) calculations of QALY gains on the basis of the NIMH MTA Study discussed earlier [139-141], and appear also concordant with utility data used in the U.S. analyses mentioned earlier [132,152]. On this basis, the ICERs (for the combined costs of government and patients per DALY averted) estimated by Donnelly *et al*. were AUS-$ 4,100 for dexamphetamine and AUS-$15,000 for methylphenidate, and the authors concluded that both interventions were cost effective [149].

Thus, cost effectiveness analyses of short-acting stimulant medications, which were based on symptomatic response rates over a time horizon over one year, have consistently found acceptable cost effectiveness ratios compared to no treatment. Differences in incremental cost effectiveness between compounds were largely driven by differences in acquisition costs, and will hence vary by jurisdiction contingent on availability of products.

CEAs of Long-Acting Stimulants

A number of separate economic evaluations - apparently all of which had been supported by the manufacturer of MPH-MR12 (Concerta®) - attempted to predict the potential cost effectiveness of treatment with MPH-MR12 (36 mg once daily) versus MPH-IR (10 mg three times daily). They have in common that they applied variants of the economic model developed by the Canadian Coordinating Office for Health Technology Assessments (CCOHTA, Fig. (**3**) [89]), combining assumptions regarding treatment adherence rates from a systematic review [153] with efficacy data from a meta-analysis of short-term clinical studies [154-156]. Reports are available for Canada from a third party payers (public and private) perspective [157], for England from the point of view of the NHS [158,159], and for Germany from the point of view of the statutory health insurance (SHI; "*Gesetzliche Krankenversicherung*", GKV) [160]. All looked at a 12-month treatment period and used core ADHD symptom improvement measured on the Conner IOWA inattention/overactivity (I/O) Scale [64,161,162] as the effect measure of interest. Across jurisdictions and despite (minor) design variations, these studies agreed in suggesting comparable ICERs for MPH-MR12 and MPH-IR, which even reached extended dominance of MPH-MR12 over MPH-IR in Canada and the United Kingdom [157-159]. Technically, extended dominance is defined as a state when one strategy under study (here, MPH-IR t.i.d.) is both less effective and more costly than a linear combination of two other strategies (no drug treatment and MPH-MR12 q.d.) with which it is mutually exclusive [2-4]. In practical terms, extended dominance occurs when an alternative (in this case, MPH-MR12) is more effective and more costly, but provides better value for money.

In subsequent evaluations, the United Kingdom model was refined and replicated using actual (instead of assumed) persistence data for MPH-IR and MPH-MR12 from retrospective database studies [163-168]. Again, results ranged from comparable cost effectiveness to extended dominance of MPH-MR12 versus MPH-IR [169].

Limited information is available concerning further studies presented at international health economics conferences. In a U.S. study, Ganapathy and Hay (2008) [170] suggested that MPH-MR12, atomoxetine (ATX), and the combination of methylphenidate (presumably MPH-MR12) and behavioral therapy were all cost effective compared to no treatment. Devine *et al*. (2007) [171] undertook a cost utility analysis of MPH-MR12, an extended-release formulation of mixed amphetamine salts (MAS-MR), and atomoxetine (ATX) for treatment of children with ADHD in the U.S. Military Health System (MHS). Results of this study remain somewhat unclear because of their high sensitivity to unspecified patient preferences for extended release and non-stimulant products. Also in 2007, Vazquez [172] presented a Mexican comparison of MPH-MR12, ATX, and MPH-IR, claiming superiority of MPH-MR12 on grounds of cost effectiveness.

Faber *et al*. (2008) [173] attempted to assess the cost effectiveness of MPH-MR12 in youths not optimally responding to MPH-IR. They published results derived from a Markov model with a cycle length of one day and a modeled time horizon of 10 years. "Functional remission" of ADHD was used as a terminal state of the Markov model [174]. Rates of "functional remission" were taken from a brief report based on five symptom measurements (but not assessments of functional impairment) in 128 boys over four years [175], and the authors did not consider more comprehensive research actually suggesting higher rates of symptomatic (again, not "functional") remission [176]. Noncompliance rates were estimated based on a Canadian 8-week study by Steele *et al*., 2006, discussed below [177]. Outcomes were expressed as quality-adjusted life years (QALYs), with utility weights taken from an English standard gamble study conducted by Secnik *et al*. [178]. This particular study by Secnik *et al*. had previously been rejected by the NICE assessment group for apparent inconsistencies of reported data [104]. On this basis, costs per QALY expressed in € for year 2005 were around €2,000 (or €12,500, if resource use assumptions for patients "in the suboptimal state" were reduced by 25%); with reported ICERs ranging from dominance of MPH-MR12 in the best-case to €38,000 (worst case considered). These findings point to cost effectiveness of the long acting formulation despite six times higher medication costs [173]. However, the value of this study is impaired by the large number of assumptions and expert estimates, including the unconventional perspective adopted for costing, the remission rates used, and the source of utility values.

It can be concluded at this point that international modeling studies suggest cost effectiveness of long-acting stimulants, at least as far as MPH-MR12 is concerned. Although two recently presented retrospective database analyses from the U.S. suggest different patterns of medication augmentation and associated costs depending on choice of long-acting product [179,180], it seems difficult to make inferences from these observations as to differences in the relative cost effectiveness of the various intermediate- and long-acting stimulant products. It should also be kept in mind that - even sophisticated - economic models are intended to be aids guiding policy decisions and, as such, should not be misconceived as establishing "truth" [181]. The value of models lies not only in the results they generate but also in their ability to reveal the logical connection between inputs (usually data from a variety of sources and assumptions) and outputs [182].

Arguably, the key advantage of long-acting medications for ADHD is linked to improved treatment compliance under conditions of routine care [69,71,183,184]. As an alternative approach to the combined use of RCT efficacy data and modeling, randomized pragmatic effectiveness trials (which are performed "under conditions that are representative of and relevant to the usual treatment situation," i.e, with minimal quality assurance and study management) are recognized as an appropriate vehicle for economic studies [185-189]. They should, *inter alia*, provide more generalizable answers in situations when there is a concern that "artificially enhanced compliance" in RCTs may be a threat to their external validity [189]. This view has been explicitly endorsed by leading child psychiatrists [190].

Against this background, a randomized "real-world" study performed in Canada [177], which compared long acting methyl-

phenidate (again, MPH-MR12 given q.d.) directly with usual care with MPH-IR, is particularly informative. The study involved 147 children between the ages of 6 and 12 with ADHD in accordance with DSM-IV criteria and had a parallel-group design, with a treatment and observation period of in each case eight weeks. The primary endpoint was normalization of ADHD core symptoms on the basis of parent-reported SNAP-IV scores, which occurred in 44% of the patients receiving MPH-MR12, compared with only 16% of the MPH-IR patients. Unfortunately, this study is impaired by the absence of teacher-reported outcome ratings. A further concern relates to the fact that 39% of the patients in the MPH-IR group were dosed twice daily (b.i.d.), which may be considered an unfair comparison. This concern was addressed by *post hoc* subgroup analyses, which confirmed a statistically significant difference in favor of MPH-MR12 (with a remission rate at study endpoint of 24% for those patients who had received MPH-IR three times daily (these were 61% of all patients in the MPH-IR group) [177]. Using this data, a trial-based economic evaluation was done from a Finnish payers perspective and reported extended dominance of MPH-MR12 q.d. over MPH-IR t.i.d. [191].

Summing up the section on long-acting stimulants, it can be concluded that there are good reasons to assume acceptable cost effectiveness, given the high level of consistency of economic study results to date. The economic argument in favor of long-acting products is grounded in their clinical efficacy [69,71,78,169,192]; the disorder-specific relevance of avoiding a midday dose in children with ADHD [183,184], supported by improved treatment persistence rates observed in retrospective database analyses [163-168]; economic modeling studies evaluating the impact of improved treatment persistence [157-160,173]; and a Canadian randomized pragmatic study broadly confirming expectations [177,191]. It should be noted, however, that most analyses dealt with MPH-MR12, and that none of the economic evaluations available to date has been without its own set of specific limitations.

CEAs of Nonstimulants

Unlike stimulants, atomoxetine (ATX) is not a controlled substance, and in most patients it is effective when given once daily. Therefore, the considerations above regarding treatment compliance can be expected to fully apply to ATX. However, some children with ADHD may require twice daily dosing of ATX, which will double the direct cost of medication owing to the flat pricing policy adopted by its manufacturer (translating into a constant price per capsule, irrespective of the amount of active compound) [82-84].

Meta-analyses of the comparative effectiveness of ATX versus stimulants have consistently pointed to inferior symptom improvement and so-defined response rates with ATX [192-196]. These findings appear largely consistent with the results of randomized head-to-head trials directly comparing ATX with stimulant treatment in children and adolescents with ADHD [197-203]. Taken together, these data strongly suggest economic dominance of long-acting stimulants (and perhaps other methylphenidate formulations as well) over atomoxetine, as on the basis of the best currently available evidence the stimulant products appear at least as or (most likely) more effective as ATX, whilst being no more or (in most jurisdictions) less expensive than ATX [144,169].

In contrast, the 2004 NICE ADHD technology assessment, which relied on a much smaller subset of studies (as discussed earlier [7,110]), failed to identify differences between the long-acting products evaluated (ATX, MPH-MR08, and MPH-MR12) [104].

Iskedijan *et al*. (2003) [204] estimated the cost per additional symptom free day for ATX compared to MPH. Using efficacy and resource use data "from the literature" and preference rates for nonstimulant medication obtained from parents, they claimed a "relatively small and quite reasonable" incremental cost ranging from CAN-$ 1.12 to CAN-$ 20.34 per symptom free day gained, from the perspectives of the Ontario Ministry of Health, government, and "society" in Canada (year 2002).

Two closely related CEAs of ATX were based on a Markov model with Monte Carlo simulation of costs and effects over a time horizon of one year [205,206]. Comparators included stimulant-based "algorithms" (incorporating both immediate-release and modified-release formulations of MPH and DEX, as well as "no medication"). Effectiveness and safety aspects were based on "a thorough review of controlled clinical trials," validated by clinical experts, and linked to utility values derived from a survey of 83 parents of ADHD children, i.e., a study by Secnik *et al*. that had first been presented at an international health economics conference in 2004 [178,207]. On this basis, cost per QALY ICERs were estimated for three subpopulations (stimulant-naïve, stimulant failure, and stimulant-contraindicated), and ranged between €13,120 (versus DEX) and €22,804 (versus MPH-MR) in The Netherlands [205], and between NOK 149,892 (versus MPH-MR) and NOK 199,178 (versus MPH-IR) in Norway [206]. In both jurisdictions, ATX represented good "value for money" in the opinion of the analysts. Two years later, Diamantopoulos *et al*. presented a similar evaluation from the "perspective of the German health service" [208], coming up with cost per QALY estimates for ATX of €7,778 (versus MPH-MR12 in stimulant-naïve patients), €18,227 (versus MPH-IR in stimulant naïve patients), and €14,385 to €14,916 (versus no medication in ADHD patients who had failed to respond to stimulants or with a contraindication to stimulant treatment), respectively [208].

A similar Markov model as had been used in the studies for The Netherlands [205], Norway [206], and Germany [208], however with slightly different treatment algorithms, was applied in analyses for the United Kingdom [209,210] and Spain [211]. The first full publication was authored by Cottrell *et al*. (2008) [209]. Their results were broadly similar to the findings reported above, with ICERs per QALY gained ranging from £11,523 to £15,224 from the perspective of the National Health Service in England and Wales [209,210]. The Spanish adaptation reported ICERs of €34,308 versus MPH-IR, and €24,310 (versus MPH-MR12), in stimulant-naïve patients with ADHD, and approximately €23,500 in the stimulant-failure and stimulant-contraindicated groups [211].

All of these studies [205,206,208-211] had been conducted by or under contract with the manufacturer of ATX. The asserted cost effectiveness versus stimulants, including long-acting formulations, may well appear somewhat surprising given the results of the meta-analyses and head-to-head clinical trials briefly mentioned earlier and the acquisition cost of ATX, as taken together these data would appear to suggest economic inferiority of ATX. This is particularly disturbing since, for each of the economic analyses of ATX discussed above, QALY gains had been calculated using effectiveness measures directly derived from core symptom response rates, which in a second step had then been linked to specific utility estimates. Actually, the study authors identified the utility inputs as a key factor influencing their results; that is, the results of their modeling exercises were highly sensitive to the utility weights applied [209]. When differences by treatment group for the utility weights of symptomatic response versus nonresponse were removed, the cost per QALY ICERs indeed rose "to unacceptable levels" [209].

Consequently, this group of economic analyses of ATX [205, 206,208-211] is open to critique on two grounds: (1) the selection of data sources used for efficacy inputs, and (2) the utility weights applied. As to (1), the model description (Cottrell *et al*., 2008, p. 381 [209]) reveals that the probability that a patient discontinues treatment for lack of efficacy was assumed to be the same for all products - none of the head-to-head trials and none of the meta-analyses were discussed. Both clinicians [212] and health economists [169] in the United States and Europe concluded, "there is now ample evidence that stimulants are the most effective treatment

for decreasing symptoms of ADHD" [212]. Regarding (2), the utility weights applied came from a survey by Secnik at al. (2005) from Eli Lilly [178,207]. In this study the utility of responders on ATX with side effects (0.937) was higher than the utility weights for responders on stimulant medication without side effects (0.913 for MPH-IR and 0.930 for MPH-MR12, respectively). These data had been rejected by the NICE assessment group because of concerns about the validity of these estimates, particularly the fact that the utility of a non-responder without side effects differed between treatments. For example, the utility associated with non-response to atomoxetine, without side effects, was estimated to be 0.902, which compared to an estimated utility of 0.880 associated with non-response and no medication (cf. King *et al*., 2004, p.240 [104]). The (only) explanation offered by the study authors was a statement concerning "a more stable and longer-lasting response" with ATX, and that "the nature of the response with atomoxetine, which was reflected in the health state descriptors used in the utility valuation study, is preferred to that of stimulant treatments" (no sources given: Cottrell *et al*., 2008, p. 385f. [209].

Hence there remain critical questions related both to the objectivity of the underlying effectiveness assumptions as well as to the reliability of the manufacturer-reported utility values, which provided a crucial input to the health economic evaluations of ATX [205,206,208-211]. As a consequence, these studies should be interpreted with great caution.

Recent Additions to the Pharmacotherapeutic Armamentarium

Recent additions to the pharmacotherapeutic armamentarium for ADHD in children and adolescents include a transdermal delivery system for methylphenidate (Daytrana®, a patch) and lisdexamphetamine (Vyvanse®, a prodrug), which were first introduced in the United States [9,78,213,214]. Both new drugs are clinically effective and appear likely to be used in a substantial number of patients [9], but at the time of writing the present overview, there is no information available providing insights into their comparative cost effectiveness.

PHARMACOECONOMIC STUDIES IN MAJOR DEPRESSION AND ANXIETY

As mentioned earlier, there are few economic evaluations of mental health conditions other than ADHD in children and adolescents. This is particularly true for pharmacotreatment. One exception is a study conducted by Haby *et al*. (2004) as part of the Australian "Assessing Cost-Effectiveness - Mental Health" (ACE-MH) program [215,216]. Using a similar approach as Donnelly *et al*. (2004) [149], Haby translated effect sizes into a change in the DALY disability weight, and compared cognitive behavioral therapy (CBT, delivered by public or private Australian psychologists or psychiatrists) and selective serotonin reuptake inhibitors (SSRIs), as first or second line treatment, with current treatment practice. They found CBP by public psychologists to be the most cost effective option (at AUS-$ 9,000 per DALY averted), followed by SSRIs at AUS-$ 23,000 per DALY averted (same for first line treatment versus current practice and for second line treatment versus no further treatment) [216]. Their analysis was limited by a paucity of quality of life data in children and adolescents with major depression, which would have allowed calculation of effect sizes, so that the evaluation was largely based on symptom measures - a remarkable parallel to the situation in ADHD discussed in detail before - and by the principal approach of an episode-based analysis, which again was necessary due to limited data on the natural history of depression in children and adolescents. Further, there were no data underpinning the assumption that CBT by public psychologists is equally effective as treatment by private psychologists or by psychiatrists. On the positive side, however, it should be noted that extensive sensitivity analyses were done supporting the conclusions of this study.

A British study reported by Byford *et al*. (2007), seems noteworthy in this context [217,218]. Based on a randomized pragmatic trial, that compared the addition of CBT to SSRI (fluoxetine) treatment alone in 208 adolescents with major depression over 28 weeks, Byford *et al*. concluded that CBT was not cost effective. These authors speculated that the provision of SSRIs in addition to routine care might have "a higher probability of improving outcomes in a cost effective manner over the first 6 months of treatment" [217], although this evaluation did not include a controlled comparison of SSRIs versus routine care alone.

More recently, clinical data from a 36-week randomized clinical trial (RCT) in the United States, the Treatment for Adolescents with Depression Study (TADS) have provided relevant further insights [219-221]. Like the MTA Study in ADHD, the TADS was funded by the National Institute of Mental Health (NIMH) in Bethesda, MD. Fluoxetine (FLX), cognitive behavioral therapy (CBT), and the combination of both were compared with placebo in a parallel group design enrolling 439 adolescent outpatients aged 12 to 18 years with major depression. After the first 12 weeks, 71% of patients showed improvement in symptoms with combination therapy (as determined by scores on the Children's depression Rating Scale - revised),.whereas 61% improved on FLX alone. Improvement on CBT was a mere 43%, not significantly better than placebo (35%) [222]. The first CEA was based on the initial 12-week study period, calculated costs for in-protocol as well as out-of-protocol service use, and included time and travel costs for adult caregivers, all expressed in US-$ for year 2003. Children Depression Rating Scale - Revised scores, representing the primary endpoint of the study, were translated into depression-free days, which in turn were transformed into QALYs derived from previously applied utility weights for adults [223]. A depression-free day was assigned a utility weight of 1.0, depression days were assumed to have a utility weight of 0.6, and days with intermediate values were linearly interpolated. This analysis came up with results which are at odds with those found by Haby *et al*. in Australia [216]: estimated ICERs per QALY gained were US-$23,700 for fluoxetine versus placebo, >US-$ 9 million for CBT versus placebo, and US-123,100 or US-$458,800 for combined treatment (CBT plus fluoxetine) versus placebo or fluoxetine, respectively. This cost effectiveness data reflected the clinical study outcome that showed CBT to be no effective treatment option after 12 weeks, as determined by the Children's Depression Rating Scale [220].

In a subsequent TADS-based CEA covering the full 36-week study period, a similar methodology but a broader range of endpoints were used. Effectiveness data at 36 weeks were less impressive for drug treatment; while combination therapy continued to yield better outcomes (86% improvement on the Children's Depression Rating Scale), improvement with fluoxetine alone (81%) was no better than that achieved with CBT alone (81%) [224]. 327 study patients receiving one of the three active treatment conditions were available for the economic analysis. Missing variables were imputed using chained equations, and, where necessary, multiple imputation was applied using regression analysis, which implied the assumption that data were only missing at random. Out-of-protocol costs in the fluoxetine arm were higher over the extended observation period due to increased hospitalization rates and increased emergency department use. In this analysis, the comparison between CBT and fluoxetine alone still indicated somewhat less QALY gains with CBT (-0.02), and a small improvement (+0.015) with combined treatment compared to fluoxetine alone [221]. In the context of the present review, it should be mentioned that the main interest of the second analysis, however, was not to demonstrate cost effectiveness of fluoxetine *per se* but rather to justify the addition of CBT. The authors concluded that the combination of CBT and FLX was likely to be more cost effective than FLX alone. The report did not specify cost per QALY ICERs. Importantly, however, the cost data, which were driven by increased hospitalization

and emergency department use of patients receiving FLX, underscore the need to always interpret economic evaluations in the clinical context [221].

Another study within the Australian ACE-MH program [215] looked into the cost effectiveness of psychological and pharmacological interventions for generalized anxiety disorder and panic disorder [225]. In line with the approach chosen for the program, the methodology was broadly similar to that used by Donnelly *et al*. [149] and by Haby *et al.* [216], and the results of this evaluation supported CBT as the most effective and cost effective intervention for the condition in Australia.

As far as pharmacotherapy was concerned, the authors noted that there was a lack of studies exploring the efficacy of combined pharmaceutical and psychological interventions, as well as an absence of evidence for long-term gains following drug treatment for panic disorder. Also long-term pharmacological treatment of generalized anxiety disorder was not supported by evidence from appropriate placebo-controlled clinical studies [225,226]. As a result of their limited effectiveness, serotonin and noradrenaline reuptake inhibitors for generalized anxiety disorder (at AUS-$ 30,000 versus current practice), as well as serotonin reuptake inhibitors and tricyclic antidepressants (at AUS-$ 78,000 and 30,000, respectively) appeared less cost effective compared with CBT [225] - a finding that was consistent with the earlier United States estimates from a group of researchers at Massachussetts General Hospital, which however had not been based on data from a randomized controlled clinical trial and did not specifically address treatment of children [227].

SOME IMPLICATIONS

There has been an impressive increase in the number of cost effectiveness evaluations in child and adolescent psychiatry since Renée Romeo and colleagues published their review in 2005 [1]. The vast majority of economic studies that addressed drug treatment were concerned with ADHD, only a few dealt with major depression in adolescents. However, anxiety disorders, conduct disorder, depressive disorders, substance abuse are common conditions in children and adolescents as well, and even less frequently diagnosed disorders such as Tourette syndrome, schizophrenia and bipolar disorder are associated with substantial burden of disease and economic impact. Any resources committed to specific interventions - such as medication - will not be available for alternative use - hence opportunity costs will be incurred. Thus it is necessary to thoroughly evaluate the benefits conferred by interventions designed to alleviate the burden associated with these disorders. It is safe to predict that health care policy makers will increasingly expect robust evidence of value for money, also for interventions for child psychiatric conditions other than ADHD.

But even for ADHD, currently available evidence of cost effectiveness is still limited. With very few exceptions [136,141,142], evaluations (like the small number of analyses addressing other child psychiatric conditions) relied on effect [usually: efficacy] measures related to symptomatic improvement, often over short periods of time only. This raises a number of important issues, such as:

(1) Do narrow band symptom scales really capture the objectives of therapeutic interventions? For example, the NIMH MTA Study illustrated that functional improvement of patients may not directly be linked to symptomatic relief, with potential implications for the cost effectiveness of treatment strategies [99, 100,136, 141,142].

(2) Are there any valid surrogate endpoints that allow predicting broader long-term benefits on grounds of short-term data? For example, the NIMH MTA [99,100] and TADS [219,222] studies illustrated that short-term treatment response rates may not be good predictors of long-term treatment outcomes [124-130,221,224]. A related question concerns the optimal duration of treatment, which has not yet been determined unequivocally.

(3) What is the impact of moderators and mediators of treatment response on cost effectiveness of treatments? (Few) exceptions notwithstanding [136,139,142,144], there remains a largely unmet need to address the relative cost effectiveness of interventions in subgroups, for example by severity or by coexisting conditions [41,56,57].

(4) Given the wide variety of measurement instruments [63,64], can a sufficient degree of harmonization of study designs and effectiveness endpoints be achieved? To date, quantitative meta-analyses of treatment effects have been difficult [104,106] if not impossible [114] because of the huge variety of effect measures used in clinical studies.

(5) Future studies should include index-instruments enabling the transformation of health-related quality of life in utility weights for QALY calculation. But there remain important methodological [228-230] as well as normative [231-234] issues to be resolved in this context, ranging from valid measurements to the debatable relationship between economic efficiency and criteria for priority-setting in child mental health care [235].

(6) Given the importance of treatment persistence and notoriously high attrition rates in child and adolescent psychiatry [183,184], there is an increasing recognition of the need for pragmatic randomized clinical trials [185,186,188-190] that combine initial randomization with a more naturalistic follow-up than RCTs in order to increase generalizability of findings ("external validity" [236]). How can this be best reconciled with the need for long-term studies assessing the impact of interventions on a broad range of benefits?

(7) From the perspective of research-based pharmaceutical companies, the additional question arises whether it will be any longer good enough to show effects in RCTs, especially in placebo-controlled experimental settings (as required for marketing authorization). Arguably, more attention should be given to more complex treatment pathways and the cost effectiveness of combined interventions, including multimodal treatments as opposed to pharmacotherapy alone [237].

(8) Finally, what should be the appropriate role of manufacturers in cost effectiveness research? For example, many of the economic analyses done to date in the ADHD field were supported by, or conducted under contract with, manufacturers. The resulting reports invariably claimed to provide scientific support in favor of the cost effectiveness of the respective manufacturer's product(s). This observation should prompt some healthy skepticism among the recipients of such studies [238-240]. This further constitutes a veritable challenge to industry and its credibility, at a time when it is becoming increasingly clear that successful new product development depends on a close interplay among multiple stakeholders [241-243].

In light of the increasing hurdles to be met in the future, risk, time, and cost of new product development in child psychiatry will almost certainly continue to rise [242,244]. Thus new products will hardly be less expensive than existing ones. As a consequence, there will be no way to escape from the need to show that new therapeutic options provide good "value for money." The onus to prove "value for money" - or in practical terms, to justify prices - will rest in the first place with manufacturers, but economic success will not be possible without multi party partnerships, including regulators, academic researchers, clinicians, independent health economists, as well as policy makers and payers [241-244].

In the field of child psychiatry, at the present time economic studies provide broad support for the cost effectiveness of current pharmacotreatment of ADHD. Beyond clinical considerations, the choice of a particular treatment strategy will be influenced by its comparative cost effectiveness, which will depend on product

availability and relative acquisition costs in a given jurisdiction. Also cost effectiveness analyses for long-acting stimulants have consistently provided encouraging results when compared to short-acting formulations, whereas the economic evidence in favor of the nonstimulant, atomoxetine, appears less compelling, in particular in comparison to long-acting stimulants. In contrast, cost effectiveness of pharmacotreatment of depression is less well established, with clinical effectiveness and safety consideration currently representing the overriding concern when contemplating drug treatment.

LIST OF ABBREVIATIONS

ADHD	=	Attention deficit hyperactivity disorder
b.i.d.	=	Divided in two doses/day, twice daily administration
CBA	=	Cost benefit analysis
CEA	=	Cost effectiveness analysis
CEAC	=	Cost effectiveness acceptability curve
CMA	=	Cost minimization analysis
CUA	=	Cost utility analysis
DEX	=	Dexamphetamine
HKD	=	Hyperkinetic disorder
HKCD	=	Hyperkinetic conduct disorder
HRQoL	=	Health-related quality of life
HTA	=	Health technology assessment
ICER	=	Incremental cost effectiveness ratio
MAS	=	Mixed amphetamine salts
MPH	=	Methylphenidate
MPH-IR	=	Methylphenidate, immediate-release formulation
MPH-MR08	=	Methylphenidate, modified-release formulation (with an average duration of action of 8 hours)
MPH-MR12	=	Methylphenidate, modified-release formulation (with an average duration of action of 12 hours)
NHS	=	National Health Service
NICE	=	National Institute for Health and Clinical Excellence
q.d.	=	One dose per day / once daily administration
QALY	=	Quality-adjusted life year
QoL	=	Quality of life
RCT	=	Randomized clinical trial
SHI	=	Statutory health insurance (*Gesetzliche Krankenversicherung* in Germany)
t.i.d.	=	Divided in three doses per day / thrice daily administration

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