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BRIEF REPORT

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Long-acting medications for the hyperkinetic disorders

A note on cost-effectiveness

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Abstract New long-acting medications for attention-deficit/hyperactivity disorder (ADHD) have become available, which combine certain advantages over conventional short-acting drugs with higher acquisition costs. Choices between these drugs should thus be driven by their clinical profiles and by an acceptable balance of increased costs and additional benefits. Accordingly, the notion of relative cost-effectiveness should be central to recommendations about the use of these drugs in practice. A recent technology assessment on behalf of the National Institute for Health and Clinical Excellence (NICE) did not identify differences between compounds in terms of clinical efficacy and described drug cost as the major driver of cost-effectiveness. The underlying economic model was restricted to a cost-utility analysis that used only a fraction of the available clinical evidence base and did not address the distinction between efficacy and effectiveness. Cost-effectiveness evaluations including the potential impact of improved treatment compliance indicate a relatively more attractive cost-effectiveness of long-acting medications than suggested by the NICE assessment. These evaluations provide health economic support to treatment recommendations recently published by the European Network for Hyperkinetic Disorders. Limitations of currently available economic evaluations include their short time horizon, and future research should assess treatment effects on long-term sequelae associated with ADHD.

Key words attention deficit-hyperactivity disorder (ADHD) – hyperkinetic disorder (HKD) – stimulants – methylphenidate – atomoxetine – cost-effectiveness

Introduction

The recent advent of new long-acting medications for attention-deficit/hyperactivity disorder (ADHD) has sparked an initiative by the "European Network for Hyperkinetic Disorders" (EUNETHYDIS), a group of clinical specialists, [4] to extend European treatment guidelines for hyperkinetic disorder (HKD) [86]. They provided recommendations about the clinical use of these drugs, which invariably entails increased costs [4, 68]. Accordingly, the recommendations state that, aside from different clinical profiles of the drugs in question (e.g., regarding side effects and contraindications), choice of medication will be influenced by cost, citing the drug acquisition costs of the National Health Service (NHS) in England and of the Statutory

Health Insurance (SHI) in Germany as current examples [4].

Economic prescribing

Rational prescribing should—beyond the consideration of acquisition costs and budgetary impact—be influenced by the balance of additional costs and additional benefits, which health economists—focusing on health-related benefits—usually express as an incremental cost-effectiveness ratio (ICER) [20, 27]. This approach enables two related but separate types of economic evaluation, i.e., cost-effectiveness and cost-utility analysis. Cost-effectiveness analysis (CEA) can accommodate any clinical outcome measure considered meaningful in a given context (for instance, improvement in hyperactivity ratings, symptomatic "normalization", functional impairment scores, response rates, etc.). It is most useful when the objective is to compare alternative ways how to achieve a specific clinical outcome, i.e., to maximize so-called "technical efficiency".

Although it can be understood as a special variant of CEA, cost-utility analysis (CUA) purports to solve the inherent problems of comparing outcomes that are different in kind (i.e., problems of "allocative efficiency")—for example, should limited resources better be used to fund bone marrow transplantation in children with leukemia, beta-interferon for patients with multiple sclerosis, or intense behavioral treatment for children and adolescents with ADHD? CUA typically relies on quality-adjusted life-years (QALYs) as a universal and comprehensive measure of health-related outcomes, which combines length and quality of life in one index [20, 27]. The relative desirability of a given medical intervention then rests on its incremental cost per QALY ratio.

NICE technology appraisals

The National Institute of Health and Clinical Excellence (NICE) has adopted CUA as its standard or "reference case" [54] and applies a cost per QALY benchmark in the range of "a most plausible ICER of £20,000/QALY [...] to £30,000/QALY" [54, 55]. Incidentally, NICE had denied existence of a benchmark until independent analyses supported the notion of a threshold, where the probability of rejection increases as the cost per QALY increases [12, 16, 88]. The specific NICE approach has further been characterized by a transparent, participatory and predictable process [66, 68, 93], by suboptimal integration of economic and clinical perspectives [66, 92], and by the apparent absence of an effective formal quality assurance system for technology assessments [66, 93].

Apart from normative concerns [17, 18, 70], the use of QALYs in pediatric populations is associated with a number of distinct problems. First, there is no consensus on how quality of life should be defined and measured in children [14]. Second, a critical review of published CUAs in child health revealed substantial variation in the methods used to calculate QALYs, with unsettling implications for comparisons across interventions for different diseases and populations [28]. Third, although children with ADHD were reported to experience impaired quality of life [42], children with ADHD tend to underestimate their disease-specific problems [13, 22], especially regarding externalizing symptoms [5, 45]; and the validity of parent-proxy ratings is not fully understood [28]. Fourth, exacerbating the broader issue of reproducibility of quality weights, QALYs often lack sensitivity for small differences [25].

NICE assessment of ADHD medications

The proposed European treatment guideline on the use of long-acting ADHD medications [4] cites the economic model results of the corresponding NICE technology assessment [40]. However, this assessment is not without problems [66, 67]. In line with NICE guidance [54], effectiveness differences between treatment strategies were expressed as QALYs and extended to the third or fourth decimal place only. In order to enable calculation of QALYs, response rates were defined as a score of 1 ("very much improved") or 2 ("much improved") on the clinical global impressions/impairment (CGI-I) subscale, thus dichotomizing a single item with dubious psychometric properties and depending on baseline assessment [6, 11, 29]. For a mere six studies with treatment durations between 3 and 8 weeks, CGI-I scores were available to inform the primary economic model. This compared to 65 randomized clinical trials that had been found eligible for the clinical effectiveness review, which had used hyperactivity scores as the primary effectiveness criterion [39, 40, 66, 67]. One of the six remaining studies involved 32 girls (no boys) with ADHD in a 3-week crossover design [79]; this study had been excluded from the prior clinical review for inadequate data presentation but was added in order to have *any* data on dexamphetamine available for modeling. None of the 14 extended treatment studies reviewed by Schachar et al. 2002 [64] were included in the primary model [39, 40, 66, 67]. With this limited evidence base, no marginal analysis [8] of effectiveness and cost-effectiveness was possible, for instance by increasing intensity (e.g., dosing) of drug treatment [39, 40, 66, 67].

Also data from double-blind randomized controlled trials (RCTs) and open-label pragmatic studies were pooled. This approach, which relied on short-term RCT data, could not account for the potential role of improved treatment compliance over prolonged treatment periods in a practice setting. Secondary model extensions used different response criteria, thus introducing additional heterogeneity.

This approach, combined with multiple violations of the search strategy for evidence specified in the assessment protocol [41, 66, 67], necessarily concealed differences between medications in clinical effectiveness. The model therefore was driven by drug cost, and the NICE assessment group asserted, "given the lack of evidence for any differences in effectiveness [...], the results of the economic model clearly identify an optimal treatment strategy of 1st line dexamphetamine, 2nd line methylphenidate immediate-release, and 3rd line atomoxetine" [40]. No doubt, this conclusion should be interpreted cautiously [66, 67]. It is noteworthy that the NICE appraisal committee did not follow this assessment, stating that it was "not possible to distinguish between the different [treatment] strategies on the grounds of cost-effectiveness" [56, 57].

Cost-effectiveness analyses (CEAs)

Meanwhile, a number of CEAs of ADHD treatment strategies have been reported. From a United States payer perspective, CEAs on the basis of the NIMH MTA Study involving 579 children with ADHD [51, 52, 85] demonstrated attractive cost-effectiveness ratios for a high-quality medication management strategy, providing insights into the cost-effectiveness of an intense pharmacological treatment strategy based on first-line methylphenidate, alone or in combination with behavioral interventions [33, 34, 77]. Subgroup analyses addressed ICERs by therapeutic objectives [23, 73, 74], by comorbidity [23, 74] and by diagnostic subgroup [72, 73, 75], confirming the validity of the primary findings also for patients with hyperkinetic disorder according to ICD-10 criteria. First European CEAs on the basis of the MTA Study were presented recently, indicating relevance of these findings for a number of European jurisdictions including Germany and the United Kingdom [72–74]. Further economic evaluations have been concerned with methylphenidate [19, 26, 47, 53] and atomoxetine [32, 44, 87] in specific settings [15, 69].

The role of treatment compliance

To be relevant, economic evaluations need to reflect the real-world conditions faced by the decision maker [9, 20]. This concerns the distinction between *efficacy* (as assessed in RCTs) and *effectiveness* (real world outcomes associated with an intervention). Whereas RCTs follow an explanatory orientation ("*can* the intervention work?"), economic evaluations to be meaningful require a pragmatic orientation ("*does* the intervention work?" [78]. This distinction is particularly relevant for the evaluation of drugs that improve treatment compliance, which has been shown to be decreasing when the number of daily doses is increasing [10]. As the senior author of the NICE assessment report noted elsewhere, "great efforts are typically made in the conduct of a clinical trial to ensure that patients consume their prescribed medications" [20]. It is therefore generally acknowledged that artificially enhanced compliance in RCTs is a threat to their external validity [60]. This is just one aspect of the generally encountered trade-off between *internal validity* of carefully designed RCTs and *external validity*, which represents an old hobby-horse for economists. Other pertinent aspects include highly selected patient populations, high prevalence of experienced, usually specialized investigators, and protocol bias, for instance due to intense monitoring [62]. The ideal conditions of RCTs are not normally duplicated in practice settings.

Specifically, non-compliance-related effects may be further obscured by a typical intent-to-treat evaluation of RCTs employing a "last-observation-carried-forward-to-endpoint" strategy, since this practice of preserving data cannot be expected to reflect the situation of a non-compliant patient, who discontinued treatment, at the time when the study was completed [7, 91]. In striking contrast, the NICE assessment group had assumed that "intention-to-treat analyses are favored ... as they mirror the non-compliance ... that is likely to occur ... in practice" [40].

There are two broadly accepted approaches to address this problem. These are the use of models to assimilate existing information from various sources combined with appropriate sensitivity analyses [27, 31, 89], and the use of information from randomized pragmatic trials capturing the "real world" situation [3, 9, 24, 61]. Only recently a call has been made for more pragmatic trials in psychiatry, which should combine initial randomization with minimal study management in order to better reflect clinical reality than efficacy trials can [46].

Modeling studies

Modeling is "an unavoidable fact of life" in economic evaluation [9], with cost-effectiveness models intended to be aids guiding clinical and policy decisions; as such, they should not be misconceived as

establishing "truth" [90]. Sometimes objections against models reflect the clash of two paradigms. In contrast to biomedical scientists, used to rely on data generated in experimental settings, social scientists have traditionally been interested in generalizations and have been accustomed to analyze observational data [9]. Actually, failure to use models can lead to greater errors than the models themselves might introduce [9, 27]. Further to this, 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 and assumptions) and outputs [89]. For its Technology Report on ADHD of December 1998 [49], the Canadian Coordinating Office for Health Technology Assessment (CCOHTA) had used a model that reflected the high attrition rates associated with long-term stimulant treatment in the real world (for a review, cf. Hack and Chow, 2001 [30], and Swanson, 2003 [83]). Adaptations of this model were developed to estimate the cost-effectiveness of a modified-release formulation of methylphenidate, with a duration of action of ~12 hours (MPH-MR12) [84], compared to conventional methylphenidate (MPH-IR) divided in three daily doses (t.i.d.) [1, 71, 76]. The evaluations for UK and Germany combined a meta-analysis of symptomatic improvement (IOWA Conners inattention/overactivity ratings from three efficacy studies), a range of conceivable assumptions on treatment persistence rates (informed by systematic reviews [10, 30]), and a cost analysis from the perspectives of the NHS or the SHI, respectively [71, 76]. These analyses suggested comparable ICERs for MPH-MR12 and MPH-IR, which for the UK might even reach *extended dominance* of MPH-MR12 [71]. A conceptually related Canadian analysis had also reported extended dominance of MPH-MR12 over MPH-IR t.i.d. [1]. Technically, extended dominance is defined as a state when one strategy under study (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) with which it is mutually exclusive [27]. In practical terms, extended dominance occurs when an alternative (MPH-MR12) is more effective and more costly, but provides better value for money.

Real world studies

Real-world data on ADHD treatment persistence provide empirical support. A randomized study comparing MPH-MR12 and MPH-IR adhered to an open-label pragmatic design thought to better reflect real world treatment conditions [80, 81], i.e., to provide effectiveness instead of efficacy data. In line with theoretical expectations, the number needed to treat to achieve one additional responder in this trial was 3.6 (response definition derived from CGI-S or SNAP-IV ratings) to 4.8 (CGI-I) and thus consistently below the range of 6.7–14.3 reported by the NICE assessment, which had pooled efficacy and effectiveness data [40, 66, 67].

Five independent analyses of administrative data extend our understanding of non-persistence with treatment in ADHD beyond those earlier studies on compliance reviewed by Hack and Chow 2001 [30]. A study from British Columbia was published in 2004 [50] and described 1-year persistence rates with methylphenidate as low as 15%. Its findings were used by the Canadian Coordinating Office for Health Technology Assessments (CCOHTA) to inform its economic evaluation of ADHD treatments [49, 94]. In an analysis of pharmacy dispensing data from the Netherlands somewhat higher 1-year persistence rates were reported, increasing from below 50% in the mid-1990s to almost 60% in the late-1990s [65]. Three U.S. database studies are of particular interest as they compared persistence rates under different formulations of methylphenidate. These studies were based on the National Managed Care Benchmark Database [36, 43] or Medicaid claims data from California [48] and Texas [63], respectively, and consistently showed significantly higher 1-year treatment persistence rates for patients receiving MPH-MR12 compared to MPH-IR t.i.d. [36, 43, 48, 63, 67]. Remarkably, evaluations based on the National Managed Care Benchmark Database also reported a reduced number of emergency room visits [35], a lower accident and injury rate [43], and less hospitalizations [36] for patients receiving the long-acting preparation.

Replicating the UK CEA model [71] with the persistence rates reported in these studies results in comparable cost-effectiveness of MPH-MR12 and MPH-IR (applying the Dutch data) or in extended dominance of MPH-MR12 over MPH-IR (applying the North American data), using symptomatic improvement on the Conners' Teacher Rating Scale (CTRS) scale over 12 months as effectiveness measure [71]. For a sensitivity analysis illustrating the relationship between assumed persistence rates, which may be influenced by different structural settings, and resulting relative cost-effectiveness, see Fig. 1.

Collectively these data strengthen, on the grounds of cost-effectiveness, the recommendation of the European expert group to use a modified-release formulation of methylphenidate [4], despite higher unit costs compared to immediate-release preparations.

Non-stimulants

On the basis of currently available data, the logic of cost-effectiveness also lends support to the recom-

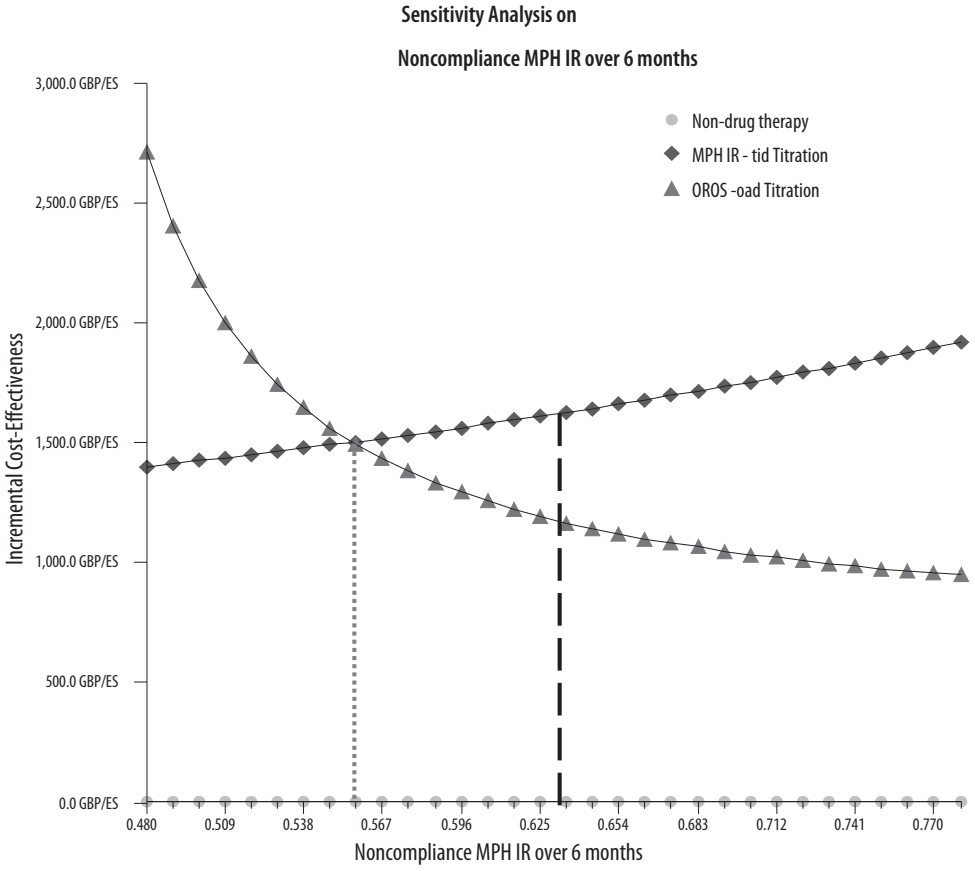

Fig. 1 Modeling the incremental cost-effectiveness of modified-release methylphenidate (MPH-MR12; "OROS", o.a.d.) compared to immediate-release methylphenidate (MPH-IR, t.i.d.) from the perspective of the UK National Health Service (NHS). Replicate of original UK analysis [71] using empirical data from Sanchez et al. (2005) [63], illustrating the sensitivity of Incremental Cost-Effectiveness Ratios (ICERs) to varying treatment persistence rates with MPH-IR. GBP = £ (2003). The low persistence rates reported by Sanchez et al. (2005) [63] translate into ICERs of £1,617 for MPH-IR/(ES × year) and £1,501 for MPH-MR12, both versus no drug treatment, and £1,179/(ES × year) for MPH-MR12 versus MPH-IR. For the original analysis [71] higher 1-year persistence rates (for MPH-IR, 65%) had been assumed, and base case results had been £1,120 (MPH-IR versus no treatment), £1,161 (MPH-MR12 versus no treatment), and £1,345 (MPH-MR12 versus MPH-IR), each per effect size CTRS improvement maintained over 1 year. Further analyses based upon parent ratings (CPRS scores) had shown extended dominance of MPH-MR12 over MPH-IR [71]. Overall, adapting the economic model developed by the Canadian Coordinating Office for Health Technology Assessment (CCOHTA) [49, 94] consistently indicates an acceptable to attractive cost-effectiveness of modified-release methylphenidate compared to immediate-release formulations. Vertical axis: incremental cost (£) for one additional patient with symptomatic improvement by an effect size (ES) of 1, IOWA Conners Teacher Rating Scale (CTRS), inattention/overactivity scores, maintained over 12 months. Horizontal axis: Varying persistence rates on MPH-IR. Numbers on axis give 6-month-attrition (non-persistence) rates. Dashed line: Base case according to claims data analysis by Sanchez et al. 2005 [63]. Dotted line: Threshold analysis: ceteris paribus (assuming constant persistence rates with MPH-MR12), MPH-MR12 will exhibit no longer extended dominance over MPH-IR if 6-months non-persistence rates on MPH-IR are below 55%. Note that a 63% (or 55 or 50%) non-persistence rate at 6 months corresponds to a 12-months persistence rate of 14% (20; 25%, respectively). For comparison, CCOHTA [49, 94] used data from a British Columbia Methylphenidate Survey (Miller et al. 2004 [50]) that indicated persistence rates on MPH-IR of 35% after 6 months and 15% after 12 months. These data are consistent with the more recent findings of Sanchez et al. 2005 [63]

mendation by the European expert group [4] to start treatment with methylphenidate, with the non-stimulant compound atomoxetine as a second-line option. As such, it may be a cost-effective alternative in patients failing on or not tolerating stimulants, although economic evaluations have been limited to date [32, 44, 87]. The reason for its second-line position is that, in economic terms, atomoxetine appears to be inferior to long-acting methylphenidate given its higher acquisition costs [4, 68] and its lower [21, 82] or (at best) equal [2, 37, 38, 58, 59] efficacy. As indicated earlier, the NICE appraisal [56, 57] had not identified this emerging ranking of long-acting treatment options on grounds of their relative cost-effectiveness, owing to the exclusive reliance of its underlying technology assessment on effect measures that were believed to enable computation of quality-adjusted life-years for reference case analysis [40, 54].

Conclusion

Summing up, the proposed European treatment guideline [4] is, to a great extent, supported by available economic evidence, although the results of cost-effectiveness evaluations suggest a more important role for modified-release methylphenidate than indicated by comparisons based on drug acquisition costs only.

It should be noted, however, that economic evaluations to date have been limited by a one-year time horizon. Further research is needed to assess treatment effects on long-term sequelae associated with ADHD, including the increased risk of adverse outcomes during adolescence and adulthood, e.g., lower educational level and socioeconomic status, tobacco use and substance abuse, as well as increased likelihood of accidents, injuries, and legal problems. Any proven positive impact on these sequelae might greatly influence treatment cost-effectiveness.

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