Long-acting methylphenidate formulations in the treatment of attention-deficit/hyperactivity disorder: a systematic review of head-to-head studies

David Coghill1,*, Tobias Banaschewski2†, Alessandro Zuddas3, Antonio Pelaz4, Antonella Gagliano5† and Manfred Doepfner6†

Abstract

Background: The stimulant methylphenidate (MPH) has been a mainstay of treatment for attention-deficit/hyperactivity disorder (ADHD) for many years. Owing to the short half-life and the issues associated with multiple daily dosing of immediate-release MPH formulations, a new generation of long-acting MPH formulations has emerged. Direct head-to-head studies of these long-acting MPH formulations are important to facilitate an evaluation of their comparative pharmacokinetics and efficacy; however, to date, relatively few head-to-head studies have been performed. The objective of this systematic review was to compare the evidence available from head-to-head studies of long-acting MPH formulations and provide information that can guide treatment selection.

Methods: A systematic literature search was conducted in MEDLINE and PsycINFO in March 2012 using the MeSH terms: attention deficit disorder with hyperactivity/drug therapy; methylphenidate/therapeutic use and All Fields: Concerta; Ritalin LA; OROS and ADHD; Medikinet; Equasym XL and ADHD; long-acting methylphenidate; Diffucaps and ADHD; SODAS and methylphenidate. No filters were applied and no language, publication date or publication status limitations were imposed. Articles were selected if the title indicated a comparison of two or more long-acting MPH preparations in human subjects of any age; non-systematic review articles and unpublished data were not included.

Results: Of 15,295 references returned in the literature search and screened by title, 34 articles were identified for inclusion: nine articles from pharmacokinetic studies (nine studies); nine articles from laboratory school studies (six studies); two articles from randomized controlled trials (two studies); three articles from switching studies (two studies) and three articles from one observational study.

Conclusions: Emerging head-to-head studies provide important data on the comparative efficacy of the formulations available. At a group level, efficacy across the day generally follows the pharmacokinetic profile of the MPH formulation. No formulation is clearly superior to another; careful consideration of patient needs and subtle differences between formulations is required to optimize treatment. For patients achieving suboptimal symptom control, switching long-acting MPH formulations may be beneficial. When switching formulations, it is usually appropriate to titrate the immediate-release component of the formulation; a limitation of current studies is a focus on total daily dose rather than equivalent immediate-release components. Further studies are necessary to provide guidance in clinical practice, particularly in the treatment of adults and pre-school children and the impact of comorbidities and symptom severity on treatment response.

Keywords: Methylphenidate, Attention-deficit/hyperactivity disorder, Comparison, Long-acting formulation, Pharmacokinetics, Review

* Correspondence: d.r.coghill@dundee.ac.uk
† Equal contributors
1 Division of Neuroscience, Medical Research Institute, Ninewells Hospital and Medical School, Dundee DD1 9SY, UK
Full list of author information is available at the end of the article

© 2013 Coghill et al; licensee BioMed Central Ltd. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.
**Background**

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurobehavioural disorder in childhood, affecting approximately 5% of children worldwide and persisting into adulthood in a majority of cases [1,2]. Stimulant medication, including methylphenidate (MPH), is a mainstay of treatment for ADHD in children, adolescents and adults [2,3]. Owing to the short half-life of MPH and the varied issues associated with multiple daily dosing of immediate-release MPH formulations (for example, social stigma, reduced compliance, inconvenience and security issues associated with controlled substances in the school or workplace), a new generation of long-acting MPH formulations has emerged (see Table 1 for a summary of MPH formulations and synonyms) [4].

Most of these newer long-acting MPH formulations differ from the first-generation, wax-matrix, continuous-release preparation (Ritalin SR®; Novartis Pharmaceutical Corporation, East Hanover, New Jersey, USA [5]) by including an immediate-release component that ensures a rapid onset of action as well as an extended-release component that continues to act throughout the course of the day. This allows for rapid onset of action with once-daily dosing while avoiding the need to take a second dose of medication during the school or work day. The various MPH formulations use different technologies that aim to provide symptom control for at least 8 hours and also incorporate differing proportions of immediate- and extended-release MPH. As a consequence, the immediate-release MPH bolus of the new formulations ranges from 22 to 50% of the total MPH dose. Ritalin LA® and Focalin XR® (both Novartis Pharmaceutical Corporation, East Hanover, New Jersey, USA) use Spheroidal Oral Drug Absorption System (SODAS®) technology to provide 50% of the MPH dose immediately and 50% as extended release [6,7]. Like most MPH formulations, Ritalin LA® contains racemic MPH comprising both the d-MPH and the l-MPH isomers; however, as when taken orally the l-isomer is metabolized rapidly via first pass through the hepatic circulation it is considered that the d-isomer is likely to be the main pharmacological contributor to efficacy in the treatment of ADHD.

**Table 1 Summary of long-acting methylphenidate (MPH) formulations**

| MPH formulation | Synonyms | Product availability | Modified-release technology | Immediate-release: extended-release ratio (%) | Duration of action* |
|-----------------|----------|----------------------|-----------------------------|-----------------------------------------------|---------------------|
| Biphentin® [10] | MPH ER   | Canada               | Multilayer-release (MLR) bead formulation 40:60 | Not stated: biphasic delivery profile          |
| Concerta® [12]  | Concerta extended release; Concerta® LP; methylphenidate hydrochloride; OROS MPH | Africa®, Asia®, Australia, Europe®, New Zealand, North America®, South America® | OROS® (Osmotic Release Oral System) 22:78 | 12 hours |
| Daytrana® [13]   | MPH transdermal system; MethyPatch; MTS | USA | Transdermal patch | Continuous delivery | 9 hours |
| Equasym XL® [11] | Equasym Depot®, Equasym Retard®, Equasym XR®, Quasym LP®; Metadate CD®, Metadate ER® | Europe®, South Korea, USA | Diffucaps® | 30:70 | 8 hours |
| Focalin XR® [7]   | D-MPH-ER | Switzerland, USA¹ | SODAS® (Spheroidal Oral Drug Absorption System) | 50:50 | Not stated: two distinct peaks approximately 4 hours apart |
| Medikinet® retard [9] | Medikinet®; Medikinet® CR; Medikinet® EM; Medikinet® MR; Medikinet® XL | Europe®, Israel, Korea, South America® | Modified-release capsules | 50:50 | 8 hours |
| Ritalin LA® [6]   | Ritalin LP®; Micalert | France, Chile, USA¹¹ | SODAS® (Spheroidal Oral Drug Absorption System) | 50:50 | Not stated: two distinct peaks approximately 4 hours apart |

*Duration of action as stated in the prescribing information.

¹Botswana, Brazil, Egypt, Namibia, Nicaragua, South Africa.

²Bahrain, China, Hong Kong, Indonesia, Israel, Japan, Jordan, Republic of Korea, Kuwait, Lebanon, Malaysia, Oman, Philippines, Qatar, Saudi Arabia, Singapore, Taiwan Province of China, United Arab Emirates, Yemen.

³Austria, Belgium, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Iceland, Ireland, Latvia, Lichtenstein, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, UK.

⁴Bahamas, Barbados, Canada, Cayman Islands, Dominican Republic, El Salvador, Guatemala, Honduras, Jamaica, Mexico, Trinidad and Tobago, USA.

⁵Argentina, Aruba, Bolivia, Chile, Columbia, Costa Rica, Ecuador, Panama, Paraguay, Peru, Uruguay, Venezuela.

⁶Denmark, Finland, France, Germany, Iceland, the Netherlands, Norway, Sweden, Switzerland, UK.

⁷Information obtained from Thomson Cortellis™.

⁸Austria, Belgium, Cyprus, Denmark, Estonia, Finland, France, Germany, Ireland, Italy, Latvia, Lithuania, Luxembourg, the Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, UK.

⁹Argentina, El Salvador, Guatemala, Honduras.
[8]. Focalin XR® contains only the d-MPH isomer and, therefore, achieve similar efficacy at a lower total daily dose than the racemic MPH formulations [8]. Medikinet® retard (MEDICE Pharma GmbH and co. KG, Iserlohn, Germany) also provides 50% of the racemic MPH dose immediately, using a 50:50 mixture of immediate release and enteric-coated beads to delay MPH delivery [9]. Biphentin® (Purdue Pharma, Pickering, Ontario, Canada) uses a multilayer-release bead formulation to provide a rapid initial release of 40% of the total racemic MPH dose followed by delivery of the remaining MPH from a controlled-release core [10]. Equasym XL® (Metadata CD®, Shire Pharmaceuticals Ireland Ltd, Dublin, Ireland) employs the Diffucaps® bead delivery technology to deliver 30% of the racemic MPH immediately and 70% from extended-release beads, while Concerta® (Janssen-Cilag Ltd, High Wycombe, UK) uses the osmotic controlled-release delivery system (OROS®) to release 22% of racemic MPH immediately followed by gradual delivery of the remaining MPH throughout the day [11,12]. Continuous delivery of racemic MPH is provided by Daytrana® (Noven Pharmaceuticals Inc., Miami, Florida, USA) via the MPH transdermal system, a diffusion-based patch applied to the skin [13].

The differing time–action profiles provided by these long-acting MPH formulations may allow clinicians to target specific periods of the day that are particularly relevant for a patient, facilitating individualization of ADHD treatment.

Response to MPH in the treatment of ADHD varies between patients. While MPH is effective in the majority of children in the short term, there is significant variation in individual response to treatment, with a minority not achieving adequate symptom control and others unable to tolerate MPH due to adverse effects [14–16]. Optimization of dose and treatment regimen is needed, therefore, and continued monitoring of response throughout the treatment period is required [16]. Given the range of MPH formulations available and the individualization of therapy that is required to ensure optimal treatment, direct head-to-head studies of long-acting MPH formulations can provide important information about the comparative pharmacokinetics (PK), pharmacodynamics and efficacy of the different formulations. While a number of studies compare long- and short-acting MPH formulations, for example Medikinet® retard versus twice-daily immediate-release MPH [17], few direct head-to-head studies of two or more long-acting MPH formulations have been performed to date.

The objective of this review was to bring together the evidence available from head-to-head studies of long-acting MPH formulations and provide evidence-based clinical guidance on treatment selection.

**Methods**

A literature search was conducted using the MEDLINE (1950–Present) and PsycINFO (1806–Present) databases to identify head-to-head studies of long-acting MPH formulations. The final search was conducted on 21 March 2012 and followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for methodology. The following search terms were developed, refined and tested for relevance by cross-checking results against a list of known relevant articles: MeSH terms: attention deficit disorder with hyperactivity/drug therapy; methylphenidate/therapeutic use; All Fields: Concerta; Ritalin LA; OROS and ADHD; Medikinet; Equasym XL and ADHD; long-acting methylphenidate; Diffucaps and ADHD; SODAS and methylphenidate. In addition, searches for Biphentin and ADHD, methylphenidate transdermal system and ADHD, and Metadate CD and ADHD were performed following the final search to corroborate findings (no additional studies were identified that met the search criteria). No filters were used during the search as key references were missed during the development and testing of the search strategy when filters were applied. No language, publication date or publication status limitations were imposed. All search results were combined into a single master database and duplicates removed. References within the master database were then screened by title for the following keywords to identify articles of possible relevance: methylphenidate; Concerta; Ritalin LA; OROS; Medikinet; Equasym XL; Diffucaps; SODAS; Spheroidal Oral Drug Absorption System; extended-release; extended release; long-acting; long acting; modified-release; modified release; single-dose; single dose; once-daily; once daily; methylphenidate transdermal system; MTS; osmotic-release; osmotic release; laboratory; meta-analysis; once-a-day; once a day. Articles were selected if the title indicated a comparison of two or more long-acting methylphenidate preparations in humans; articles with ambiguous titles were selected for further screening by abstract and/or full text. Studies involving subjects of any age with ADHD of any subtype receiving long-acting MPH were considered. Study diagnostic criteria and inclusion criteria were not assessed during the screening process. Both switching studies and observational studies were included; however, non-systematic review articles and non-peer-reviewed data were not included in this review. Articles selected by title screening were then assessed independently for eligibility by a second person; potentially eligible articles were then screened by abstract and disagreement regarding eligibility was resolved through discussion. If the suitability of an article was unclear, the full-text article was assessed. Reference lists of relevant systematic reviews and meta-analyses were cross-referenced against identified articles. Data extraction, performed independently by two people, included article category, drug and dosing, age group, sample size, diagnosis,
inclusion/exclusion criteria, comorbid conditions, outcome measures, main findings and conclusions. Possible sources of bias were identified as multiple reports from single studies and variability in outcome measures and parameters among studies. Meta-analysis was not feasible owing to the heterogeneity in outcomes reported across all study types included in the review; however, a systematic approach was applied to identify comparisons of interest and synthesize the findings of multiple studies.

Results and discussion
The master database included 15,295 references, which were screened by title for relevant articles (Figure 1). Of these, 287 articles were screened by abstract and 33 articles were identified for inclusion in the review. One additional article, which was not in the master database (Silva et al., 2008 [18]), was identified from the reference list of a systematic review (Brams et al., 2010 [19]). Publications included in the review are summarized in Table 2 and comprised nine articles from PK studies (nine studies); nine articles from laboratory school studies (six studies); two articles from randomized controlled trials (RCTs; two studies); three articles from switching studies (two studies) and three articles from one observational study. As the studies were diverse and the reported outcomes were heterogeneous, consistent comparisons of interest could not be made across all study types. For PK articles (n = 9), comparisons of interest were bioequivalence of long-acting MPH formulations to Concerta®, overall MPH exposure, time to peak plasma MPH concentration, plasma MPH concentrations across the day, and the effect of long-acting MPH formulations on dopamine transport occupancy. Comparisons of interest for laboratory school study articles (n = 9) were efficacy of long-acting MPH formulations across the day, and the effect of symptom severity and gender on MPH response. For RCTs, switching and observational study articles, similarities and differences between outcomes relating to different long-acting MPH formulations are reported, as available. An overview of the main conclusions from eight systematic reviews and meta-analyses addressing long-acting ADHD medications, including MPH, are also presented.

Effect sizes were reported in only five articles from two studies (excluding meta-analyses); therefore, effect sizes are presented in the text where appropriate but are not included in Table 2.

![Figure 1 Flow diagram of screened and included articles.](http://www.biomedcentral.com/1471-244X/13/237)
## Table 2 Summary of articles identified in the literature search that compare ≥2 long-acting MPH formulations

| Author, year | Long-acting MPH formulation and dosing* | Sample size | Age range | Diagnosis | Comorbid conditions | Outcome measures |
|--------------|----------------------------------------|-------------|-----------|-----------|---------------------|-----------------|
| **Pharmacokinetic studies** | | | | | | |
| Gonzalez et al., 2002 [20] | Concerta® (18, 36, 54 mg) | n = 36 | 21–40 years | Not applicable | Not stated | PK parameters for 24 hours post-dose, including bioequivalence |
| | Equasym XL® (20, 40, 60 mg) | | | | | |
| Haessler et al., 2008 [26] | Ritalin LA® (40 mg) | n = 28 | 18–30 years | Not applicable | Not stated | PK parameters for 24 hours post-dose, including bioequivalence |
| | Medikinet® retard (40 mg) | | | | | |
| Markowitz et al., 2003 [22] | Concerta® (18 mg) | n = 20 | 21–34 years | Not applicable | Not stated | PK parameters for 24 hours post-dose, including bioequivalence |
| | Ritalin LA® (20 mg) | | | | | |
| Modi et al., 2000 [23] | Concerta® (18 mg) | n = 36 | 18–41 years | Not applicable | Not stated | PK parameters for 24 hours post-dose |
| | Ritalin SR® (20 mg) | | | | | |
| Pierce et al., 2010 [24] | Concerta® (18, 27, 36, 54 mg) | n = 71 | 6–17 years | ADHD according to DSM-IV criteria | Possibly ODD | PK properties of d,l-MPH after single, multiple, fixed and escalating doses of Concerta® and Daytrana® |
| | Daytrana® (10, 15, 20, 30 mg/9 hours) | | | | | |
| Reiz et al., 2008 [25] | Concerta® (18 mg) | n = 24 | 19–25 years | Not applicable | Not stated | PK parameters for 24 hours post-dose, including bioequivalence |
| | Biphentin® (20 mg) | | | | | |
| Schutz et al., 2009 [28] | Equasym XL® (20 mg) | n = 14 | 22–43 years | Not applicable | Not stated | PK parameters for 24 hours post-dose, including bioequivalence |
| | Medikinet® retard (20 mg) | | | | | |
| Spencer et al., 2010 [21] | Concerta® (36 mg) | n = 21 | 18–55 years | Not applicable | Not stated | PET imaging |
| | Equasym XL® (40 mg) | | | | | |
| Tuerck et al., 2007 [27] | Focalin XR® (20 mg) | n = 25 | 19–45 years | Not applicable | Not stated | PK parameters for 24 hours post-dose, including bioequivalence |
| | Ritalin LA® (40 mg) | | | | | |
| **Laboratory school studies** | | | | | | |
| Lopez et al., 2003 [31] | Concerta® (18, 36 mg) | n = 36 | 6–12 years | ADHD according to C-DISC criteria | Not stated | SKAMP-Attention; SKAMP-Depportment; SKAMP-Combined; Math-Attempted; Math-Correct |
| | Ritalin LA® (20 mg) | | | | | |
| Muniz et al., 2008 [33] | Concerta® (36, 54 mg) | n = 84 | 6–12 years | Combined-type ADHD (89%); Inattentive-type ADHD (11%) according to DSM-IV criteria, established by C-DISC | Not stated | SKAMP-Combined; SKAMP-Attention; SKAMP-Depportment; Math-Attempted; Math-Correct; CPRS |
| | Focalin XR® (20, 30 mg) | | | | | |
| Schulz et al., 2010 [38] | Ritalin LA® (20 mg) | n = 147 | 6–14 years | Combined-type ADHD (55%); Inattentive-type ADHD (37%); Hyperactive/impulsive-type ADHD according to DSM-IV criteria, confirmed by K-SADS | Disturbance in social behaviour (n = 4), initial insomnia (n = 2), ODD (n = 2), dysphemia (n = 1), encopresis (n = 1) | SKAMP-Combined; Math-Attempted; Math-Correct; NCBR-TIQ |
Table 2 Summary of articles identified in the literature search that compare ≥2 long-acting MPH formulations (Continued)

| Study Authors, Year | MPH Formulations | Sample Size | Duration | Primary Diagnoses | Outcome Measures | Additional Comments |
|---------------------|------------------|-------------|----------|-------------------|-----------------|-------------------|
| Silva et al., 2005 [32] | Concerta® (18 mg) Ritalin LA® (20 mg) | n = 54 | 6-12 years | Combined: inattentive/hyperactive-type ADHD (70%); inattentive-type ADHD (28%); Hyperactive/impulsive-type ADHD (2%) according to DSM-IV criteria | Not stated | SKAMP-Attempted, SKAMP-Deporation; SKAMP-Combined; Math-Attempted; Math-Correct |
| Silva et al., 2008 [18] | Concerta® (36, 54 mg) Focalin XR® (20, 30 mg) | n = 82 | 6-12 years | Combined-type ADHD (94%); Inattentive-type (6%) according to DSM-IV criteria | Not stated | SKAMP-Attention; SKAMP-Deporation; SKAMP-Combined; Math-Attempted; Math-Correct; CPRS |
| Sonuga-Barke et al., 2004 [34] | Concerta® (18, 36, 54 mg) Equasym XL® (20, 40, 60 mg) | n = 184 | 6-12 years | Combined-type (82%); Inattentive-type (13%); Hyperactive/impulsive-type (5%) according to DSM-IV criteria and confirmed by DISC | Comorbid condition (25%), including anxiety and ODD | Placebo-adjusted SKAMP-Combined |
| Sonuga-Barke et al., 2007 [35] | Concerta® (18, 36, 54 mg) Equasym XL® (20, 40, 60 mg) | n = 184 | 6-12 years | Females: Combined-type (77%); Inattentive-type (15%); Hyperactive/impulsive-type (8%); Males: Combined-type (84%); Inattentive-type (12.4%); Hyperactive/impulsive-type (4%) | Comorbid condition (25%), including anxiety and ODD | SKAMP-Combined; PERMP |
| Sonuga-Barke et al., 2008 [36] | Concerta® (18, 36, 54 mg) Equasym XL® (20, 40, 60 mg) | n = 184 | 6-12 years | Combined-type (82%); Inattentive-type (13%); Hyperactive/impulsive-type (5%) according to DSM-IV criteria, confirmed by DISC | Comorbid condition (25%), including anxiety and ODD | GMM analysis |
| Swanson et al., 2004 [37] | Concerta® (18, 36, 54 mg) Equasym XL® (20, 40, 60 mg) | n = 184 | 6-12 years | Combined-type (82%); Inattentive-type (13%); Hyperactive/impulsive-type (5%) according to DSM-IV criteria, confirmed by DISC | Comorbid condition (25%), including anxiety and ODD | SKAMP-Attention; SKAMP-Deporation; PERMP |

**Randomized controlled trials**

| Study Authors, Year | MPH Formulations | Sample Size | Duration | Primary Diagnoses | Outcome Measures | Additional Comments |
|---------------------|------------------|-------------|----------|-------------------|-----------------|-------------------|
| Doepfner et al., 2011 [42] | Concerta® (18, 36 mg) Medikinet® retard (10, 20, 30 mg) | n = 113 | 6-16 years | Combined-type ADHD according to DSM-IV, confirmed by interview (DCL-ADHD) | ODD or conduct disorder (36%) | SKAMP-D; DAYAS; FBB-ADHD |
| Findling et al., 2008 [43] | Concerta® (18, 27, 36, 54 mg) Daytrana® (10, 15, 20, 30 mg) | n = 282 | 6-12 years | Combined-type ADHD (71–86%); Inattentive-type ADHD (11–26%); Hyperactive/impulsive-type ADHD (1–2%) according to DSM-IV-TR criteria | Possibly ODD | ADHD-RS-IV mean total score; CTRS-R; CPRS-R; CGI–S; CGI-I; PGA; MPH plasma concentrations at 7.5, 9 and 10 hours post-dose |

**Switching studies**

| Study Authors, Year | MPH Formulations | Sample Size | Duration | Primary Diagnoses | Outcome Measures | Additional Comments |
|---------------------|------------------|-------------|----------|-------------------|-----------------|-------------------|
| Arnold et al., 2010 [46] | Concerta® (18, 27, 36, 45, 54 mg) Ritalin LA® (10, 20, 30, 40, 50 mg) Equasym XL® (10, 15, 20, 30, 40, 50 mg) Daytrana® (10, 15, 20, 30 mg) | n = 171 | 6-12 years | Combined-type ADHD (77%); Inattentive-type ADHD (21%); Hyperactive/impulsive-type ADHD (2%) according to DSM-IV-TR criteria | Possibly ODD | ADHD-RS-IV mean total scores; CGI–I; PGA; CPRS-R; CGI–S |
Table 2 Summary of articles identified in the literature search that compare ≥2 long-acting MPH formulations (Continued)

| Study | MPH Formulations | Sample Size | Sample Characteristics | Outcome Measures | Notes |
|-------|------------------|-------------|------------------------|-----------------|-------|
| Bukstein et al., 2009 [47] | Concerta®, (18, 27, 36, 54 mg), Ritalin LA®, (10, 20, 30, 40, 50 mg), Equasym XL®, (10, 15, 20, 30, 40, 50 mg), Daytrana® (10, 15, 20, 30 mg) | n = 171 | 6–12 years | See Arnold et al., 2010 [46] | Possibly ODD | AIM-C; MSS |
| Dirksen et al., 2002 [48] | Equasym XL® (20, 40, 60 mg), Concerta® (18, 36, 54, 72 mg) | n = 308 | 6–17 years | ADHD according to DSM-IV criteria (diagnostic code 314.01) | Not stated | CGI-I; CGI-S; CGI-Efficacy Index |
| Observational studies | | | | | |
| Doepfner et al., 2011 [49] | Equasym XL® (10–120 mg), Other long-acting MPH (most commonly Medikinet® retard; approximately 0.85 mg/kg/day) | n = 822 | 6–17 years | Disturbance of activity/attention (F90.0; 55%); hyperkinetic conduct disorder (F90.1; 36%); other hyperkinetic disorders (F90.8; 8%) according to ICD-10 criteria | Not stated | CGI-S; CGI-I; FBB-ADHD; DAYAS; SDQ-P |
| Doepfner et al., 2011 [50] | Equasym XL® (10–120 mg), Other long-acting MPH (mean [SD] 29.2 [11.28] mg) | n = 782 | 6–17 years | For total study sample (n = 822) see Doepfner et al., 2011 [49] | Not stated | FBB-ADHD; CGI-S; DAYAS; KINDL |
| Rothenberger et al., 2011 [51] | See Doepfner et al., 2011 [49] | n = 822 | 6–17 years | See Doepfner et al., 2011 [49] | Not stated | KINDL; SAMS |
| Meta-analyses | | | | | |
| Faraone et al., 2006 [55] | Equasym XL®, Ritalin LA®, Concerta®, Daytrana® | n = 29 articles | | Effect size expressed as SMD |
| Faraone and Buitelaar, 2010 [56] | Equasym XL®, Ritalin LA®, Concerta®, Daytrana® | n = 23 articles | | Effect size expressed as SMD |
| Faraone and Glatt, 2010 [57] | Concerta®, Focalin XR® | n = 18 articles | Adults | Effect size expressed as SMD |
| Peterson et al., 2008 [58] | Concerta®, Focalin XR® | n = 22 articles | Adults | Ratio of relative risks |
| Systematic reviews | | | | | |
| Banaschewski et al., 2006 [52] | Concerta®, Ritalin LA®, Equasym XL®, Medikinet® retard | Not stated | | Effect size expressed as SMD |
| Authors                  | Long-Acting Stimulants | Study Population                  | Outcome Measures                                                                 |
|-------------------------|------------------------|-----------------------------------|-----------------------------------------------------------------------------------|
| Brams et al., 2008 [53] | Concerta®, Daytrana®, Focalin XR®, Equasym XL®, Ritalin LA® | n = 18 articles Children and adolescents | SKAMP, CADS-T, IOWA Conners’ Rating Scale, ADHD-RS-IV, PERMP, CGIS-T               |
| Brams et al., 2010 [19] | Concerta®, Focalin XR®, Equasym XL®, Ritalin LA® | n = 15 articles Children, adolescents and adults | PERMP                                                                            |
| Swanson et al., 2002 [54]| Concerta®, Equasym XL®, Ritalin LA® | Not stated                        | SKAMP, 10-Minute Math Test, PK measures, effect size                              |

ADHD, attention deficit hyperactivity disorder; ADHD-RS-IV, ADHD Rating Scale-version IV; AIMS-C, ADHD Impact Module-Children; C-DISC, Diagnostic Interview Schedule for Children 1997; CADS-T, Conners’ ADHD/DSM-IV Scale for teachers; CGI-I, Clinical Global Impressions–Improvement; CGI-S, Clinical Global Impressions–Severity of Illness; CGIS-T, Conners’ Global Index Scale for teachers; CPRS, Conners’ Parent Rating Scale; CTRS-R, Conner’s Teacher Rating Scale-Revised; DAYAS, Day Profile of ADHD Symptoms; DCL, Diagnostic Checklist for ADHD; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition, Text Revision; FBB-ADHD, Fremdbeurteilungsbogen für Aufmerksamkeitsdefizit–Hyperaktivitätsstörung (German symptom checklist for attention deficit hyperactivity disorder); GM, Growth Mixture Modelling; ICD-10, International Classification of Diseases, version 10; KINDL, Kinder Lebensqualitätsfragebogen; IOWA, Inattention/Overactivity With Aggression; K-SADS, Kiddie Schedule for Affective Disorders and Schizophrenia; MPH, methylphenidate; MSS, Medication Satisfaction Survey; NCBR-TIQ, Nisonger Child Behaviour Rating Form; ODD, oppositional defiant disorder; PERMP, permanent product measure of performance; PET, Positron Emission Tomography; PGA, Parent Global Assessment; PK, pharmacokinetic; SAMS, Satisfaction with Medication Scale; SD, Standard deviation; SDQ-P, Strengths and Difficulties Questionnaire for Parents; SKAMP, Swanson, Kotkin, Agler, M-Flynn and Pelham Rating Scale; SKAMP-D, German version of Swanson, Kotkin, Agler, M-Flynn and Pelham Rating Scale; SMD, Standard Mean Difference.

*Long-acting stimulants other than methylphenidate have not been included.
PK studies

In total, nine studies investigated the PK properties of

long-acting MPH formulations in head-to-head compar-
sions. Six studies used Concerta® as a comparator; of these,
two studies compared Concerta® with Equasym XL®
[20,21], while four individual studies compared
Concerta® with Ritalin LA® [22], Ritalin SR® [23],
Daytrana® [24] and Biphentin® [25]. Therefore, this
provides head-to-head comparisons of Concerta® with
five long-acting MPH formulations. Additional com-
parisons of long-acting MPH formulations were Ritalin
LA® versus Medikinet® retard [26], Ritalin LA® versus
Focalin XR® [27], and Equasym XL® versus
Medikinet® retard [28]. All, apart from one of these,
studies, were performed in adults. The Concerta® ver-
sus Daytrana® study was performed in children and
adolescents [24].

Head-to-head PK studies of Concerta® versus Equasym XL®,
Ritalin LA®, Ritalin SR®, Daytrana® and Biphentin®
Bioequivalence to Concerta® and overall MPH exposure

Three studies assessed the bioequivalence of long-acting
MPH formulations with Concerta® [20,22,25]. In each,
bioequivalence was considered present if the 90% confi-
dence interval (CI) ratio of the two MPH formulations
under comparison was within 80–125%. Concerta® was
not bioequivalent to comparable daily doses of Equasym
XL® (maximum concentration [Cmax], area under the
curve [AUC0–4], AUC0–6) or Ritalin LA® (AUC0–∞) [20,22].
While Concerta® and Biphentin® were bioequivalent
according to AUC0–4 (90% CI 105.62–116.41) and AUC0–∞
(90% CI 106.25–116.33), they were, however, not bio-
equivalent according to Cmax (90% CI 113.85–130.39)
[25]. Bioequivalence between Concerta® and Ritalin
SR® or Daytrana® was not evaluated [23,24].

While Concerta® (18 mg) had similar overall (24 hour)
MPH exposure (AUC) to Equasym XL® (20 mg) and
Ritalin LA® (20 mg) [20,22], exposure to MPH over
24 hours was significantly higher for Biphentin® (20 mg)
compared with Concerta® (18 mg, p = 0.002) [25]. This
was due to a concentration–time profile for Biphentin®
that resulted in the delivery of a significantly greater pro-
portion of MPH compared with Concerta® in the first
4 hours post-dose followed by comparable levels of MPH
later in the day [25]. Systemic exposure to d-MPH during
treatment with Daytrana® was higher in children than ad-
olescents [24]. Systemic exposure to d-MPH from a single
dose of Daytrana® (10 mg/9 hours) was similar to that from
a single dose of Concerta® (18 mg) in children, but only
60–80% of that of Concerta® (18 mg) in adolescents [24].
This difference in systemic exposure was attributed to the
lower body weight in children compared with adolescents
[24]. After multiple escalating doses of Daytrana® in chil-
dren (final dose of 30 mg/9 hours), systemic exposure to d-

MPH was 1.4-fold to 1.6-fold higher compared with mul-
tiple escalating doses of Concerta® (final dose: 54 mg) [24].
The investigators concluded that higher accumulation of d-
MPH with Daytrana® compared with Concerta® was a
result of continued long-term administration rather than
frequency of dosing or changes in clearance, and also that
changes in skin permeability resulting from application-
site erythema may be a cause of increased absorption of
MPH from Daytrana® during multiple dosing [24]. In
contrast with the findings in children, systemic exposure
to d-MPH was similar in adolescents for both Daytrana®
and Concerta® [24].

Time to peak plasma MPH concentration (Tmax)

In head-to-head studies of Concerta® with five long-acting
MPH formulations, Concerta® generally reached peak
 plasma MPH concentration later (5–8 hours post-dose) than
the other long-acting MPH formulations investigated (Rit-
alin LA®, Biphentin®, Ritalin SR® and Equasym XL®; 4–
6 hours post-dose) with the exception of Daytrana® which
reached peak levels 10 hours post-dose (Table 3) [20,22-25].
Tmax was not provided by Gonzalez et al. for Equasym XL®
versus Concerta® and therefore could not be included
in Table 3; however, both MPH formulations displayed
biphasic characteristics, providing a sharp initial increase in
MPH plasma concentration at approximately 1 hour post-
dose and a second peak 6 hours post-dose (Equasym
XL®) and 6–8 hours post-dose (Concerta®) [20].

Plasma MPH concentrations across the day

Morning: In the first 4 hours post-dose, Equasym XL® (20, 40, 60 mg),
Ritalin LA® (20 mg), Ritalin SR® (20 mg) and Biphentin®
(20 mg) reached higher plasma MPH concentrations
(AUC0–4 and Cmax0–4) than comparable daily doses of
Concerta® (Table 3) [20,23-25]. Data for AUC0–4 and
Cmax0–4 for Concerta® versus Daytrana® were not
presented by Pierce and colleagues; however, a delay of ap-
proximately 2 hours in the absorption of d-MPH in chil-
dren and adolescents following a single dose of Daytrana®
(10 mg/9 hours) was reported, which was not apparent in
those receiving Concerta®, or following multiple fixed or
escalating doses of Daytrana® [24].

Afternoon and evening: While Equasym XL® (20, 40, 60 mg) produced greater MPH concentrations compared
with the nearest daily dose of Concerta® (18, 36, 54 mg) up
to 6 hours post-dose, this reversed later in the day, with
Concerta® sustaining greater plasma MPH concentrations
than Equasym XL® at 8, 10 and 12 hours post-dose [20]. A
similar pattern of MPH concentrations was observed with
Ritalin LA® (20 mg), which had higher peak MPH concen-
trations than Concerta® (18 mg) over the first 8 hours
post-dose, followed by similar concentrations at 10 hours
and lower concentrations at 12 hours post-dose [22]. The
biphasic PK profile of Ritalin LA® resulted in a trough in
Table 3 Pharmacokinetic parameters across the day for head-to-head pharmacokinetic studies (presented for single-dose comparison only)

|                  | C$_{\text{max}}$, ng/mL | T$_{\text{max}}$, hours | AUC, ng • h/mL |
|------------------|--------------------------|--------------------------|----------------|
|                  | C$_{\text{max0-4}}$ | C$_{\text{max4-10}}$ | C$_{\text{max}}$ | T$_{\text{max0-4}}$ | T$_{\text{max4-10}}$ | T$_{\text{max}}$ | AUC$_{0-4}$ | AUC$_{4-10}$ | AUC$_{0-\infty}$ |
| **Gonzalez et al., 2002 [20] (fasted state)** |                     |                          |                  |                          |                          |                          |                  |                  |                    |
| Concerta® (18 mg) | –                       | –                        | –                | –                        | –                        | –                        | 6.28             | –                | 36.43              |
| Equasym XL® (20 mg) | –                       | –                        | –                | –                        | –                        | –                        | (2.65)           | (13.50)           |
| Concerta® (36 mg) | –                       | –                        | –                | –                        | –                        | –                        | (3.06)           | (11.75)           |
| Equasym XL® (2 x 20 mg) | –                       | –                        | –                | –                        | –                        | –                        | (5.86)           | (44.51)           |
| Concerta® (54 mg) | –                       | –                        | –                | –                        | –                        | –                        | (7.18)           | (64.83)           |
| Equasym XL® (3 x 20 mg) | –                       | –                        | –                | –                        | –                        | –                        | (8.74)           | (52.05)           |
| **Haessler et al., 2008 [26] (fed state)** |                     |                          |                  |                          |                          |                          |                  |                  |                    |
| Ritalin LA® (40 mg) | 11.8                    | 12.8                     | 13.3             | –                        | –                        | –                        | 33.5             | 57.8             | 126.8              |
| Medikinet retard (40 mg) | (3.95)                  | (4.13)                   | (4.04)           | (–)                      | (–)                      | (–)                      | (11.07)          | (16.91)          | (34.5)             |
| **Haessler et al., 2008 [26] (fasted state)** |                     |                          |                  |                          |                          |                          |                  |                  |                    |
| Ritalin LA® (40 mg) | 10.0                    | 14.5                     | 14.5             | –                        | –                        | –                        | 27.6             | 57.1             | 114.1              |
| Medikinet retard (40 mg) | (3.51)                  | (3.02)                   | (3.02)           | (–)                      | (–)                      | (–)                      | (8.89)           | (14.36)          | (30.8)             |
| **Markowitz et al., 2003 [22] (fasted state)** |                     |                          |                  |                          |                          |                          |                  |                  |                    |
| Concerta® (18 mg) | 3.4                     | –                        | 5.9              | 3.3                      | –                        | 6.0                      | 9.3              | –                | 66.9               |
| Ritalin LA® (20 mg) | 7.0                     | –                        | 9.9              | 2.1                      | –                        | 5.5                      | 18.5             | –                | 78.7               |
| **Modi et al., 2000 [23] (fasted state)** |                     |                          |                  |                          |                          |                          |                  |                  |                    |
| Concerta® (18 mg) | –                       | –                        | 3.75             | –                        | –                        | 6.7                      | –                | –                | 42.0               |
| Ritalin SR® (20 mg) | –                       | –                        | 4.84             | –                        | –                        | 3.7                      | –                | –                | 46.7               |
| **Pierce et al., 2010 [24] (fasted state; age 6–12 years)** |                     |                          |                  |                          |                          |                          |                  |                  |                    |
| Concerta® (18 mg) | –                       | –                        | 7.80             | –                        | –                        | 6.02                     | –                | –                | 94.2               |
| Daytrana® (10 mg/9 hours) | –                       | –                        | 9.30             | –                        | –                        | 10.0                     | –                | –                | 99.2               |
| **Pierce et al., 2010 [24] (fasted state; age 13–17 years)** |                     |                          |                  |                          |                          |                          |                  |                  |                    |
| Concerta® (18 mg) | –                       | –                        | 4.95             | –                        | –                        | 8.0                      | –                | –                | 60.1               |
| Daytrana® (10 mg/9 hours) | –                       | –                        | 4.15             | –                        | –                        | 10.0                     | –                | –                | 48.7               |
| **Pierce et al., 2010 [24] (fasted state)** |                     |                          |                  |                          |                          |                          |                  |                  |                    |
plasma MPH concentration at approximately 5 hours post-dose, which may coincide with a typical lunchtime school break [22]. Following a rapid increase in plasma MPH concentration with a mean peak concentration at 3.7 hours for Ritalin SR (20 mg; Table 3), plasma MPH concentration declined rapidly compared with Concerta (18 mg), which had a higher plasma MPH concentration at 8, 10 and 12 hours post-dose [23].

Although AUC_{0-12} and C_{max} for Biphentin (20 mg) were significantly higher for Biphentin (20 mg) compared with Concerta (18 mg, p = 0.037 and p = 0.002, respectively; Table 3), plasma MPH concentrations for the two formulations were not significantly different at 8–12 hours post-dose (AUC_{0-12}), suggesting the potential for similar efficacy between the two formulations in the evening [25]. For the period covering the school day (AUC_{0-8}), plasma MPH concentration for Biphentin (20 mg) was 128.4% that of Concerta (18 mg) [25]. The investigators noted that if switching a patient from Concerta to Biphentin, it may be appropriate to initiate treatment with Biphentin at a lower daily dose than that of previously received Concerta; however, if switching a patient from Biphentin to Concerta, the closest marketed dose could be used [25].

As mentioned above, Daytrana was the only long-acting MPH formulation to reach peak plasma MPH concentration later than Concerta in head-to-head studies [24]. C_{max} reached at 10 hours post-dose in a single-dose comparison, was greater in children receiving Daytrana (10 mg/9 hours) compared with those receiving Concerta (18 mg), and higher in children than adolescents for both MPH formulations (Table 3). This pattern was also observed following multiple fixed doses for 7 days and multiple escalating doses over 28 days [24].

**Head-to-head PK study of Medikinet retard versus Ritalin LA**

In a head-to-head comparison of Medikinet retard (40 mg) and Ritalin LA (40 mg), food intake was shown to affect the bioavailability of Medikinet retard but not that of Ritalin LA [26]. Under fasted conditions, Medikinet retard showed a steady absorption profile with a single T_{max} in healthy adult volunteers; however, under fed conditions, a biphasic kinetic profile more closely resembling a twice-daily dosing regimen was observed. Food intake also affected overall exposure to MPH (AUC_{0-∞}), which was lower in the fasted than in the fed state (Table 3). In contrast, Ritalin LA (40 mg) had a biphasic kinetic profile under both fasted and fed conditions [26]. Ritalin LA and Medikinet retard were bioequivalent in the fasted state but not in the fed state (when a biphasic kinetic profile was observed for both formulations), during which C_{max} for Ritalin LA was lower compared with that of Medikinet retard [26]. Haessler and colleagues suggested that, as regular breakfast intake is often challenging in children with ADHD, the unaffected bioavailability with regard to food intake may be a potential advantage of Ritalin LA over Medikinet retard [26].
recommended (Medikinet® retard after breakfast, Equasym XL® before breakfast), the two MPH formulations were not bioequivalent in the first 4 hours post-dose (AUCl-4) [28]. Medikinet® retard had a slightly higher and slightly earlier peak MPH plasma concentration (mean [standard deviation] 4.83 [1.87] ng/mL at 2.82 [1.00] hours post-dose) compared with Equasym XL® (3.82 [0.96] ng/mL at 3.24 [1.13] hours post-dose; Table 3) [28]. Bioequivalence was demonstrated 4–24 hours post-dose (AUCl-4; 90% CI 88.6–103.1), however [28]. While a significant gender x treatment interaction (p = 0.018) for maximum plasma MPH concentration from 4 hours to last observation (Cmax-t) was noted, no other significant gender effects were observed for other PK parameters [28].

**Head-to-head PK study of Focalin XR® versus Ritalin LA®**

Focalin XR® (20 mg), a long-acting formulation containing pure d-MPH, and a 40 mg daily dose of the long-acting racemic MPH formulation, Ritalin LA®, were bioequivalent and had very similar plasma MPH concentration profiles over the course of the study [27]. No gender effects on body-weight-adjusted AUC values were reported [27].

**Effects of MPH formulation on dopamine transport occupancy**

Spencer et al. employed positron emission tomography to investigate dopamine transporter (DAT) occupancy in the brain 10 hours after dosing with Concerta® (36 mg) and Equasym XL® (40 mg) in 21 healthy adults [21]. Plasma d-MPH concentration was also determined 9, 10 and 11 hours post-dose to enable a comparison between peripheral PK and central brain effects. Concerta® resulted in greater plasma d-MPH concentrations and greater brain effects (DAT occupancy) at 10 hours compared with a similar daily dose of Equasym XL®, suggesting that both peripheral and brain PK profiles can be predicted based on the MPH delivery profile of the long-acting MPH formulation. Plasma concentration was a predictor of DAT occupancy for both MPH formulations, but the correlation between plasma DAT occupancy and d-MPH concentration was stronger with Equasym XL® compared with Concerta®. While the reasons for this were unclear, the authors noted that this may be associated with a more rapid rate of change in plasma MPH concentration following dosing with Equasym XL®, owing to the greater immediate-release component of this MPH formulation compared with Concerta® [21].

**Adverse events**

Overall, adverse events associated with long-acting MPH formulations were similar and consistent with the known pharmacological effects of MPH, most commonly including loss of appetite, insomnia, nausea, dizziness, headache and tachycardia [20,23-25,27,28]. Unfortunately, the available data do not permit us to address questions about clinically relevant adverse events specific to different MPH preparations; for example, are the lower peak plasma MPH concentrations observed with long-acting MPH formulations compared with immediate-release formulations associated with lower levels of adverse events, such as appetite loss or increases in blood pressure and pulse rate? Does the absence of a drop in plasma MPH concentration observed towards the end of the 4-hour dosing period for immediate-release MPH result in more consistent appetite suppression? Furthermore, and most pertinent to this review, do the different PK profiles of the long-acting MPH formulations result in different adverse event profiles in certain patients? Reviews of the adverse effects of medication for ADHD, including MPH, can be found elsewhere [29,30].

**Laboratory school studies**

Of 34 publications, nine head-to-head comparisons of long-acting MPH formulations were laboratory school studies; eight of which employed Concerta® as a comparator. Two studies each compared Concerta® with Ritalin LA® [31,32] and Focalin XR® [18,33], while Concerta® was compared with Equasym XL® in four publications derived from one study (the COMACS Study) [34-37]. A single study compared Ritalin LA® with Medikinet® retard [38].

With increasing treatment of school-aged children with stimulant and non-stimulant medications for ADHD, it is important to examine the efficacy and safety of such therapies across the day in an educational setting as well as at home. The laboratory school methodology employs a standardized, regular and repeated cycle of classroom and less-structured activities, representing those encountered in a typical school day, to assess both academic performance and child behaviour in a controlled environment [39]. Regular collection of safety measures also allows the observation of adverse treatment effects in patients with ADHD in a simulated educational setting [39]. Pharmacodynamic data (behaviour and performance) in laboratory school studies are typically collected using the Swanson, Kotkin, Atkins, M-Flynn, Pelham (SKAMP) scale; a questionnaire completed by trained observers at regular intervals [40]. The SKAMP scale comprises six deportment items (interacting with other children, interacting with adults, remaining quiet, staying seated, complying with the teacher’s requests or directions, and following the rules) and seven attention items (getting started on assignments, sticking with tasks, sticking with activities, completing assigned work, performing work accurately, and being neat and tidy while writing or drawing) [40]. An objective measure of academic productivity is provided by a 10-minute written math test administered during the classroom period (consistently used across studies but variably referred to as permanent product or PERMP), from which the number of math test problems attempted (Math-Attempted) and the number correctly answered (Math-Correct) are derived...
SKAMP-Attention, SKAMP-Depormt and math tests scores are used as surrogate measures of treatment efficacy. While the main purpose of laboratory school studies is to assess treatment effects in an educational setting, the protocol can be extended into the evening (up to 12 hours post-dose) to assess whether the observed effects extend beyond the traditional school day.

**Head-to-head laboratory school studies of Concerta®, versus Equasym XL®, Ritalin LA® and Focalin XR®**

Efficacy of long-acting MPH formulations across the day Morning: Equasym XL® and Ritalin LA® provided superior symptom control to comparable daily doses of Concerta® in the morning [31,37]. The COMACS Study evaluated differences in the efficacy of bioequivalent doses of Equasym XL® and Concerta® using the laboratory school protocol [37]. Equasym XL® (20 mg) was superior to comparable daily doses of Concerta® (18, 36, 54 mg) for SKAMP-Attention, SKAMP-Depormt and correct math test scores at 1.5–4.5 hours post-dose [37] (Figure 2). Effect sizes for overall, combined dose levels for each formulation, shown in Figure 2, were greatest for Equasym XL® at 3 hours post-dose (SKAMP-Attention 0.72 versus 0.48 for Concerta®; SKAMP-Depormt 0.89 versus 0.50 for Concerta®). In a post-hoc analysis of the COMACS Study, it was predicted that lower doses of Equasym XL® (20 mg) would provide similar levels of symptom control to 36 and 54 mg doses of Concerta®, respectively, in the morning [34]. This hypothesis was based on the similar immediate-release components of the two formulations at the stated, respective, doses. While Equasym XL® 20 mg was associated with a stronger effect and more rapid onset of action than Concerta® (36 mg) at 1.5 hours post-dose, there was no significant overall difference in placebo-adjusted SKAMP scores between the two formulations at 3, 4.5 or 6 hours post-dose and no significant difference in placebo-adjusted SKAMP scores was observed between Equasym XL® 40 mg and Concerta® 54 mg from 1.5 to 6.0 hours post-dose [34].

Two laboratory school studies examined the comparative efficacy of Concerta® and Ritalin LA® [31,32]. Lopez and colleagues compared Concerta® (18 mg) and Ritalin LA® (20 mg) [31]. In line with observations from PK studies [22], they observed that, in the first 4 hours post-dose, Ritalin LA® (20 mg) resulted in significantly greater improvements from baseline than Concerta® (18 mg) in SKAMP-Attention (p = 0.015) (Figure 3), SKAMP-Depormt (p < 0.001), SKAMP-Combined (p < 0.001) and correct math test scores (p = 0.026) [31]. In contrast, Silva and colleagues demonstrated equivalent efficacy for Ritalin LA® (20 mg) and Concerta® (18 mg) during the first 4 hours (and 8 hours) post-dose for SKAMP-Attention, SKAMP-Depormt and math test scores [32]. It is possible that the findings of Silva and colleagues, however, may be a consequence of including a clinically more heterogeneous study population than the Lopez et al. study. In the study by Silva et al., 64% of subjects had
been receiving a stable dose of 40 mg/day MPH prior to enrolment compared with all subjects stabilized to 20 mg/day MPH in the Lopez et al. study. This may have resulted in a suboptimal response in the Silva et al. study [31,32].

Ritalin LA® (20 and 40 mg) also demonstrated superior symptom control compared with the 36 mg dose of Concerta® in the first 4 hours post-dose [31,32]. Lopez and colleagues demonstrated a significantly greater mean change from baseline in SKAMP-Attention (p = 0.043), SKAMP-Deportment (p = 0.004) and SKAMP-Combined (p = 0.003) scores for Ritalin LA® (20 mg) compared with Concerta® (36 mg) in the first 4 hours post-dose [31] (Figure 3). While Silva et al. also demonstrated significant improvements in SKAMP-Attention (p = 0.022) and Math-Correct (p = 0.033) scores for this dose comparison and time period, Ritalin LA® (20 mg) and Concerta® (36 mg) were equivalent in SKAMP-Deportment and Math-Attempted scores [32]. For all efficacy measures, improvements from baseline were significantly greater with Ritalin LA® (40 mg) than with Concerta® 36 mg over the first 4 hours post-dose, evident within 1 hour of dosing and persisting until 8 hours of evaluation [32].

Focalin XR® was superior to higher daily doses of Concerta® (20 versus 36 mg, and 30 versus 54 mg, respectively) at 0.5–6 hours post-dose [18,33]. Two head-to-head laboratory school comparisons of Focalin XR® with higher daily doses of Concerta® (20 versus 36 mg, and 30 versus 54 mg, respectively) demonstrated that Focalin XR® had an earlier onset of efficacy compared with Concerta®, with significantly greater improvements from baseline in SKAMP-Combined, SKAMP-Attention, SKAMP-Deportment scores and math test scores with Focalin XR® than with Concerta® at time points between 0.5 and 6 hours post-dose [18,33] (Figure 4).
Post-hoc analyses of AUC_{0-8} for SKAMP-Combined scores showed trends nearing statistical significance in favour of Focalin XR® over Concerta® (Focalin XR® 20 mg versus Concerta® 36 mg, p = 0.074; Focalin XR® 30 mg versus Concerta® 54 mg, p = 0.068) [33]. Significantly greater improvements from baseline with Focalin XR® compared with Concerta® were also observed in Math-Attempted and Math-Correct scores at 3 hours (20 versus 36 mg) and 4–5 hours (30 versus 54 mg) post-dose [18,33].

Afternoon and evening: While the COMACS Study demonstrated the superior efficacy of Equasym XL® compared with Concerta® in the morning, similar efficacy of comparable daily doses of the two MPH formulations was observed at 6.0–7.5 hours post-dose, and Concerta® demonstrated superiority over comparable doses of Equasym XL® at 12 hours post-dose [37] (Figure 2). In cross-dose comparisons, lower doses of Concerta® (18 and 36 mg) provided equivalent symptom control to higher doses of Equasym XL® (40 and 60 mg, respectively) at 7.5 hours and 12 hours post-dose [34]. In a reversed-dose comparison, a lower dose of Equasym XL® (20 mg) was comparable at 7.5 hours post-dose with a higher dose of Concerta® (36 mg) but Concerta® (36 mg) was superior to Equasym XL® (20 mg) at 12 hours post-dose [34]. However, when Equasym XL® (40 mg) was compared with Concerta® (54 mg) in a similar cross-dose comparison, Concerta® was superior to Equasym XL® at both 7.5 and 12 hours post-dose [34].

Over the 8-hour classroom period employed by Lopez et al., Ritalin LA® (20 mg) resulted in a significantly greater mean change from baseline (AUC_{0-8}) compared with Concerta® (18 mg) in SKAMP-Combined (p = 0.010) and SKAMP-Depportment (p = 0.018) scores and demonstrated trends towards significance in SKAMP-Attention (p = 0.074) [31]. Ritalin LA® (20 mg) also demonstrated trends towards superiority over a higher daily dose of Concerta® (36 mg) in SKAMP-Combined (p = 0.061) and SKAMP-Depportment (p = 0.078) scores over the 8-hour assessment period [31]. Silva and colleagues aimed to replicate and extend the findings of Lopez et al. using a similar study design but a longer, 12-hour classroom protocol. However, in contrast with Lopez et al., Silva and colleagues demonstrated comparable efficacy of Ritalin LA® (20 mg) and Concerta® (18 mg) over the first 8 hours post-dose (AUC_{0-8}), possibly, as stated earlier, owing to a clinically more heterogeneous study population [32]. Using the extended 12-hour classroom protocol, Silva et al. observed significantly greater changes from baseline at 8–12 hours post-dose (AUC_{8-12}) in SKAMP-Combined and SKAMP-Depportment scores with Concerta® 18 and 36 mg compared with Ritalin LA® 20 mg (but not 40 mg), and significantly more correct math test responses with Concerta® 36 mg than with Ritalin LA® 20 mg (p = 0.046) were observed [32].

While post-hoc analyses of AUC_{0-8} for SKAMP-Combined scores showed trends, nearing statistical significance, favouring Focalin XR® (20 and 30 mg) over higher daily doses of Concerta® (36 and 54 mg), differences between the two MPH formulations from 6 to 12 hours post-dose (AUC_{6-12}) failed to reach significance (20 versus 36 mg, p = 0.244; 30 versus 54 mg, p = 0.594) [33]. Although Concerta® and Focalin XR® demonstrated similar efficacy at 7–9 hours post-dose [18], Concerta® demonstrated significantly greater improvements in SKAMP-Combined, SKAMP-Attention and SKAMP-Depportment scores at 10–12 hours post-dose compared with lower daily doses of Focalin XR® (36 versus 20 mg, and 54 versus 30 mg, respectively) [18,33].

Both laboratory school studies comparing Concerta® with Focalin XR® employed the Conners’ Parent Rating Scale (CPRS) to obtain additional parental ratings of their child’s behaviour during the previous week. Muniz and colleagues demonstrated that, while Focalin XR® (20 mg) had a significantly greater effect on parent-rated symptom control than Concerta® (36 mg), no significant differences between the change in CPRS scores for Focalin XR® 30 mg and Concerta® 54 mg were observed [33]. In contrast, Silva et al. found no significant difference for change from baseline in CPRS scores, between formulations for the lower dose comparison (Focalin XR® 20 mg versus Concerta® 36 mg) and found Concerta® (54 mg) to be superior to Focalin XR® (30 mg); however, no explanation is provided for this disparity between study findings [18].

**Head-to-head laboratory school study of Ritalin LA® versus Medikinet® retard**

One laboratory school study compared Ritalin LA® (20 mg) with Medikinet® retard (20 mg) using a 7.5 hour laboratory school protocol and found no clinically relevant differences between the two MPH formulations [38] (Figure 5). Both treatment groups demonstrated comparable improvements in SKAMP-Combined score and math test scores until peak efficacy was reached at 3 hours post-dose [38]. Change from screening visit in Nisonger Child Behaviour Rating Form score (a parent-rated assessment of child and adolescent behaviour) demonstrated that both Ritalin LA® and Medikinet® retard improved disruptive behaviours [38].

**Effect of symptom severity on treatment choice**

A secondary analysis of the COMACS Study using growth mixture modelling analysis (a statistical technique to identify subgroups within a population with different trajectories of change over time) of total SKAMP scores investigated the effect of symptom severity on MPH response to Equasym XL® and Concerta® [36]. Results suggested heterogeneity in pharmacodynamic response to MPH by children with ADHD that is dependent on both symptom severity and
A significant effect of gender on response to MPH was observed in a further secondary analysis of the COMACS Study [35]. This was independent of MPH formulation (Concerta® or Equasym XL®), however. Females demonstrated a superior response to MPH, measured using SKAMP-Combined scores (controlled for placebo and baseline scores, and for the presence of comorbid anxiety) when compared with males at 1.5 and 3 hours post-dose, an equivalent response to males between 4.5 and 6 hours post-dose and a greater decline in response compared with males between 7.5 and 12 hours post-dose [35]. Analyses using PERMP scores confirmed this faster decline in response to MPH in females compared with males [35]. The response of female patients to MPH may, therefore, require additional assessments later in the day to determine the optimal dose of MPH [35]. Unfortunately, as most studies include only small numbers of females, the power of other head-to-head studies to investigate the effect of gender in MPH response is limited. While a significant gender by treatment interaction (p = 0.018) for maximum plasma MPH concentration from 4 hours to last observation (C_{max,t}) was noted in a head-to-head PK study of Equasym XL® and Medikinet® retard performed in healthy adults, no other significant gender effects were observed [28]. In addition, no gender effects were noted in a head-to-head PK study of Focalin XR® and Ritalin LA® [27].

**Effect of gender on response to MPH**

An important general observation from the laboratory school studies comparing Equasym XL® and Concerta® is that superiority at any point in time was achieved by the formulation with the highest expected plasma MPH concentration (predicted from PK data available) [37,42]. Despite dose selection based on clinical titration, the size of the drug effect obtained in the early morning appears to be directly related to the absolute dose delivered by the immediate-release MPH bolus of each formulation [37,42]. The duration of action of clinical effects is also in line with what would be predicted from PK data. Adverse events for all of the oral long-acting MPH formulations were generally mild to moderate in severity and commonly included abdominal pain, headache and decreased appetite [18,31-33,37,38]. While adverse events were generally similar between different formulations, in one study treatment-related abdominal pain and anorexia were more frequent in subjects receiving Medikinet® retard (5/147; 3.4% and 6/147; 4.1%, respectively) than those receiving Ritalin LA® (1/147; 0.7% and 3/147; 2.0%, respectively) [38]. This difference in frequency was not assessed for significance and the investigators concluded that there were no relevant differences between Medikinet® retard and Ritalin LA® regarding the profile, frequency or intensity of adverse events [38].

**Head-to-head RCTs of long-acting MPH formulations**

To date, only two head-to-head non-laboratory school RCTs have been performed, both of which included Concerta® as a comparator.

**Concerta® versus Daytrana®**

In a Phase III, double-blind, double-dummy, parallel-group, placebo-controlled, naturalistic home and school trial, children (n = 282) were randomized to receive either Concerta®, Daytrana® or placebo [43]. Following a 5-week dose optimization period, children who reached
an acceptable level of efficacy and tolerability entered a 2-week dose-maintenance phase during which assessment of treatment efficacy and safety were performed at the end of each week. Blood samples were collected from participants at 7.5, 9 and 10.5 hours post-dose during one of the last three study visits for determination of plasma MPH concentration. By the end of the dose optimization period, the majority of children were receiving Concerta® at a dose of 36 mg (32.4%) or 54 mg (44.1%) or Daytrana® at 20 mg/9 hours (34.2%) or 30 mg/9 hours (36.8%). Results at study endpoint revealed no significant differences between Concerta® and Daytrana® for: mean change from baseline in ADHD Rating Scale-version IV (ADHD-RS-IV) scores (the primary efficacy measure of the study); mean change from baseline in Conner’s Teacher Rating Scale- Revised (CTRS-R) total score; or mean change from baseline in CPRS-R total score in the morning or the afternoon. Furthermore, the majority of children receiving Daytrana® (71.9%; n = 69) and Concerta® (66.3%; n = 59) were rated as improved using the Clinical Global Impressions—Improvement (CGI—I) scale at study endpoint, while 69.8% (n = 67) and 60.7% (n = 54), respectively, were rated as improved using the Parent Global Assessment (PGA) scale.

Higher plasma concentrations of d-MPH and l-MPH were observed after 9 hours of treatment with Daytrana® compared with 9 hours post-dosing with Concerta®, indicating that greater systemic exposure to MPH is observed in the latter part of the day with Daytrana®.

**Concerta® versus Medikinet® retard**

A randomized, double-blind, cross-over study design was used to investigate the efficacy of Concerta® and Medikinet® retard with equivalent daily doses (but different immediate-release components) and different daily doses (but similar immediate-release components) in the school and home environment [42]. Efficacy was rated by teachers using the German version of the SKAMP scale (SKAMP-D), while both teachers and parents rated ADHD symptoms using the Day Profile of ADHD Symptoms (DAYAS) [42].

Medikinet® retard with a higher immediate-release component and similar daily dose to Concerta® was superior to Concerta® (20 versus 18 mg and 30 versus 36 mg, respectively) in the first 3 hours of school and 4–6 hours into the school day, as assessed using SKAMP-D [42]. Medikinet® retard with a similar immediate-release component to Concerta® in the morning but with a lower daily dose was non-inferior to Concerta® (10 versus 18 mg and 20 versus 36 mg, respectively) in the first 3 hours and 4–6 hours of the school day (SKAMP-D) [42]. No evidence for the superiority of Concerta® over Medikinet® retard with equivalent daily doses in the late afternoon and evening was observed using DAYAS teacher or parent ratings [42].

**Adverse events**

No significant difference in the frequency of adverse events was observed between Concerta® and Daytrana®; the majority of adverse events were mild to moderate in severity [43]. Application-site reactions were noted as being among adverse events resulting in study discontinuation for patients receiving Daytrana®. While mild erythema was common, 77% of subjects reported either no or minimal evidence of irritation. A higher incidence of tic disorders was observed in patients receiving Daytrana® (n = 7, 7.1%; nine events) compared with Concerta® (n = 1, 1.1%; one event); however, this was deemed unlikely to reflect a greater risk of tics associated with Daytrana® [43-45]. The most frequent adverse events noted in RCTs were headache, abdominal pain, decreased appetite, nausea, vomiting and insomnia [42,43]. In addition, there was no evidence of differences in overall tolerance (assessed by the investigator, parents and teachers) between Concerta® and Medikinet® retard [42].

**Switching and observational studies**

Of 34 publications included in the review, three publications derived from two open-label switching studies [46-48] and three publications derived from one observational study [49-51] were identified. All studies included Concerta® as a comparator.

**Switching studies**

In one switching study, children aged 6–12 years with ADHD on a stable dose of oral long-acting MPH (Concerta®, Equasym XL® or Ritalin LA®), not exceeding 54 mg/day, underwent abrupt switching to Daytrana® using a pre-defined dose-transition schedule. Titration was based on changes in ADHD-RS-IV score and Clinical Global Impressions—Severity (CGI–S) scale score. Measures of ADHD symptoms and quality of life were obtained using ADHD-RS-IV, CPRS-R, CGI—I, PGA and the ADHD Impact Module-Child (AIM-C) [46,47].

Abrupt conversion from oral long-acting MPH formulations to an optimum dose of Daytrana® using a dose-transition schedule was not associated with deterioration of symptom control [46,47]. After 1 week of treatment with Daytrana®, the majority of children (78%) had a CGI—I score indicating improvement or no change and mean ADHD-RS-IV total score was similar to that at baseline, indicating little change in ADHD symptoms when subjects switched to Daytrana® from oral long-acting MPH formulations [46]. After 4 weeks of treatment with Daytrana®, 96% of children had CGI—I scores rated as ‘improvement or no change’ relative to baseline. Furthermore, a significant improvement from baseline was observed in ADHD-RS-IV mean total score (p < 0.0001). Forty-two
percent of children received dose-optimization adjustments during the study, most of which were dose increases (38% of subjects) [46]. Optimal nominal doses of Daytrana®, which ranged from 10 mg/9 hours (n = 23) to 30 mg/9 hours (n = 59) were below the nominal doses of oral long-acting MPH from which subjects were switched. Clinicians could consider initiating treatment with Daytrana® at a smaller patch size than the oral dose received previously. However, treatment for each patient should be optimized on an individual basis [46,47].

Improvements from baseline in behaviour (PGA, CPRS-R), health-related quality of life (HRQoL; AIM-C) for both the child and the family, compliance and economic impact (number of missed school days; hours of tutoring, nursing, home healthcare and use of other services required; number of work days missed by parent/caregiver) were also observed after treatment for 4 weeks with Daytrana® [47]. Differences between subgroups were noted: greater improvements from baseline to endpoint in child HRQoL were reported for: children switching from Ritalin LA®, children aged 6–9 years; and females rather than males [47]. In addition, greater improvement in the AIM-C School/Missed-Doses Worry Scale was observed in subjects who switched to Daytrana® from Equasym XL® than in those who switched from Concerta® or Ritalin LA® [47]. For all prior-treatment groups, caregiver satisfaction with treatment was high and 82.6% of caregivers reported improvements in their child’s social interactions since switching to Daytrana® [47]. According to the authors, the apparent superiority of Daytrana® observed during the study, however, is more likely to be due to careful titration and clinical monitoring for the study duration rather than to the product itself [46,47].

In a second switching study, 308 children with ADHD who were either untreated or currently receiving treatment with MPH (immediate-release MPH, extended-release MPH excluding Concerta®, or Concerta®) were switched to Equasym XL® for 3 weeks [48]. Children currently receiving MPH started Equasym XL® at a dosage based on clinical judgement and the patient’s current MPH dose, while previously untreated children started Equasym XL® treatment at a dose of 20 mg. Equasym XL® was titrated for all patients on a weekly basis according to clinical judgement. Measures of ADHD symptom control and therapeutic response were obtained at weeks 1, 2 and 3 using CGI-I and the CGI–Efficacy Index and compared with baseline scores. Of those who were previously receiving ADHD medication (181; 59%), most switched from Concerta® (41.4%) or immediate-release MPH (36.5%) with only 9% switching from a long-acting MPH other than Concerta®. Overall, 60.6% of children switching from a previous MPH formulation were responders to Equasym XL® (CGI-I score of 1 [very much improved] or 2 [much improved]) at week 3 and approximately half (55%) of children switching from Concerta® demonstrated improvement from baseline in CGI–I at week 3. The majority of children (63%) switching from a previous MPH treatment also demonstrated a moderate or marked therapeutic effect with either no or minimal side-effects, as measured using the CGI–Efficacy Index. The authors suggested that improvements observed in patients previously receiving MPH may be due to treatment optimization and differences in PK between the two MPH formulations.

**Adverse events** Consistent with commonly reported adverse events associated with MPH, 59.6% of caregivers agreed that Daytrana® decreased their child’s appetite and 34.8% agreed that treatment with Daytrana® made it more difficult for their child to fall asleep at night [47]. Such late-day side effects may be attenuated by early removal of the patch [44]. Adverse events with Daytrana® and Equasym XL® were mostly mild to moderate in severity and most commonly included headache, decreased appetite, insomnia and abdominal pain [48]. Despite a transdermal route of administration, Daytrana® was associated with those adverse events typically observed with oral long-acting MPH, with the added issue of application-site reactions that included normal appearance at the patch site with moderate itching, as well as erythema with severe itching. However, most subjects reported no or mild discomfort [46,47]. One subject reported two serious adverse events (acute depression and suicide attempt) while receiving 30 mg Daytrana® for 16 days that were considered possibly related to treatment.

**Observational study** The OBSEER study was a non-interventional, non-controlled, observational study. Patients with ADHD intended for treatment with Equasym XL®, either previously treatment-naive, receiving treatment with other MPH formulations (immediate-release or long-acting, most commonly immediate-release Medikinet® and Medikinet® retard, respectively), receiving a different pharmacological therapy or receiving non-pharmacological therapy were observed for 6–12 weeks in routine care. As this was a non-interventional study, treatment optimization was not part of the study remit and MPH dose adjustments were at the discretion of the treating physician. Measures of ADHD symptoms and quality of life were obtained using the CGI–S scale, the German ADHD symptom checklist (Fremdbeurteilungsfragebogen für Aufmerksamkeitsdefizit–Hyperaktivitätsstörung [FBB-ADHD]; rated by teachers and parents), DAYAS (rated by teachers and parents) and a HRQoL questionnaire (Kinder Lebensqualitätsfragebogen [KINDL]) [49]. Despite most children (69.8%) previously receiving MPH medication, improvement in ADHD symptoms was observed following the switch to Equasym XL®.
The largest reduction in clinician-rated ADHD symptoms (CGI–S) was observed in the treatment-naive subgroup (Cohen’s $d = 1.73$); however, a reduction in CGI–S was also observed in patients previously receiving a long-acting MPH formulation (Cohen’s $d = 0.76$) [50].

The reduction in parent-rated ADHD symptoms (Cohen’s $d = 0.79$; FBB-ADHD) was larger than the reduction in teacher-rated ADHD symptoms (Cohen’s $d = 0.41$; FBB-ADHD) [50]. For parent-rated DAYAS scores, the largest reduction in ADHD and oppositional defiant disorder symptoms in patients previously receiving a long-acting MPH formulation was observed in the early afternoon (Cohen’s $d = 0.63$), with smaller but still substantial improvements observed in the morning before school, late afternoon and evening (Cohen’s $d$ range 0.44–0.49). No significant difference was observed between prior treatment subgroups in the evening [50]. Less improvement was noted in teacher-rated DAYAS scores for the first 2–3 hours and second 2–3 hours of the school morning (Cohen’s $d = 0.14$ and 0.39, respectively) compared with parent-rated DAYAS scores for the morning before school (Cohen’s $d = 0.49$), afternoon until 4 pm (Cohen’s $d = 0.63$), late afternoon until 7 pm (Cohen’s $d = 0.45$) and evening (Cohen’s $d = 0.44$) [50]. While parents and physicians were not blinded to study treatment or dose, teachers were not formally notified of the change in treatment. The lower effect sizes in the teacher ratings may be a more accurate representation of treatment effect, therefore, as they were not influenced by expectation and dissatisfaction with prior treatment [49].

Improvement following the initiation of treatment with Equasym XL® was also observed in mean KINDL score and KINDL scales for self-esteem, friends and school (parent and patient ratings) and family (patient ratings). The largest effect size in patients formerly receiving long-acting MPH in parent-rated quality of life was on the KINDL friends scale (Cohen’s $d = 0.42$), while the largest effect size noted for patient-rated quality of life was on the KINDL family scale (Cohen’s $d = 0.37$) [50,51]. Overall, adherence during Equasym XL® treatment was frequently rated as superior to adherence during prior treatment; however, 12.8% of patients previously receiving long-acting MPH had better adherence to prior treatment, compared with 8.0% for all treatments overall [51].

**Adverse events** The most frequent adverse events recorded during the OBSEER study were psychiatric disorders (19.8% of all patients), metabolism and nutrition disorders (2.4%), and gastrointestinal disorders (2.2%), with tics being the most frequent single adverse event recorded (106 events in 100/822 [12.2%] patients). While the frequency of tics was high, the authors noted that conclusions regarding the emergence of treatment-related tics were limited as patients with pre-existing tics were not excluded from the study and emergent tics were not differentiated from those pre-existing. Serious adverse events (n = 38) were recorded for 21/822 (2.5%) patients, which the investigators noted was high compared with previous studies. The investigators proposed that this may be due to various factors, including the long duration of observation in the OBSEER study, a lack of data regarding whether the adverse events were present under the previous medication, missing data for 10.7% of patients and possible incorrect categorization of adverse event seriousness by the investigators.

**Meta-analyses and systematic reviews** Eight systematic reviews and meta-analyses addressed long-acting ADHD medications, including, but not limited to, MPH for the treatment of ADHD. An overview of the main conclusions of these reviews is presented.

Consideration of the onset and duration of efficacy of long-acting MPH formulations in the context of the patient’s individual needs when selecting an appropriate formulation was highlighted [19,52,53]. The pattern of efficacy generally follows that predicted by the PK profile of the MPH formulation [53]. As such, efficacy offset varies between long-acting MPH formulations, although whether this is clinically perceptible outside the research setting is unknown [19,53]. Greater efficacy during the first 8 hours post-dose compared with later in the day may be beneficial for parents/caregivers during the pre-school period (getting the child ready for school and travelling to school) and during the school day; however, some families may prefer greater symptom control in the evenings to improve concentration for homework completion, or for greater behavioural control in social/familial interactions [19,53]. Selection of the optimal MPH formulation may be influenced by the individual’s sensitivity to appetite problems and insomnia; therefore, MPH formulations with shorter duration of action may be more appropriate over longer-acting formulations to reduce interference with dinnertime and sleep [52,54].

With regard to administration of medication, Equasym XL®, Medikinet® retard and Ritalin LA® capsules can be opened and sprinkled on food, which may have a compliance benefit over Concerta® in patients who have difficulty swallowing. However, surreptitious administration of medication by parents/caregivers should not be undertaken as this may result in a lack of trust between the patient and parent/caregiver [52].

The importance of head-to-head studies for the direct comparison of the efficacy of different medications was highlighted but the lack of uniformity in study design parameters used to assess medication efficacy, particularly for studies assessing long-acting stimulants was noted as a significant limitation with current studies [55-57].
In meta-analyses examining treatment efficacy in adults with ADHD, Peterson et al. found that short-acting stimulants were more effective than long-acting stimulants in the treatment of adults with ADHD [58]. While an initial analysis by Farah et al. supported this finding, no significant difference between the effect sizes for long- and short-acting stimulants in the treatment of adults with ADHD was detected after study confounders and publication bias were accounted for [57]. Furthermore, differences in study methodology (inclusion/exclusion criteria, outcome measures analysed and literature search timing) were also suggested to contribute to the contradiction in findings from the two meta-analyses [57].

Conclusions
The objective of this review was to bring together the evidence available from head-to-head studies of long-acting MPH formulations and to increase understanding of their basic properties, discuss similarities and differences, and provide information that can guide treatment selection.

In addition to supporting the conclusions of existing meta-analyses and systematic reviews on long-acting MPH formulations, our review of head-to-head studies reinforces the finding that, at a group level, the pattern of efficacy across the day generally follows that predicted by the PK profile of the formulation. The timecourse of both plasma MPH concentration and central brain effects (DAT occupancy) may be predicted based on the MPH delivery profile of a long-acting formulation [21]. It must be noted, however, that there is significant variability in PK profiles across the day at an individual level and that, as a consequence of this, the individual response to any given product and dosing strategy may vary substantially. The clinical consequences of this variability are that no one treatment is superior for all patients and that individualized treatment optimization is an important clinical task. To make the best use of the various long-acting MPH preparations clinicians need to understand the similarities and differences between them and how to harness these to achieve the best results for their patients.

For patients achieving significant but suboptimal effects with a long-acting MPH medication, switching to another MPH formulation should be considered. This advice relates to situations in which there has been at least a partial response to MPH (e.g., adequate symptom coverage for a certain period of the day) and the clinician is trying to fine tune and optimize treatment. Such an approach may prove beneficial and can often be undertaken without loss of symptom control during the period of transition from one formulation to another. As noted previously, responses to formulations may vary between individuals and the time–action profile of the medication should be considered during switching and tailored to the patient’s needs. The availability of the different long-acting MPH formulations varies across the world, and even within continents, and clearly impacts on the options available to the clinician. At the present time the greatest range is available to patients in the USA (Table 1). In cases where a lower daily dose of MPH is preferred, data have shown that children and adolescents could be treated with a lower daily dose of Medikinet® retard and Daytrana® than Concerta® without clinically relevant deterioration in symptom control during school time [42,47,50]. However, it is also acceptable to increase the daily dose of MPH in order to achieve optimal symptom control [52] and indeed higher daily doses should not necessarily be seen as negative [59]. Clinicians are often uncertain about correct dosing when switching patients from immediate- or extended-release MPH to a long-acting MPH formulation with an immediate-release component of <50% (Concerta® in particular). As a consequence, many patients receive suboptimal treatment. It is usually appropriate to use the immediate-release component of each formulation as the reference and try to adjust for this when switching between MPH formulations. A limitation of current studies is that they have mostly focused on the total daily dose rather than equivalent immediate-release components. Data from head-to-head studies of long-acting MPH formulations suggest that, across formulations, equivalent immediate-release components provide similar symptom control in the morning and this would be our clinical suggestion. As an example, if one wants to switch a patient from 20 mg of Medikinet® retard (50:50 immediate- and extended-release) to Concerta® (22:78 immediate- and extended-release) to try to alleviate breakthrough symptoms at the end of the school day, then 45 mg of Concerta® would give the equivalent immediate-release dose. Although the supporting data are not reviewed here, when there is little clinical response to MPH at the end of a careful titration, switching from MPH to another stimulant or a non-stimulant medication is likely to be the most beneficial for such patients who are poor responders to MPH.

Duration of required symptom control may vary between individuals. Although it has been argued that an ascending PK profile is required to combat acute tolerance [60] it is likely that for some individuals, reaching a peak plasma MPH concentration at a minimum of 6–8 hours post-dose, as observed for Concerta® and Daytrana®, may be quite late in the day as the school/work morning is over and symptom control may not be optimal when required. In such cases clinicians may favour one of the 8-hour formulations. However, there is also evidence that for many patients, ADHD symptoms continue into the late afternoon and evening [61]. Where this is the case, extending symptom control beyond 8 hours has the potential to benefit many, if not most, patients with ADHD. This may be particularly important for adults and adolescents, who are often required to maintain high levels of functioning over
these periods. The various long-acting MPH formulations allow for flexibility in duration of symptom control, which can be tailored to the individual patient's needs. Twelve-hour symptom coverage can be obtained using a formulation such as Concerta® on its own, or by combining one of the 8-hour preparations with an additional immediate-release dose at around 4 pm. Female patients have been shown to have a faster decline in response to MPH compared with males [35] and may require closer assessments of their afternoon symptom control to determine optimal MPH dose.

Flexibility in how the medication can be taken may be of particular benefit for some patients. For example, the ability to open capsules and sprinkle the medication on food may be of benefit for patients who have difficulty taking tablets and offers an advantage for pre-school children who are not yet able to swallow pills. If regularly eating breakfast is a challenge for the patient, a formulation for which bioavailability is not affected by food intake may be preferred. In such cases, Ritalin LA® may have a potential advantage over Medikinet® retard [26]. Alternatively, a transdermal rather than an oral mode of action may be preferred by some patients. While the side-effect profiles are similar between different long-acting MPH formulations, Daytrana® may be associated with application-site reactions.

This review has highlighted several unmet needs. While we recognize that the evidence to date suggests that the profile of clinical action across the day can generally be predicted from the PK profile of a particular preparation, the direct evidence to support this proposition is almost all from head-to-head studies that compared Concerta® with one other long-acting MPH formulation. The laboratory school protocol seems to be the ideal methodology for addressing outstanding questions; however, at the time of writing, only one laboratory school study had been performed in which Concerta® was not the comparator. This study compared equivalent daily doses of Ritalin LA® and Medikinet® retard, both of which have a 50/50 immediate-release/extended-release delivery profile, and showed no clinically relevant differences between the two formulations [38]. We therefore believe that more head-to-head laboratory school studies of alternative combinations of long-acting formulations are required to provide evidence-based guidance on treatment selection and guide the development of clinical guidelines, and to inform the decisions of regulators and those making decisions about reimbursement and ultimately the decisions made in day-to-day clinical practice. In particular, further studies comparing the efficacy of formulations containing racemic d,l-MPH with d-MPH (Focalin XR®) would be of particular interest. Pragmatic head-to-head studies looking at dose optimization across the day in the short- and long-term, and longer-term comparative studies to assess efficacy and safety over time, are also required as well as laboratory school studies comparing MPH with other ADHD medications.

In addition to these studies, which would be applicable to all ages, further studies using an age-appropriate laboratory school-style protocol in adults are needed to assess real-life medication effects across the day. More studies of the effects of long-acting MPH formulations in pre-school children, both within age-appropriate laboratory school settings and assessing their impact in more naturalistic settings on developmental and academic outcomes would also be of interest. Further research into the effect of comorbidities and symptom severity as modifiers of treatment response with the various long-acting MPH formulations available is also necessary. Compliance and adherence may differ between different long-acting medications; however, it is unknown whether this is a true reflection of medication adherence or an effect of study involvement. More studies investigating the impact of the different formulations and related dosing strategies on adherence could throw light on these questions.

This review has a number of potential limitations. While two extensive databases were searched to identify relevant articles for inclusion in the review, the authors are aware of studies that were not retrieved by the search terms. These include an open-label study of 447 children and adolescents switching from immediate-release MPH, extended-release MPH, or no treatment, to Medikinet® retard [62]. Significant improvements from baseline at 4–6 weeks were observed in ADHD symptom severity, as evaluated by physicians and parents, in patients switching from Concerta® (n = 64) but not in those switching from Ritalin SR®/Ritalin LA® (n = 26). The superior efficacy of Medikinet® retard compared with Concerta® is probably due to the larger immediate-release bolus from Medikinet® retard (50%, versus 22% for Concerta®), while the lack of significant improvement with Medikinet® retard compared with Ritalin SR®/Ritalin LA® may be explained by the motivation of patients to participate in the study, and not necessarily because the prior therapy was suboptimal.

The diversity of head-to-head studies of long-acting MPH formulations and their reported outcomes creates a challenge when drawing general conclusions and providing clinical recommendations. Emerging studies provide important data on the comparative efficacy of formulations available, but further studies are necessary to provide more evidence-based guidance for clinical practice. Effect sizes have been cited in the review where appropriate; however, heterogeneity in study design and reported outcomes precluded the undertaking of meta-analysis.

Despite these limitations there are several clear messages for clinicians using long-acting MPH preparations to treat patients with ADHD. Different patients have both different treatment needs and responses to MPH. There is now clear evidence that, in order to optimize
the treatment of ADHD symptoms, a tailored approach to treatment is required. This involves both an initial titration onto medication and a continued follow up, with careful adjustments in dose and often in MPH formulation. It is important to track symptoms and response across the day. One possible tool for this is the Dundee Difficult Times of the Day Scale (D Coghill, personal communication, available from [63]). It is clear from this review that no one long-acting MPH preparation is clearly superior to another. However, even though some of the formulations are very similar to each other, each has its own particular profile and there are differences with respect to mode of delivery, PK/pharmacodynamic profile, dosing, duration of action, interaction with food and adverse effects. In addition to carefully collecting information about ADHD symptoms and the way that they change across the day, clinicians need to be aware of the, often subtle, differences between formulations when trying to optimize treatment for their individual patients. A reasonable starting position is to titrate to an adequate morning response, as for many patients this will be followed by good symptom control across the rest of the day. If not, further adjustments in dose, a change of MPH formulation or change to a different class of drug may be required. Such an approach is likely to lead to improved clinical care and should result in fewer patients requiring to be managed on multiple medications.

Competing interests
A Gagliano received conference attendance support and speaker’s fees from Lilly, Novartis and Shire. She or is has been involved in clinical trials conducted by Lilly and Shire. The present work is unrelated to the above grants and relationships. A Pelaz served in an advisory role for Lilly, and has received conference attendance support or received speaker’s fees from Bristol-Myers Squibb, Janssen, Juste, Lilly, Otsuka, Rubio and Shire. He has been involved in clinical trials conducted by Janssen and Rubio. The present work is unrelated to the above grants and relationships. T Banaschewski served in an advisory or consultancy role for Bristol-Myers Squibb, Deveto Pharma, Lilly, Medice, Novartis, Shire and Vifor Pharma. He received conference attendance support, conference support or received speaker’s fees from Lilly, Janssen McNeil, Medice, Novartis and Shire. He is or has been involved in clinical trials conducted by Lilly and Shire. The present work is unrelated to the above grants and relationships. T Banaschewski served in an advisory role for Flynn Pharma, Otsuka, Lilly, Janssen, Medice, Pfizer, Schering-Plough, Shire and Vifor. He received conference attendance support, conference support or received speaker’s fees from Flynn Pharma, Lilly, Janssen, Medice, Novartis and Shire. He is or has been involved in clinical trials conducted by Lilly and Shire and has received research funding from Lilly, Janssen and Shire and Vifor. The present work is unrelated to the above grants and relationships. M Doepfner served in an advisory or consultancy role for Lilly, Medice, Novartis, Shire and Vifor Pharma. He received conference attendance support, conference support or received speaker’s fees from Lilly, Medice, Novartis and Shire. M Doepfner or is has been involved in clinical trials conducted by Lilly and Vifor. The present work is unrelated to the above grants and relationships. A Zuddas served in an advisory or consultancy role for Astra-Zeneca, Bristol-Myers Squibb, Otsuka, Lilly, Lundbeck, Shire and Vifor Pharma. He received conference attendance support and conference support or received speaker’s fees from Lilly and Shire. He is has been involved in clinical trials conducted by Lilly, Shire and Vifor. The present work is unrelated to the above grants and relationships.

Authors’ contributions
AG, TB, DC, MD and AZ made substantial contributions to the conception and design of the systematic review, and interpretation of data; AP made substantial contributions to interpretation of data. All authors have been involved in revising the manuscript critically for important intellectual content. All authors have read and approved the final manuscript.

Authors’ information
Dr Antonella Gagliano, MD, PhD is Assistant Professor of Research in Child and Adolescent Psychiatry in the Department of Pediatric Science, University of Messina–Policlinico Universitario G. Martino, Hospital, Italy. Dr Antonio Pelaz, MD is a Child and Adolescent Psychiatrist at Hospital Clinico Universitario San Carlos, Madrid, Spain. Professor Dr Tobias Banaschewski, MD, PhD is Medical Director at the Department of Child and Adolescent Psychiatry and Psychotherapy, Central Institute of Mental Health, University of Heidelberg, Mannheim, Germany. Dr David Coghill, MB ChB, MD is a Reader in Child and Adolescent Psychiatry in the division of Neuroscience, Medical Research Institute, Ninewells Hospital, Dundee, UK. Professor Dr Manfred Doepfner, PhD is Professor of Psychotherapy and Chief Psychologist in the Department of Child and Adolescent Psychiatry and Psychotherapy at the University of Cologne, Cologne, Germany. Professor Alessandro Zuddas, MD is Associate Professor of Child and Adolescent Psychiatry at the Department of Biomedical Science, University of Cagliari, and Director of the Child and Adolescent Neuropsychiatry Unit at Cagliari University Hospital, Sardinia, Italy. David Coghill and Tobias Banaschewski are joint first authors. Antonella Gagliano and Manfred Doepfner are joint last authors.

Acknowledgements
Under the direction of the authors, support with the literature search, data extraction, writing of the outline, initial draft of the manuscript and collation of author comments was provided by Alyson Beaufield, PhD, and Debbi Moss, PhD, employees of Caudex Medical, Oxford, UK. Editorial assistance in formatting, proofreading, and copy editing was also provided by Caudex Medical. Although Shire AG were involved in the topic concept, the content of this manuscript, the ultimate interpretation, and the decision to submit it for publication in BMC Psychiatry was made by the authors independently.

Author details
1 Division of Neuroscience, Medical Research Institute, Ninewells Hospital and Medical School, Dundee DD1 9SY, UK. 2Department of Child and Adolescent Psychiatry, Central Institute of Mental Health, Medical Faculty of Mannheim, University of Heidelberg, Mannheim, Germany. 3Department of Biomedical Sciences, University of Cagliari, Cagliari, Sardinia, Italy. 4Department of Child and Adolescent Psychiatry, Hospital Clinico Universitario San Carlos, Madrid, Spain. 5Department of Pediatric Science, University of Messina, Policlinico Universitario G. Martino, Messina, Italy. 6Department of Child and Adolescent Psychiatry, University of Cologne, Cologne, Germany.

Received: 24 February 2013 Accepted: 11 September 2013 Published: 27 September 2013

References
1. Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA: The worldwide prevalence of ADHD: a systematic review and metaregression analysis. Am J Psychiatry 2007, 164:942–948.
2. Kooij SJ, Bejerot S, Blackwell A, Caci H, Casas-Brugue M, Carpenter PJ, Edvinsson D, Fayaad J, Feilern K, Fitzgerald M, Gallia V, Ginsberg Y, Henry C, Krause J, Lening MB, Manor I, Niederhofer H, Nunes-Filipe C, Ohlmeier MD, Oswald P, Paillanti S, Pehlivanidis A, Ramos-Quiroga JA, Rastam M, Ryffel-Rawak D, Stes S, Asherson P: European consensus statement on diagnosis and treatment of adult ADHD: The European Network Adult ADHD. BMC Psychiatry 2010, 10:67.
3. Wolraich M, Brown L, Brown RT, DuPaal G, Earls M, Feldman HM, Ganiats TG, Kaplanen B, Mayer B, Perrin J, Pierce K, Reff M, Stein MT, Vissers S: ADHD: clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. Pediatrics 2011, 128:1007–1022.
4. Greenhill LL, Pihlaja S, Dunlan MK, Bernet W, Arnold V, Behrman J, Benson RS, Bukstein O, Kirlin J, McClellan J, Rue D, Shaw JA, Stock S: Practice parameter for
the use of stimulant medications in the treatment of children, adolescents, and adults. J Am Acad Child Adolesc Psychiatry 2002, 41:265–495.
5. Ritalin SR®, prescribing information. http://www.pharma.us.novartis.com/product/pi/pdf/ritalin_ritalin-sr.pdf. Date accessed 10/1/13.
6. Ritalin LA®, prescribing information. http://www.pharma.us.novartis.com/product/pi/pdf/ritalin_ritalin-la.pdf. Date accessed 10/1/13.
7. Focalin XR®, prescribing information. http://www.pharma.us.novartis.com/product/pi/pdf/focalinXR.pdf. Date accessed 10/1/13.
8. Heal DJ, Pierce DI: Methylphenidate and its isomers: their role in the treatment of attention-deficit hyperactivity disorder using a transdermal delivery system. CNS Drugs 2006, 20:73–78.
9. Medikinet®. XL big summary of product characteristics. http://www. medikinet.com.uk/medicines/34854/. Date accessed 10/1/13.
10. Biphenthrin® product monograph. http://www.purdue.com/files/Biphenthrin% 20Capsules%20PM%20EN.pdf. Date accessed 10/1/13.
11. Equasym XL®. Summary of product characteristics. http://www.medicines.org. uk/emc/medicine/131904/S/EquasymXL+10+S+mg+20+S+mg+30+S+mg+Capsules. Date accessed 10/1/13.
12. Concerta® XL. summary of product characteristics. http://www.medicines.org.uk/ emc/medicine/93831/S/Concerta%20XL+18+S+mg+36+S+mg+prolonged+release+tablets/. Date accessed 10/1/13.
13. Daytrana™ prescribing information. http://www.daytrana.com/documents/ daytrana-prescribing-information.pdf. Date accessed 10/1/13.
14. Froehlich TE, Epstein JN, Nick TG, Melguizo Castro MS, Stein MA, Brinkman WB, Graham AJ, Langemak JM, Kahn RS: Pharmacogenetic predictors of methylphenidate dose-response in attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 2011, 50:129–139.
15. Greenhill LL, Abbkoff HB, Alden LE, Cantwell DP, Conners CK, Elliott G, Hechtman L, Hinshaw SP, Hoza B, Jensen PS, March JS, Newcorn J, Pelham WE, Severe JB, Swanson JM, Vitiello B, Wells K: Medication treatment strategies in the MTA study: relevance to clinicians and researchers. J Am Acad Child Adolesc Psychiatry 1996, 35:1304–1313.
16. Vitiello B, Severe JB, Greenhill LL, Arnold LE, Abbkoff HB, Bukseth OG, Elliott GR, Hechtman L, Jensen PS, Hinshaw SP, March JS, Newcorn JH, Swanson JM, Cantwell DP: Methylphenidate dosage for children with ADHD over time under controlled conditions: lessons from the MTA. J Am Acad Child Adolesc Psychiatry 2001, 40:188–196.
17. Döpfner M, Gerber WD, Banaschewski T, Breuer D, Freihedler FJ, Gerber-von MG, Gunter M, Hassler F, Oehler KU, Lehmkuhl G: Comparative efficacy of once-a-day extended-release methylphenidate, two-times-daily immediate-release methylphenidate, and placebo in a laboratory school setting. Eur Child Adolesc Psychiatry 2004, 13(Suppl 1):93–101.
18. Silva R, Muniz R, McCague K, Childress A, Brans M, Mao A: Treatment of children with attention-deficit/hyperactivity disorder: results of a randomized, multicenter, double-blind, crossover study of extended-release dexmethylphenidate and D,L-methylphenidate and placebo in a laboratory classroom setting. Psychopharmacol Bull 2008, 41:19–33.
19. Brans M, Moon E, Pucci M, Lopez FA: Duration of effect of oral long-acting stimulant medications for ADHD throughout the day. Curr Med Res Opin 2010, 26:1809–1825.
20. Gonzalez MA, Pentikis HS, Anderl N, Benedict MF, DeCory HH, Dirksen SJ, Hatch SJ: Methylphenidate bioavailability from two extended-release formulations. Int J Clin Pharmacol Ther 2002, 40:175–184.
21. Spencer TJ, Bonab AA, Dougherty DD, Martin J, McDonnell T, Fischman AJ: A PET study examining pharmacokinetics and dopamine transporter occupancy of two long-acting formulations of methylphenidate in adults. Int J Mol Med 2010, 25:261–265.
22. Markowitz JS, Stough AB, Patrick KS, DeVane CL, Prestliech L, Lee J, Wang Y, Muniz R: Pharmacokinetics of methylphenidate after oral administration of two modified-release formulations in healthy adults. Clin Pharmacokinet 2003, 42:393–401.
23. Modi NB, Lindemulder B, Gupta SK: Single- and multiple-dose pharmacokinetics of an oral once-a-day osmotic controlled-release OROS (methylphenidate) formulation. J Clin Pharmacol 2000, 40:379–388.
24. Pierce DI, Katsa BK, Buckwalter M, Webster K: Single- and multiple-dose pharmacokinetics of methylphenidate administered as methylphenidate transdermal system or osmotic-release oral system methylphenidate to children and adolescents with attention deficit hyperactivity disorder. J Clin Psychopharmacol 2010, 30:554–564.
Adderall in the treatment of children with ADHD in a controlled laboratory classroom setting. Psychopharmacol Bull 1998; 34:55-60.

Döpfner M, Ose C, Fischer R, Ammer R, Schenag A: Comparison of the efficacy of two different modified release preparations for children and adolescents with attention-deficit/hyperactivity disorder in a natural setting: comparison of the efficacy of Medikinet Retard and Concerta - a randomised, controlled, double-blind multicentre clinical cross-over trial. J Child Adolesc Psychopharmacol 2011, 21:445-56.

Findling RL, Bukstein OG, Melmed RD, Lopez FA, Sallee FR, Arnold LE, Pratt RD: A randomized, double-blind, placebo-controlled, parallel-group study of methylphenidate transdermal system in pediatric patients with attention-deficit/hyperactivity disorder. J Clin Psychiatry 2008, 69:149-159.

Pelham WE, Burrows-Maclean L, Gnagy EM, Fabiano GA, Coles EK, Tesco KE, Chacko A, Wymbys BT, Wienke AL, Walker KS, Hoffman MT: Transdermal methylphenidate, behavioral, and combined treatment for children with ADHD. Exp Clin Psychopharmacol 2005, 13:111-126.

Pelham WE, Manos MJ, Ezelzz CE, Tesco KE, Gnagy EM, Hoffman MT, Onyango AN, Fabiano GA, Lopez-Williams A, Wymbys BT, Caserta D, Chonis TR, Burrows-Maclean L, Monroe G: A dose-ranging study of a methylphenidate transdermal system in children with ADHD. J Am Acad Child Adolesc Psychiatry 2005, 44:522-529.

Arnold LE, Bozzo DR, Hodgkins P, McKay M, Beckett-Thurman L, Greenbaum M, Bukstein O, Patel A: Switching from oral extended-release methylphenidate to the methylphenidate transdermal system: continued attention-deficit/hyperactivity disorder symptom control and tolerability after abrupt conversion. Curr Med Res Opin 2010, 26:129-137.

Bukstein OG, Arnold LE, Langgraf JM, Hodgkins P: Does switching from oral extended-release methylphenidate to the methylphenidate transdermal system affect health-related quality-of-life and medication satisfaction for children with attention-deficit/hyperactivity disorder? Child Adolesc Psychiatry Ment Health 2009, 3:9.

Dirksen SJ, D’Imperio JM, Biedsall D, Hatch SJ: A postmarketing clinical experience study of Metadate CD. Curr Med Res Opin 2002, 18:371-380.

Döpfner M, Götz-Dorsten A, Breuer D, Rothenberger A: An observational study of once-daily modified-release methylphenidate in ADHD: effectiveness on symptoms and impairment, and safety. Eur Child Adolesc Psychiatry 2011, 20:524-5255.

Döpfner M, Breuer D, Walter D, Rothenberger A: An observational study of once-daily modified-release methylphenidate in ADHD: the effect of previous treatment on ADHD symptoms, other externalising symptoms and quality of life outcomes. Eur Child Adolesc Psych 2011, 20:5277-5288.

Rothenberger A, Becker A, Breuer D, Döpfner M: An observational study of once-daily modified-release methylphenidate in ADHD: quality of life, satisfaction with treatment and adherence. Eur Child Adolesc Psychiatry 2011, 20:5257-5265.

Banaschewski T, Coghill D, Santosh P, Zuddas A, Asherson P, Buitelaar J, Danckaerts M, Dopfner M, Faraone SV, Rothenberger A, Sergeant J, Steinhausen HC, Sonuga-Barke EJ, Taylor E: Long-acting medications for the hyperkinetic disorders. A systematic review and European treatment guideline. Eur Child Adolesc Psychiatry 2006, 15:476-495.

Brams M, Mao AR, Doyle RL: Onset of efficacy of long-acting psychostimulants in pediatric attention-deficit/hyperactivity disorder. Postgrad Med 2008, 120:89-98.

Swanson JM, Lerner M, Wigal T, Steinhoff K, Greenhill L, Posner K, Reid J, Wigal S: The use of a laboratory school protocol to evaluate concepts about efficacy and side effects of new formulations of stimulant medications. J Atten Disord 2002, 6(Suppl 1):S73–S88.

Faraone SV, Bederman J, Spencer TJ, Aleardi M: Comparing the efficacy of medications for ADHD using meta-analysis. Med Gen Med 2006, 8:4.

Faraone SV, Buitelaar J: Comparing the efficacy of stimulants for ADHD in children and adolescents using meta-analysis. Eur Child Adolesc Psychiatry 2010, 19:333-364.

Faraone SV, Glatt SJ: A comparison of the efficacy of medications for adult attention-deficit/hyperactivity disorder using meta-analysis of effect sizes. J Clin Psychiatry 2010, 71:754-763.

Peterson K, McDonagh MS, Fu R: Comparative benefits and harms of competing medications for adults with attention-deficit hyperactivity disorder: a systematic review and indirect comparison meta-analysis. Psychopharmacology (Berl) 2008, 197:11-11.

Swanson J, Arnold LE, Kramer H, Hechtman L, Molina B, Hinshaw S, Vitiello B, Jensen P, Steinhoff K, Lerner M, Greenhill L, Abikoff H, Wells K, Epstein J, Elliott G, Newcomb J, Hoza B, Wigal T: Evidence, interpretation, and qualification from multiple reports of long-term outcomes in the multimodal treatment study of children with ADHD (MTA): part II: supporting details. J Atten Disord 2008, 12:15-43.

Swanson J, Volkow N: Pharmacokinetic and pharmacodynamic properties of methylphenidate in humans. In Stimulant drugs and ADHD. Edited by: Solanto MV, Amstein AF, Castellanos FX. New York: Oxford University Press; 2001:259-282.

Coghill D, Soutullo C, d’Aubuisson C, Preus U, Lindback T, Silverberg M, Buitelaar J: Impact of attention-deficit/hyperactivity disorder on the patient and family: results from a European survey. Child Adolesc Psychiatry Ment Health 2008, 2:21.

Döpfner M, Breuer D, Ose C, Fischer R: Modified-release methylphenidate in routine care. Monatschr Kinderheilkd 2011, 159:1119-1125.

Healthcare Improvement Scotland: Difficult times of the Day scale. http://www.healthcareimprovementscotland.org/our_work/mental_health/adhd_services_over_scotland/stage_3_adhd_final_report.aspx. Date accessed 14/1/13.
Author/s:
Coghill, D; Banaschewski, T; Zuddas, A; Pelaz, A; Gagliano, A; Doepfner, M

Title:
Long-acting methylphenidate formulations in the treatment of attention-deficit/hyperactivity disorder: a systematic review of head-to-head studies

Date:
2013-09-27

Citation:
Coghill, D; Banaschewski, T; Zuddas, A; Pelaz, A; Gagliano, A; Doepfner, M, Long-acting methylphenidate formulations in the treatment of attention-deficit/hyperactivity disorder: a systematic review of head-to-head studies, BMC PSYCHIATRY, 2013, 13

Persistent Link:
http://hdl.handle.net/11343/221182

File Description:
Published version