ADHD Atten Def Hyp Disord (2014) 6:49–58
DOI 10.1007/s12402-013-0122-x

REVIEW ARTICLE

The use of actigraphy in the monitoring of methylphenidate versus placebo in ADHD: a meta-analysis

Franco De Crescenzo · Marco Armando · Luigi Mazzone · Mario Ciliberto · Marco Sciannamea · Caroline Figueroa · Luigi Janiri · Digby Quested · Stefano Vicari

Received: 10 August 2013 / Accepted: 18 November 2013 / Published online: 28 November 2013

Abstract Attention-deficit/hyperactivity disorder (ADHD) is the most common neurobehavioral disorder of childhood. There is an increasing need to find objective measures and markers of the disorder in order to assess the efficacy of the therapy and to improve follow-up strategies. Actigraphy is an objective method for recording motor activity and sleep parameters using small, computerized, watch-like devices worn on the body, and it has been used in many clinical trials to assess methylphenidate efficacy and adverse effects in ADHD. Our article aim is to systematically review and perform a meta-analysis of the current evidence on the role of actigraphy in both the detection of changes in activity and in sleep patterns in randomized clinical trials that compared methylphenidate against placebo in the treatment of ADHD. A comprehensive literature search of PubMed/MEDLINE, Scopus, Embase, Cochrane Library, CINHAL and PsycINFO databases was carried out to find randomized clinical trials comparing methylphenidate versus placebo in children with ADHD, using actigraphic measures as an outcome. No start date limit was used and the search was updated until June 2013. The primary outcome measures were 'total sleep time' and daytime 'activity mean'. As secondary outcomes, we analyzed 'sleep onset latency', 'sleep efficiency' and 'wake after sleep onset'. Eight articles comprising 393 patients were included in the analysis. Children with ADHD using MPH compared to placebo have a significant difference of a large effect with a diminishing value in the activity mean. For the total sleep time, we found a significant and large effect in the decrease in sleep in MPH group. This study shows that MPH may effectively reduce mean activity in ADHD children, but it may negatively affect total sleep time.

Keywords Methylphenidate · Actigraphy · Attention-deficit disorder with hyperactivity · Children · Meta-analysis

F. De Crescenzo (✉) · M. Armando · L. Mazzone · D. Quested · S. Vicari
Department of Neuroscience, Bambino Gesù Children's Hospital, IRCCS, Piazza Sant'Onofrio 4, 00100 Rome, Italy
e-mail: decrescenzo.franco@gmail.com

F. De Crescenzo · L. Janiri
Institute of Psychiatry and Psychology, Catholic University of Sacred Heart, Rome, Italy

M. Ciliberto
Department of Radiology, Catholic University, Rome, Italy

M. Sciannamea
Department of Physics, Sapienza University of Rome, Rome, Italy

C. Figueroa
Department of Psychiatry, Warneford Hospital, University of Oxford, Headington, Oxford, UK

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurobehavioral disorder and among the most extensively studied mental disorders of childhood. It is characterized by inattention, including increased distractibility and difficulty in sustaining attention; poor impulse control and decreased self-inhibitory capacity; and motor over activity and motor restlessness and can affect learning, behavior, self-esteem, social skills and family function (Kliegman et al. 2011). ADHD has a lifetime prevalence of 8.1 % (Kessler et al. 2005). The median age of onset is between seven and nine (Kessler et al. 2007) and

95 % of people affected are diagnosed before 12 years old (Kessler et al. 2005). It is highly associated with disability in adulthood, and it causes a substantial economic burden on society, with the 30 % of adult patients receiving a disability pension (Mordre et al. 2012).

The features of ADHD are not yet completely characterized as the diagnosis is made subjectively with diagnostic criteria which vary in different countries (e.g., DSM IV TR criteria are different from ICD 10). There is an increasing need to find objective measures and markers of the disease that overcome the differences in definitions which still exist. It is important to find objective measures for many reasons, including clinical and research purposes, in order to assess the efficacy of the therapy and to thereby improve follow-up strategies.

The treatments most widely used for this condition, alongside the psychosocial and/or the behaviorally orientated treatment—whose efficacy has not been effectively proven though (Sonuga-Barke et al. 2013)—are psychostimulant medications, including methylphenidate (MPH), amphetamine and/or various amphetamine and dextro-amphetamine preparations (Kliegman et al. 2011). MPH is considered as the medication of first choice for children with ADHD in order to reduce inappropriate levels of inattention, impulsivity and hyperactivity (Taylor et al. 2004). It belongs to the class of amphetamines which act by blocking both the dopamine and norepinephrine transporters and enhancing dopamine release from presynaptic terminals in the central nervous system. Dopamine is dysregulated in ADHD (Rosa-Neto et al. 2005; Ludolph et al. 2008), and MRI voxel-based morphometry studies have shown that basal ganglia regions such as the right globus pallidus, the right putamen and the caudate nucleus are structurally affected in children with ADHD. Variations in limbic regions such as the anterior cingulate cortex and amygdala are more pronounced in the untreated population, and treatment seems to have positive effects on brain structure resulting in the recovery of structural deficits (Frodl and Skokauskas 2012). The results from functional studies have been pooled together in a recent meta-analysis (Cortese et al. 2012), which showed in ADHD, relative to comparison subjects, a hypoactivation in the frontoparietal network and in the ventral attentional network, and a hyperactivation in the default, ventral attention, and somatomotor networks.

MPH efficacy has been widely evaluated and demonstrated by various meta-analyses of clinical trials, which used qualitative measures of hyperactivity such as clinical or parent and teacher ratings as the primary outcomes (Hanwella et al. 2011; Van Wyk et al. 2012; Castells et al. 2011; Faraone 2012; Van der Oord et al. 2008; Faraone et al. 2002; Schachter et al. 2001).

Actigraphy is an objective method for recording motor activity and sleep parameters using small, computerized, watch-like devices (actigraphs) worn on the body (usually on the wrist of the nondominant arm). The raw activity scores (e.g., in minute-long epochs) are translated to sleep-wake scores based on computerized scoring algorithms. The main motor activity parameter assessed by actigraphy is the 'activity mean,' which is the mean of raw activity scores recorded by the actigraph and translated to digital counts across a predetermined period of time. This method allows reliable data collection of general or highly specific motor activities for extended time periods without disturbance of everyday activities, and hence reflecting the child's spontaneous behavior (Sadeh 2011). Sleep parameters are derived from nighttime activity scores. The sleep time period considered for the analysis is manually set, and it is normally derived from sleep diaries. Sleep bouts are differentiated from wake bouts by considering the activity as lower than a certain threshold, which is variable and depends on the type of device. Based on that threshold then, computer algorithms generate various measures of sleep parameters: 'total sleep time' (which is the sleep time excluding all periods of wakefulness); 'wake after sleep onset' (which is the periods of wakefulness after the sleep onset); 'sleep onset latency' (which is the time in minutes from getting into bed to actigraphically defined sleep onset, which happens after the first 10 min interval of activity below the threshold set for determining wake); and 'sleep efficiency' (which is the ratio of total sleep time, to nocturnal time in bed). Poor reliability may be due to additional time spent inactive, which may be interpreted as 'sleep' by the actigraph, or to frequent nocturnal arousals, which may cause sleep to be underestimated. The parameter 'total sleep time' is considered as the most reliable (Martin and Hakim 2011).

Over the last two decades, actigraphy has become a major assessment tool, especially in sleep research and sleep medicine with a higher rate of publications when compared to polysomnography (PSG). It is a reliable (Martin and Hakim 2011), valid (Morgenthaler et al. 2007), cost-effective (Sadeh 2011), noninvasive assessment method. In addition to ADHD, it is also used to evaluate motor activity for other medical conditions in addition to ADHD, namely circadian rhythm disorders (Martin and Hakim 2011), autistic spectrum disorder (Hare et al. 2006) and mood disorders (St-Amand et al. 2012; Indic et al. 2012; Ritter et al. 2012), although on this parameter less evidence is available (Quested et al. in preparation).

Actigraphic outcomes reported in the studies have never been reviewed nor are they considered as outcomes in a Cochrane Collaboration protocol published for a systematic review considering MPH efficacy (Storebø et al. 2012). Nonetheless many clinical trials in children use actigraphic

devices. The only meta-analysis currently available is from Cortese et al. (2009), which differentiates subjective (reported by parents or child) and objective parameters (PSG and actigraphy) in observational studies on sleep in ADHD. It showed that children with ADHD have significantly more sleep disturbances than controls.

Our hypothesis is that actigraphy may be a valid measure of the benefits and harms of MPH, by establishing efficacy by the reliable measurement of the mean activity level in ADHD patients and in monitoring its impact on the sleep patterns of patients.

Our study therefore aims to systematically review and quantitatively synthesize the current evidence on the role of actigraphy in the detection of changes in activity and sleep patterns in randomized clinical trials (RCTs) that compared methylphenidate against placebo in the treatment of ADHD. We will not make a distinction among ADHD subtypes, since some studies have not succeeded in finding differences in the activity pattern between them (Dane et al. 2000).

Methods

A comprehensive computer literature search of the PubMed/MEDLINE, Scopus, Embase, Cochrane Library, CINHAL and PsycINFO databases was carried out to find relevant peer-reviewed articles on randomized clinical trials comparing methylphenidate versus placebo in children with ADHD and having actigraphic measures as an outcome. A search algorithm based on a combination of the terms: (a) 'ADHD OR attention deficit OR hyperactivity disorder' AND (b) 'actigrap* OR actimet* OR actograp* OR actomet* OR accelerometer OR motor activity' was used. No start date limit was used, and the search was updated until June 2013. To expand our search, references of the retrieved articles and reviews were screened for additional studies.

All studies or subsets of studies using MPH in an ADHD population and with actigraphic measures as outcomes were eligible for inclusion.

The exclusion criteria were (a) articles not within the field of interest of this review (i.e., studies with no therapy, or with no ADHD population or with no actigraphic outcome); (b) review articles, editorials or letters, comments and conference proceedings; (c) case reports, case series, observational studies and other studies which were not RCTs; (d) studies with a comparison population who used other therapies and not placebo; (e) studies with patients aged more than 18 years; and (f) MPH trials in ADHD patients with a serious concomitant medical illness.

Three researchers (MC, CF and FDC) independently reviewed the titles and the abstracts of the retrieved articles, applying the inclusion and exclusion criteria mentioned above. These three researchers then independently reviewed the full-text version of the articles to confirm their eligibility for inclusion. Disagreements were resolved in a consensus meeting.

Data were extracted independently and entered into RevMan 5.1 software by two review authors (MC, FDC) who also assessed the risk of bias in the included studies using the tool described in the Cochrane Collaboration Handbook as a reference guide (Higgins and Green 2011). We paid particular attention to the adequacy of random sequence generation, allocation concealment and double blinding, and we included only studies with a low or unclear risk of bias in these parameters. For each included study, information was collected concerning the basic study (author names, journal, year of publication, country of origin and type of study), patient characteristics (number of patients with MPH vs. placebo, mean age, gender and diagnosis), methodological aspects of actigraphy (device used, where it was worn, the storage rate of the information done mechanically by the device and in which part of the day the actigraph was used) (Table 1) and intervention. Any final disagreements were resolved by consensus. The primary outcome measures were the analyses of 'total sleep' time and of 'activity mean'. As secondary outcomes, we analyzed 'sleep onset latency', 'sleep efficiency' and 'wake after sleep onset', which are considered less reliable parameters (Martin and Hakim 2011).

Crossover design in clinical trials offers a number of advantages over parallel group trials: each participant acts as his or her own control eliminating between-participant variation, fewer participants are required to obtain the same power and every participant receives the same intervention, which allows the determination of the best intervention for an individual (Higgins and Green 2011). The most important problem is that of carryover in which the intervention given in a period persists and interferes with a subsequent period. In view of the pharmacokinetic properties of MPH (Shram et al. 2012), in particular its short half-life (2.4 h in children), we considered crossover trials suitable for a data analysis, even in those crossover trials in which a washout period was not considered. There is no statistical evidence of changes in actigraphic outcomes in clinical trials of MPH if comparing, within-therapeutic boundaries, different doses (Corkum et al. 2008), formulation (Pelham et al. 2001) or number of times per day administered (Stein et al. 1996), so we did not exclude studies on these bases, but we recorded information on the intervention in the table of included studies. When more than one group using MPH was available for data extraction, we extracted data on the group with the highest doses. When more than one group was considered in the analysis with the same dose of MPH, we combined groups to create

Table 1 Methodological aspects of actigraphic devices in studies included

Included studies	Type of device	Where worn	When recorded	Storage rate used
Uebel et al. (2010)	Actitrac device individual monitoring system	Dominant ankle	8 h from 9 a.m. to 5 p.m.	0, 5 min epoch
Corkum et al. (2008)	Basic mini-motionlogger actigraph, AMI Inc.	Nondominant wrist	24 h	NR
Gruber et al. (2007)	Miniature actigraph AW-64 series	Nondominant wrist	Night time	1 min epoch
Konrad et al. (2005)	Tiny actigraph, Cambridge Neurotechnology Version 2.56	Preferred wrist	First 90 min of each school day and 80 min of neuropsychological assessment	0, 25 min epoch
Schwartz et al. (2004)	Miniature actigraph AW-64 series	Nondominant wrist	Night time	1 min epoch
Swanson et al. (2002)	Basic mini-motionlogger actigraph, AMI Inc.	Nondominant wrist	24 h	1 min epoch
Stein et al. (1996)	NR	Wrist	18 h from 4 p.m. to 8 a.m.	NR
Tirosh et al. (1993)	Actigraph, Ambulatory Monitoring Inc.	Nondominant wrist	Night time	1 min epoch

a single pair-wise comparison as in Higgins and Green (2011).

Data for each study were expressed as standardized mean differences (SMD), since differences between the actigraphic devices and on-storage rate used suggested we should consider them as different measurement scales, using the random effects model which is more conservative than the fixed effects model (Higgins and Green 2011). Qualitative data have been presented descriptively. We used the I^2 index to assess the heterogeneity of effect sizes (Higgins et al. 2003). Its value lies between 0 and 100 and estimates the percentage of variation among effect sizes that can be attributed to heterogeneity. A significant I^2 suggests that the effect sizes analyzed are not estimating the same population effect (Higgins and Green 2011). Following Higgins et al. (2003), we agreed I^2 thresholds of 25, 50 and 75 % to differentiate low, moderate and high heterogeneity. We analyzed crossover trials using the generic inverse variance method in RevMan 5.1 software as described in Higgins and Green (2011). When SMD or standard errors (SE) were not directly reported, we calculated or imputed them following the Higgins technique. In interpreting SMD values, we considered SMD 'small' if <0.4, 'moderate' from 0.4 to 0.7 and 'large' >0.7.

Results

Selected studies

The literature search generated 1,110 articles. Reviewing titles and abstracts, articles were excluded applying the criteria mentioned above: 1,093 studies were excluded because they were not within the field of interest of this review and seventeen articles were retrieved in full text. Of these, two articles were excluded because of duplicate data (Gruber et al. 2006; Ironside et al. 2010); one article was excluded because it was not a RCT (Miller and Kraft 1994); two articles were excluded because they included adult patients aged more than 18 years (Kooij et al. 2001; Boonstra et al. 2007); one RCT was excluded because the comparison was atomoxetine and not placebo (Sangal et al. 2006); one study was not in humans but in rats (Fowler et al. 2010); one was a case report (Lahti et al. 2009); one was a review (Huang et al. 2011); and one was a RCT with MPH on a population of ADHD with fragile X syndrome (Hagerman et al. 1988). One additional study was found screening the references of the included and excluded articles (Tirosh et al. 1993).

Finally, eight articles comprising 393 patients were included in a qualitative and quantitative analysis (Corkum et al. 2008; Pelham et al. 2001; Stein et al. 1996; Tirosh et al. 1993; Uebel et al. 2010; Gruber et al. 2007; Konrad et al. 2005; Schwartz et al. 2004; Swanson et al. 2002) (see Fig. 2). The characteristics of the included studies are presented in Table 2.

Primary outcomes

Effect sizes with 95 % confidence intervals for each parameter from each individual study are shown in Fig. 1. Regarding the primary outcomes, the meta-analysis indicated that children with ADHD using MPH compared to placebo have a significant difference of a large effect with a diminishing value in the activity mean (SMD = −0.77;

Table 2 Table of included studies

Included studies	Methods	Participants	Interventions	Outcomes
Uebel et al. (2010)	Randomized double blind placebo-controlled crossover trial	82 children with ADHD and MPH-IR responders originally, finally 49 children with a mean age of 10 years, 43 males	Two and a half weeks with 6 days of each of Placebo, twice-daily MPH-IR or once-daily extended-release MPH with a mean dose of 22 ± 6 mg	Day-long actigraphy, German ADHD Rating Scale FBB-HKS
Corkum et al. (2008)	Randomized* double blind placebo-controlled crossover trial	28 children of ages 6–12 originally. Finally 21 children (15 males)	1-week baseline, plus 3 weeks randomized to placebo or 5–10 mg MPH or 10–15 mg MPH (depending whether under or above 25 kg), thrice a day	24-h actigraphy, sleep diary, Sleep Disturbances Scale For Children (SDSC), Conners' Parents and Teachers Rating Scale-Revised Short Form(CRS-R: S)
Gruber et al. (2007)	Randomized double blind placebo-controlled crossover trial	37 Children with ADHD (6–12 years) 31 males	1 week of placebo, 1 week of 0.5 mg/kg MPH twice a day	Sleep actigraphy, sleep diary, Cbcl, Conners' Continuous Performance Test (CPT), Clinical Global Impression Scale (CGI)
Konrad et al. (2005)	Randomized* double blind placebo-controlled crossover trial	44 Children with ADHD (8–12 years) 37 males	6-day period. Randomized administration of placebo, 0.25 mg/kg or 0.5 mg/kg MPH (but high never after placebo) twice a day	24-h actigraphy, Teacher Questionnaire, sustained attention task, stop-signal paradigma
Schwartz et al. (2004)	Randomized double blind placebo-controlled crossover trial	44 Children with ADHD (6–12 years) 37 males	1 week of Placebo, 1 week of 0.5 mg/kg MPH twice a day	Sleep actigraphy, Conners' Parents and Teachers Rating Scale-Revised (CRS-R), CGI, Restricted Academic Situation Scale (RASS), Conners' Continous Performance Task (CPT)
Swanson et al. (2002)	Randomized double blind placebo-controlled crossover trial	32 Children with ADHD (7–12), 28 males.	8-h period, every 30-min Placebo, or doses amounting to 18, 36 or 54 mg MPH	24-h Actigraphy, Swanson Kotkin Agler M-Flynn and Pelham rating scale (SKAMP)
Stein et al. (1996)	Randomized triple blind placebo-controlled crossover trial	25 Children with ADHD (6-12 years) 25 males	1-week baseline and 4 weeks with 1 week of each of Placebo, titration, two or three doses from 5 to 20 mg MPH based on weight	Conners' Parents Rating Scale (CPRS), ADD-H Comprehensive Teacher Rating Scale, Child Conflict Index (CCI), Sleep actigraphy, sleep diary, Child Depression Inventory (CDI), Stimulant Side Effects Rating Scale (SSERS), Test of Variables of Attention (TOVA)
Tirosh et al. (1993)	Randomized double blind placebo-controlled crossover trial	Eleven children with ADHD originally, finally ten children (6–12 years), eight males	8 days of Placebo, 8 days of 10 to 15 mg MPH, separated by a 3-day washout interval	Sleep actigraphy, Conners' Teacher Rating Scale

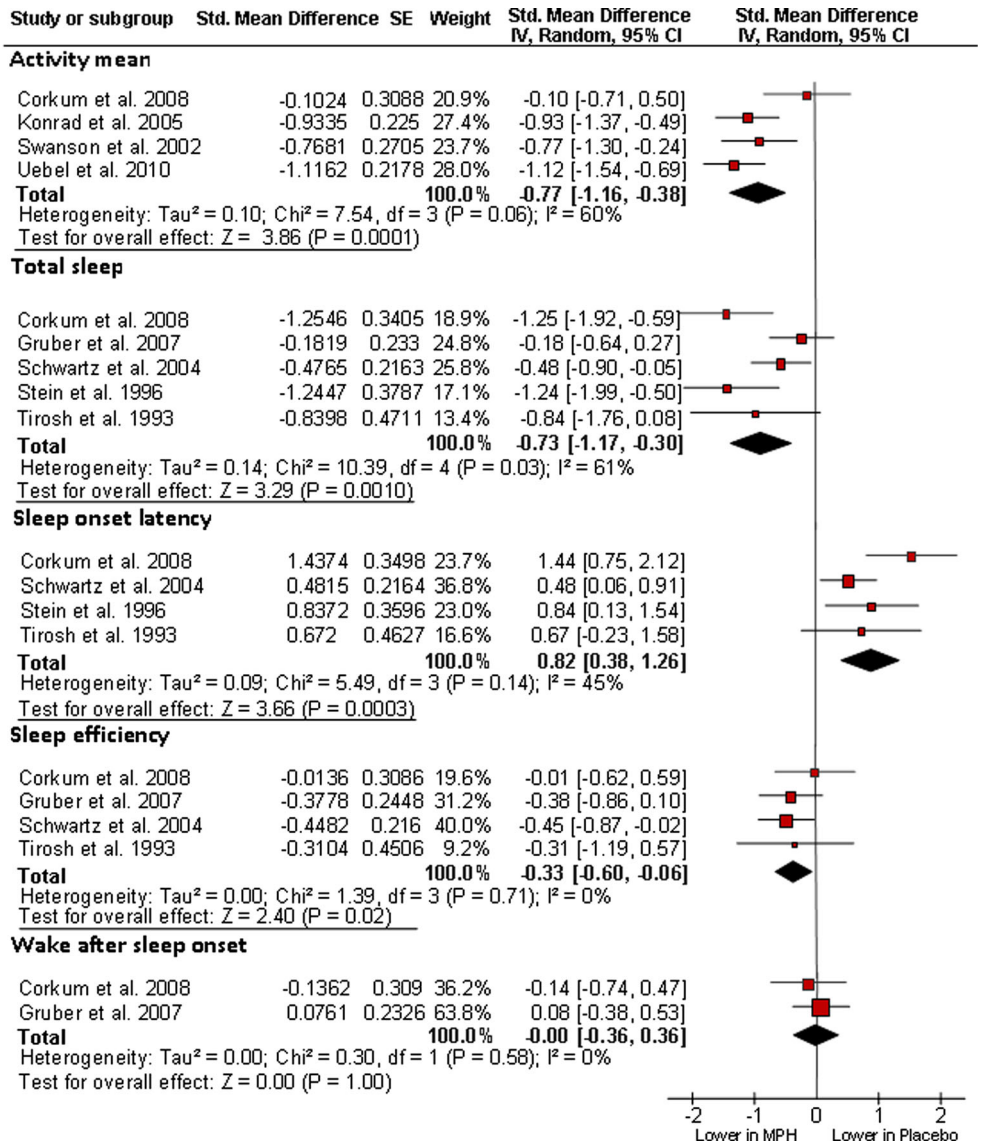

Fig. 1 Analyses of actigraphic outcomes in RCTs using MPH in ADHD children

CI = −1.16, −0.38; $z = 3.86$; $P = 0.0001$; $I^2 = 60$ %). For the total sleep time, the meta-analysis shows a significant and large effect in the decrease in sleep in MPH group with a moderate heterogeneity among the studies (SMD = −0.73; CI = −1.17, −0.3; $z = 3.29$; $P = 0.001$; $I^2 = 61$ %).

Secondary outcomes

The four secondary outcomes considered are all sleep parameters. Actigraphy data show:

(a) that ADHD children taking MPH take significantly longer after getting into bed to falling asleep than placebo (Sleep onset latency: SMD = 0.82; CI = 0.38, 1.26; $z = 3.66$; $P = 0.0003$; $I^2 = 45$ %).

(b) Sleep efficiency, which is the ratio of total sleep time to nocturnal time in bed, is slightly, but significantly diminished in the MPH group compared to placebo (SMD = −0.33; CI = −0.6, −0.06; $z = 2.4$; $P = 0.02$; $I^2 = 0$ %). For the 'wake after sleep onset' outcome, we found only two studies which were comparable, and following the analysis no significant differences resulted (SMD = 0; CI = −0.36, 0.36; $z = 0$; $P = 1.00$; $I^2 = 0$ %).

Discussion

This study shows that MPH can negatively affect total sleep and reduce mean activity in ADHD children. To our knowledge, this is the first meta-analysis assessing actigraphic outcomes to evaluate MPH effects in children with ADHD. Its clinical efficacy is well documented in numerous studies, and it is not the aim of this article to

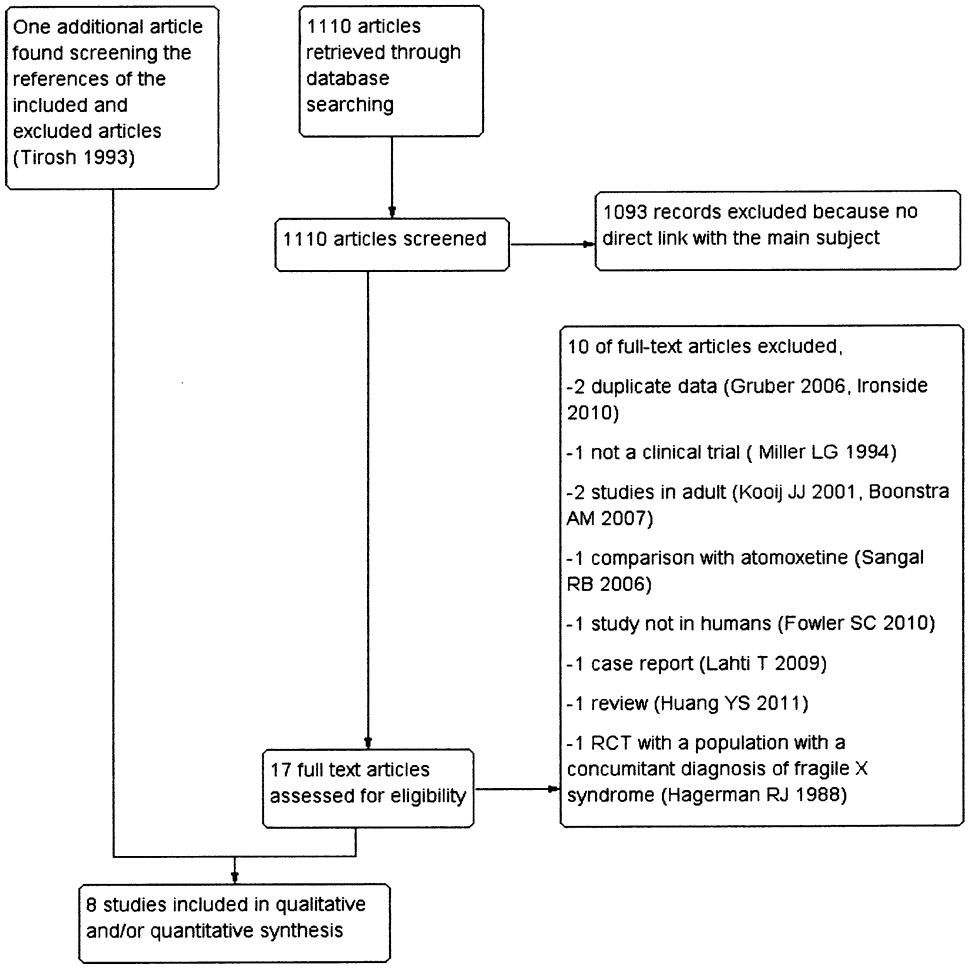

Fig. 2 Flow chart

demonstrate it but rather to consider the use of actigraphy as a tool in the studies, either assessing negative or positive outcomes.

We found a large effect of MPH with a significant difference to placebo in 'mean activity' (SMD $= -0.77$; $P = 0.0001$). The heterogeneity is moderate ($I^2 = 60$ %), due to different settings. In fact, we have to consider that Corkum et al. (2008) utilizes both daytime and nighttime activity, while Uebel et al. (2010), Konrad et al. (2005) and Swanson et al. (2002) consider only daytime activity during structured and unstructured sessions. A subgroup analysis of these three shows a higher homogeneity and a higher effect and level of significance (SMD $= -0.96$; CI $= -1.23$, -0.7; $z = 7.11$; $P < 0.00001$; $I^2 = 0$ %). Stein et al. (1996) also evaluated both daytime and nighttime activity pooled together; however, results were not statistical significant and have not been published. We must therefore interpret the results cautiously, although Stein et al. (1996) have a limited power, and we think it would not have affected the overall results excessively. We preferred to be conservative and to maintain Corkum et al. (2008) in the final analyses, but results would have been very homogeneous without this study. It is interesting that the only two studies, which failed in finding a significant difference in mean activity, were Corkum et al. (2008) and Stein et al. (1996) that used a mean activity from both daytime and nighttime. Swanson et al. (2002) and Konrad et al. (2005) focus their analysis on structured sessions. MPH may thus allow a significant loss of activity in structured sessions, while overall, considering the 24 h, the basal children's motor activity may be preserved. We think that the reduction in the activity mean—but not the 24-h children's motor activity—is desired in ADHD and that it can be interpreted as a proof of MPH efficacy.

Regarding the activity mean measurement, actigraphic studies have up to now failed to find a difference among different ADHD subtypes (Dane et al. 2000), but different studies found a significant difference between ADHD and healthy children (Kam et al. 2011). One possible hypothesis is that hyperactivity underlies all ADHD subtypes, although sometimes not being clinically evident.

Total sleep time seems to be significantly diminished by MPH compared to placebo. Although observing a moderate heterogeneity in the studies ($I^2 = 61$ %), there is a

significant and large effect (SMD = −0.73; $P = 0.001$) that, in view of an already recognized higher sleep disturbances rate among children affected by ADHD (Cortese et al. 2009), may be aggravating the problem. Indeed, sleep problems should be considered as undesired consequences of an otherwise effective treatment of ADHD hyperactivity symptoms. We think that this result is not strong though, since two studies of five (Tirosh et al. 1993, Gruber et al. 2007) fail to demonstrate a significant difference and one (Schwartz et al. 2004) finds a moderate effect. Basically a large effect is only based on Corkum et al. (2008) and Stein et al. (1996).Sleep onset latency (time in minutes from getting into bed to actigraphically detected sleep onset) is the secondary outcome with the largest effect and the highest significance (SMD = 0.82; $P = 0.0003$), but it is not a particularly reliable parameter. We know that actigraphy underestimates sleep onset latency, since actigraphy records as 'sleep onset' the first 10-min interval in which there is activity below a certain threshold (expressed in epochs and varying through the studies), and this implies that some immobile and awake individuals may be considered as sleeping (Cortese et al. 2009). Therefore, although we have a certain amount of evidence, we have to be cautious in saying that ADHD children taking MPH take longer to fall asleep. MPH has a small but significant effect in diminishing sleep efficiency (SMD = −0.33; $P = 0.02$), while we do not have enough evidence for the 'wake after sleep onset'.

A degree of caution should be expressed in the interpretation of our results because our rigorous criteria-based selection led to a somewhat limited number of studies to be included in the meta-analysis. Moreover, some trials had a smaller sample size with a larger standard error and less significance, and we had to impute some standard deviations because they were not published. We did not find significant evidence of allocation concealment, blinding or publication biases in the studies, but there were some dropouts, including sometimes for only actigraphic technical reasons. We also found a moderate heterogeneity in relation to the primary outcomes.

Although noting the concerns expressed above, we think that there is sufficient evidence to observe that actigraphy is able to determine that MPH affects sleep and improves the activity pattern in ADHD children. This may be related to the modifications that MPH can have on the circadian clock—as recently demonstrated in mice (Antle et al. 2012). In humans, a recent RCT showed the beneficial effect of melatonin for sleep problems in ADHD (Mohammadi et al. 2012); however, this effect will need to be replicated in future RCTs as other meta-analyses have not consistently supported the use of melatonin as a hypnotic.

The analysis of actigraphic signal have become very sophisticated and accurate (Martìn-Martìnez et al. 2012), and we think that actigraphy in ADHD may be used as a noninvasive, objective tool—complementary to the clinical criteria—to support the diagnosis and the follow-up.

In this study, we have assessed whether actigraphy shows consistency in the evaluation of side-effects and efficacy of MPH in ADHD children in both the experimental and clinical environments, and these findings open up new perspectives on the treatment of sleep problems in ADHD, which increase with treatment on MPH. Moreover, with DSM-V, the main concept of ADHD will remain unchanged, but some modifications in the criteria will likely lead to an increase in prevalence of the condition (Dalsgaard 2013); this could in turn lead to an increase in the use of MPH and the related sleep problems which need to be resolved.

Acknowledgments MA was supported by a NARSAD Young Investigator Award. This research project would not have been possible without the support of Luke Patrick Moynihan (University College of London), who was abundantly helpful and offered invaluable assistance, support and guidance. We would like to thank also Ann Sharpley (University of Oxford) and Andrea Cipriani (University of Verona), whose work inspired this study.

References

Antle MC, van Diepen HC, Deboer T, Pedram P, Pereira RR, Meijer JH (2012) Methylphenidate modifies the motion of the circadian clock. Neuropsychopharmacology 37(11):2446–2455. doi:10.1038/npp.2012.103

Boonstra AM, Kooij JJ, Oosterlaan J, Sergeant JA, Buitelaar JK, Van Someren EJ (2007) Hyperactive night and day? Actigraphy studies in adult ADHD: a baseline comparison and the effect of methylphenidate. Sleep 30(4):433–442

Castells X, Ramos-Quiroga JA, Bosch R, Nogueira M, Casas M (2011) Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults. Cochrane Database Syst Rev 6:CD007813. doi:10.1002/14651858

Corkum P, Panton R, Ironside S, Macpherson M, Williams T (2008) Acute impact of immediate release methylphenidate administered three times a day on sleep in children with attention-deficit/hyperactivity disorder. J Pediatr Psychol 33(4):368–379

Cortese S, Faraone SV, Konofal E (2009) Sleep in children with attention-deficit/hyperactivity disorder: meta-analysis of subjective and objective studies. J Am Acad Child Adolesc Psychiatry 48(9):894–908. doi:10.1097/CHI.0b013e3181ac09c9

Cortese S, Kelly C, Chabernaud C, Proal E, Di Martino A, Milham MP, Castellanos FX (2012) Toward systems neuroscience of ADHD: a meta-analysis of 55 fMRI studies. Am J Psychiatry 169(10):1038–1055. doi:10.1176/appi.ajp.2012.11101521

Dalsgaard S (2013) Attention-deficit/hyperactivity disorder (ADHD). Eur Child Adolesc Psychiatry 22(Suppl 1):43–48. doi:10.1007/s00787-012-0360-z

Dane AV, Schachar RJ, Tannock R (2000) Does actigraphy differentiate ADHD subtypes in a clinical research setting? J Am Acad Child Adolesc Psychiatry 39(6):752–760

Faraone SV, Biederman J, Roe C (2002) Comparative efficacy of Adderall and methylphenidate in attention-deficit/hyperactivity disorder: a meta-analysis. J Clin Psychopharmacol 22(5):468–473

Faraone SV (2012) Understanding the effect size of lisdexamfetamine dimesylate for treating ADHD in children and adults. J Atten Disord 16(2):128–137. doi:10.1177/1087054710379738

Fowler SC, Zarcone TJ, Levant B (2010) Methylphenidate attenuates rats' preference for a novel spatial stimulus introduced into a familiar environment: assessment using a force-plate actometer. J Neurosci Methods 189(1):36–43. doi:10.1016/j.jneumeth.2010.03.014

Frodl T, Skokauskas N (2012) Meta-analysis of structural MRI studies in children and adults with attention deficit hyperactivity disorder indicates treatment effects. Acta Psychiatr Scand 125(2):114–126

Gruber R, Grizenko N, Schwartz G, Ben Amor L, Gauthier J, de Guzman R, Joober R (2006) Sleep and COMT polymorphism in ADHD children: preliminary actigraphic data. J Am Acad Child Adolesc Psychiatry 45(8):982–989

Gruber R, Grizenko N, Schwartz G, Bellingham J, Guzman R, Joober R (2007) Performance on the continuous performance test in children with ADHD is associated with sleep efficiency. Sleep 30(8):1003–1009

Hagerman RJ, Murphy MA, Wittenberger MD (1988) A controlled trial of stimulant medication in children with the fragile X syndrome. Am J Med Genet 30(1–2):377–392

Hanwella R, Senanayake M, de Silva V (2011) Comparative efficacy and acceptability of methylphenidate and atomoxetine in treatment of attention deficit hyperactivity disorder in children and adolescents: a meta-analysis. BMC Psychiatry 10(11):176. doi:10.1186/1471-244X-11-176

Hare DJ, Jones S, Evershed K (2006) Objective investigation of the sleep–wake cycle in adults with intellectual disabilities and autistic spectrum disorders. J Intellect Disabil Res 50(Pt 10):701–710

Higgins JPT, Green S (2011) Cochrane handbook for systematic reviews of interventions version 5.1.0. The cochrane collaboration. Available from www.cochrane-handbook.org

Higgins JP, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. BMJ 327(7414):557–560

Huang YS, Tsai MH, Guilleminault C (2011) Pharmacological treatment of ADHD and the short and long term effects on sleep. Curr Pharm Des 17(15):1450–1458

Indic P, Murray G, Maggini C, Amore M, Meschi T, Borghi L, Baldessarini RJ, Salvatore P (2012) Multi-scale motility amplitude associated with suicidal thoughts in major depression. PLoS ONE 7(6):e38761. doi:10.1371/journal.pone.0038761

Ironside S, Davidson F, Corkum P (2010) Circadian motor activity affected by stimulant medication in children with attention-deficit/hyperactivity disorder. J Sleep Res 19(4):546–551. doi:10.1111/j.1365-2869.2010.00845.x

Kam HJ, Lee K, Cho SM et al (2011) High-resolution actigraphic analysis of ADHD: a wide range of movement variability observation in three school courses: a pilot study. Healthc Inform Res 17(1):29–37

Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE (2005) Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 62(6):593–602

Kessler RC, Angermeyer M, Anthony JC et al (2007) Lifetime prevalence and age-of-onset distributions of mental disorders in the World Health Organization's World Mental Health Survey Initiative. World Psychiatry 6(3):168–176

Kliegman RM, Stanton B, ST Géme J, Schor N, Behrman E (2011) Nelson textbook of pediatrics, 19th edn. Elsevier Saunders, Philadelphia

Konrad K, Günther T, Heinzel-Gutenbrunner M, Herpertz-Dahlmann B (2005) Clinical evaluation of subjective and objective changes in motor activity and attention in children with attention-deficit/hyperactivity disorder in a double-blind methylphenidate trial. J Child Adolesc Psychopharmacol 15(2):180–190

Kooij JJ, Middelkoop HA, van Gils K, Buitelaar JK (2001) The effect of stimulants on nocturnal motor activity and sleep quality in adults with ADHD: an open-label case–control study. J Clin Psychiatry 62(12):952–956

Lahti T, Leppämäki S, Tani P, Partonen T (2009) Actigraphic recording of manic symptoms induced by methylphenidate. Case Rep Med 2009:286430. doi:10.1155/2009/286430

Ludolph AG, Kassubek J, Schmeck K, Glaser C, Wunderlich A, Buck AK, Reske SN, Fegert JM, Mottaghy FM (2008) Dopaminergic dysfunction in attention deficit hyperactivity disorder (ADHD), differences between pharmacologically treated and never treated young adults: a 3, 4-dihdroxy-6-[18F]fluorophenyl-L-alanine PET study. Neuroimage 41(3):718–727

Martin JL, Hakim AD (2011) Wrist actigraphy. Chest 139(6):1514–1527. doi:10.1378/chest.10-1872

Martín-Martínez D, Casaseca-de-la-Higuera P, Alberola-López S, Andrés-de-Llano J, López-Villalobos JA, Ardura-Fernández J, Alberola-López C (2012) Nonlinear analysis of actigraphic signals for the assessment of the attention-deficit/hyperactivity disorder (ADHD). Med Eng Phys 34(9):1317–1329

Miller LG, Kraft IA (1994) Application of actigraphy in the clinical setting: use in children with attention-deficit hyperactivity disorder. Pharmacotherapy 14(2):219–223

Mohammadi MR, Mostafavi SA, Keshavarz SA, Eshraghian MR, Hosseinzadeh P, Hosseinzadeh-Attar MJ, Kooshesh SM, Chamari M, Akhondzadeh S (2012) Melatonin effects in methylphenidate treated children with attention deficit hyperactivity disorder: a randomized double blind clinical trial. Iran J Psychiatry 7(2):87–92

Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 6(6):e1000097. doi:10.1371/journal.pmed1000097

Mordre M, Groholt B, Sandstad B, Myhre AM (2012) The impact of ADHD symptoms and global impairment in childhood on working disability in mid-adulthood: a 28-year follow-up study using official disability pension records in a high-risk in-patient population. BMC Psychiatry 19(12):174. doi:10.1186/1471-244X-12-174

Morgenthaler T, Alessi C, Friedman L, Owens J, Kapur V, Boehlecke B, Brown T, Chesson A Jr, Coleman J, Lee-Chiong T, Pancer J, Swick TJ (2007) Practice parameters for the use of actigraphy in the assessment of sleep and sleep disorders: an update for 2007. Sleep 30(4):519–529

Pelham WE, Gnagy EM, Burrows-Maclean L, Williams A, Fabiano GA, Morrisey SM, Chronis AM, Forehand GL, Nguyen CA, Hoffman MT, Lock TM, Fielbelkorn K, Coles EK, Panahon CJ, Steiner RL, Meichenbaum DL, Onyango AN, Morse GD (2001) Once-a-day Concerta methylphenidate versus three-times-daily methylphenidate in laboratory and natural settings. Pediatrics 107(6):E105

Ritter PS, Marx C, Lewtschenko N, Pfeiffer S, Leopold K, Bauer M, Pfennig A (2012) The characteristics of sleep in patients with manifest bipolar disorder, subjects at high risk of developing the disease and healthy controls. J Neural Transm 119(10):1173–1184

Rosa-Neto P, Lou HC, Cumming P, Pryds O, Karrebaek H, Lunding J, Gjedde A (2005) Methylphenidate-evoked changes in striatal dopamine correlate with inattention and impulsivity in adolescents with attention deficit hyperactivity disorder. Neuroimage 25(3):868–876

Sadeh A (2011) The role and validity of actigraphy in sleep medicine: an update. Sleep Med Rev 15(4):259–267. doi:10.1016/j.smrv.2010.10.001

Sangal RB, Owens J, Allen AJ, Sutton V, Schuh K, Kelsey D (2006) Effects of atomoxetine and methylphenidate on sleep in children with ADHD. Sleep 29(12):1573–1585

Schachter HM, Pham B, King J, Langford S, Moher D (2001) How efficacious and safe is short-acting methylphenidate for the treatment of attention-deficit disorder in children and adolescents? A meta-analysis. CMAJ 165(11):1475–1488

Schwartz G, Amor LB, Grizenko N, Lageix P, Baron C, Boivin DB, Joober R (2004) Actigraphic monitoring during sleep of children with ADHD on methylphenidate and placebo. J Am Acad Child Adolesc Psychiatry 43(10):1276–1282

Shram MJ, Quinn AM, Chen N, Faulknor J, Luong D, Sellers EM, Endrenyi L (2012) Differences in the in vitro and in vivo pharmacokinetic profiles of once-daily modified-release methylphenidate formulations in Canada: examination of current bioequivalence criteria. Clin Ther 34(5):1170–1178. doi:10.1016/j.clinthera.2012.02.010

Sonuga-Barke EJ, Brandeis D, Cortese S, Daley D, Ferrin M, Holtmann M, Stevenson J, Danckaerts M, van der Oord S, Döpfner M, Dittmann RW, Simonoff E, Zuddas A, Banaschewski T, Buitelaar J, Coghill D, Hollis C, Konofal E, Lecendreux M, Wong IC, Sergeant J (2013) Nonpharmacological interventions for ADHD: systematic review and meta-analyses of randomized controlled trials of dietary and psychological treatments. Am J Psychiatry 170(3):275–289. doi:10.1176/appi.ajp.2012.12070991

St-Amand J, Provencher MD, Bélanger L, Morin CM (2012) Sleep disturbances in bipolar disorder during remission. J Affect Disord 146(1):112–119. doi:10.1016/j.jad.2012.05.057

Stein MA, Blondis TA, Schnitzler ER, O'Brien T, Fishkin J, Blackwell B, Szumowski E, Roizen NJ (1996) Methylphenidate dosing: twice daily versus three times daily. Pediatrics 98(4 Pt 1):748–756

Storebø OJ, Gluud C, Winkel P, Simonsen E (2012) Social-skills and parental training plus standard treatment versus standard treatment for children with ADHD: the randomised SOSTRA trial. PLoS ONE 7(6):e37280. doi:10.1371/journal.pone.0037280

Swanson JM, Gupta S, Williams L, Agler D, Lerner M, Wigal S (2002) Efficacy of a new pattern of delivery of methylphenidate for the treatment of ADHD: effects on activity level in the classroom and on the playground. J Am Acad Child Adolesc Psychiatry 41(11):1306–1314. Erratum in: J Am Acad Child Adolesc Psychiatry 42(2):260

Taylor E, Döpfner M, Sergeant J, Asherson P, Banaschewski T, Buitelaar J, Coghill D, Danckaerts M, Rothenberger A, Sonuga-Barke E, Steinhausen HC, Zuddas A (2004) European clinical guidelines for hyperkinetic disorder—first upgrade. Eur Child Adolesc Psychiatry 13(Suppl 1):I7–I30

Tirosh E, Sadeh A, Munvez R, Lavie P (1993) Effects of methylphenidate on sleep in children with attention-deficient hyperactivity disorder: an activity monitor study. Am J Dis Child 147(12):1313–1315

Uebel H, Albrecht B, Kirov R, Heise A, Döpfner M, Freisleder FJ, Gerber WD, Günter M, Hässler F, Ose C, Poustka F, Fischer R, Banaschewski T, Rothenberger A (2010) What can actigraphy add to the concept of labschool design in clinical trials? Curr Pharm Des 16(22):2434–2442

Van der Oord S, Prins PJ, Oosterlaan J, Emmelkamp PM (2008) Efficacy of methylphenidate, psychosocial treatments and their combination in school-aged children with ADHD: a meta-analysis. Clin Psychol Rev 28(5):783–800

Van Wyk GW, Hazell PL, Kohn MR, Granger RE, Walton RJ (2012) How oppositionality, inattention, and hyperactivity affect response to atomoxetine versus methylphenidate: a pooled meta-analysis. J Atten Disord 16(4):314–324. doi:10.1177/1087054710389989