Practitioner Review: Current best practice in the management of adverse events during treatment with ADHD medications in children and adolescents

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Background: Medication is an important element of therapeutic strategies for ADHD. While medications for ADHD are generally well-tolerated, there are common, although less severe, as well as rare but severe adverse events AEs during treatment with ADHD drugs. The aim of this review is to provide evidence- and expert-based guidance concerning the management of (AEs) with medications for ADHD. Methods: For ease of use by practitioners and clinicians, the article is organized in a simple question and answer format regarding the prevalence and management of the most common AEs. Answers were based on empirical evidence from studies (preferably meta-analyses or systematic reviews) retrieved in PubMed, Ovid, EMBASE and Web of Knowledge through 30 June 2012. When no empirical evidence was available, expert consensus of the members of the European ADHD Guidelines Group is provided. The evidence-level of the management recommendations was based on the SIGN grading system. Results: The review covers monitoring and management strategies of loss of appetite and growth delay, cardiovascular risks, sleep disturbance, tics, substance misuse/abuse, seizures, suicidal thoughts/behaviours and psychotic symptoms. Conclusion: Most AEs during treatment with drugs for ADHD are manageable and most of the times it is not necessary to stop medication, so that patients with ADHD may continue to benefit from the effectiveness of pharmacological treatment. Keywords: ADHD, medication, adverse events, management, recommendations, European.

Introduction
Pharmacological treatments form an important component of the comprehensive multimodal therapeutic strategy for Attention-Deficit/Hyperactivity Disorder (ADHD) (Banaschewski et al., 2006; Taylor et al., 2004). A large body of empirical research has consistently demonstrated the efficacy of ADHD drugs over the short to intermediate term (Faraone & Buitelaar, 2010; Faraone & Glatt, 2010). As with all medications, and some nonpharmacological interventions, adverse events (AEs) can and do occur. Despite empirical reports and clinical experience showing that most of these AEs are mild and/or transitory (Graham & Coghill, 2008), the tolerability and safety of medications used to treat ADHD remains of concern to regulatory authorities as well as to many clinicians and families. This may result in individuals with ADHD being exposed to harm, if AEs are overlooked; or not benefitting from effective medications, if the potential AEs are overestimated.

In the latter case, limiting children’s access to effective treatment for ADHD could have serious implications, given the substantial risks of not treating ADHD (Barkley, 2008).

In 2011, a workgroup of the European Network for Hyperkinetic Disorders (EUNETHYDIS), namely the European ADHD Guidelines Group (EAGG), published the European guidelines on managing adverse effects of medications for ADHD (Graham et al., 2011), based on an extensive research review.

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The aim of the present article was to provide an updated and user-friendlier summary of that research, focusing on practical implications for clinicians who face the uncertainties in the management of AEs during treatment with drugs for ADHD in their day-to-day clinical practice. We also provide a quantitative appraisal of the level of empirical evidence supporting the recommendations.

Methods
We have generated a list of frequently asked questions regarding the management of the AEs during treatment with ADHD drugs and we have searched the published peer-review literature to find evidence-based and practical answers. The questions were generated by Cortese and Holtmann and reviewed and refined by other EAGG members, who are clinicians and/or researchers with expertise in the clinical management of ADHD and across the main areas of research pertaining to this disorder (including epidemiology, neuropsychology, neuroimaging, genetics, pharmacological and nonpharmacological treatment) (see Acknowledgements section).

The previous review by the EAGG (Graham et al., 2011) was based on empirical evidence published until October 2010. Here, we have supplemented this literature by performing an updated search up to 30 June 2012. We searched the following databases: PubMed, Ovid, EMBASE and Web of Knowledge. The list of the search terms is provided in the supplementary online material (Appendix S1). We have limited our search to ADHD drugs licensed in the EU and to studies conducted in children/adolescents (≤18 years). Adverse events during treatment with medications nonlicensed in the EU are briefly discussed at the end of the paper. The practical recommendations on the management of AEs provided in the present review are based on the EAGG 2011 guidelines plus additional more recent guidelines or meta-analyses, where available. The evidence-level of the management recommendations is based on the SIGN grading system (http://www.sign.ac.uk/; see Table S1 in the online supplementary information), which refers to the level of evidence for the recommendation rather than for the association between drug and AE. Grades of recommendation (A–D) follow from the level of evidence (1++ to 4) according to the SIGN grading system (Table S1).

We present below a series of questions and answers that, we hope, will act as a practical implementation of the EAGG Guidelines (Graham et al., 2011) and help clinicians use these guidelines in their clinical practice. The questions and answers are organized according to the specific areas/topics/systems: appetite & growth, cardiovascular system, sleep, tics, misuse/abuse, seizures, suicidal thoughts and behaviours and psychotic symptoms.

Loss of appetite and growth delay
Reduced caloric intake and suboptimal nutrition due to appetite suppression are likely causes of growth suppression (Faraone, Biederman, Morley, & Spencer, 2008). Therefore, loss of appetite and growth delay is considered together in this section. However, evidence on loss of appetite and growth reduction during pharmacological treatment of ADHD is treated separately, since it derives, in most cases, from different studies.

What evidence is there for an association between drugs used to treat ADHD and loss of appetite/growth delay?

Loss of appetite: A meta-analysis including selected randomized controlled trials (RCTs) of methylphenidate immediate release (MPH-IR) in children and adolescents reported that loss of appetite was significantly more frequent in treated individuals than comparisons (mean intergroup difference in prevalence: 30.3%, 95% CI: 18.0–42.6) (Schachter, Pham, King, Langford, & Moher, 2001). “Serious” appetite reduction (although the definition of “serious” was not provided) occurred in 10.5% (95% CI: 7.0–14.0) of treated cases versus 1.8% (95% CI: 0.0–5.5) of individuals on placebo according to parent/self-report, and in 26.4% (95% CI: 7.0–14.0) of treated subjects versus 20.3% (95% CI: 14.6–26.1) of those in the placebo arm according to teacher/staff reports (we note the high rate of AEs in the placebo arm). Of note, the mean dosage varied across studies and was generally quite low (up to 0.6 mg/kg body weight, once or twice daily). Moreover, studies included in the meta-analysis lasted, on average, 3 weeks; hence, it is not possible to draw evidence on possible attenuation of appetite loss over time. No meta-analyses or systematic reviews are available regarding the frequency of appetite reduction with long-acting MPH formulations or other psychostimulants. In a double-blind comparison of placebo, MPH-IR three times/day and OROS MPH once/day, appetite reduction was found in 24% of individuals treated with MPH-IR, 18% of those assigned to OROS methylphenidate, and 4% of individuals in the placebo condition (Pelham et al., 2001), with a significant difference between each formulation and placebo (p = 0.001 and p = 0.013, respectively), but not between the two formulations. In another study, appetite reduction was significantly greater in subjects treated with OROS MPH than in those assigned to placebo (p < 0.05). In addition, the proportion of subjects who reported severe decreased appetite increased as OROS MPH dose increased from 18 mg/day to 54 mg/day (p < 0.05) (Stein et al., 2003).

As for atomoxetine (ATX), a meta-analysis of RCTs in children showed that 15.4% (95% CI not provided) of treated cases and 4.1% of participants in the placebo arm presented with appetite decrease
Appetite reduction following treatment initiation with an ADHD drug often attenuates with time (Adler et al., 2011). To help limit appetite reduction, the EAGG guidelines (Graham et al., 2011) recommend giving medication after meals, rather than before. This is indirectly supported by evidence from one study that found no significant difference in behavioural and cognitive measures of efficacy when MPH-IR was given either with breakfast or 30 min before breakfast (Swanson, Sandman, Deutsch, & Baren, 1983). EAGG also suggests encouraging the use of high-calorific snacks and late evening meals. The EAGG guidelines (Graham et al., 2011) also suggest that drug holidays may be useful in managing loss of appetite. However, the EAGG advises that further evidence is needed on the efficacy of drug holidays in reducing AEs, including appetite reduction and growth retardation. To date, only one randomized trial showed a trend ($p = 0.08$) for an association between drug holidays on the weekend and less interference on appetite (Martins et al., 2004). The EAGG suggests that the risk-benefit balance of drug holidays during weekend must be taken into account and better investigated. Evidence on the beneficial effects on appetite of stopping medication during longer drug holidays (e.g., summer holidays) to allow for catch-up growth is mixed (Faraone et al., 2008).

There is not enough good-quality evidence to recommend switching to a different class or formulation to reduce appetite loss and growth delay, although this may be effective in certain cases and has been recommended by the American Academy of Child
and Adolescent Psychiatry in their practice parameter (Pliszka, 2007) as a general strategy to manage AEs with ADHD drugs. Current guidelines do not specify the length of time after which it is suggested to switch to another medication.

If, despite the implementation of the previous management strategies, weight and/or height values are below critical thresholds, a referral to the pediatric endocrinologist or growth specialist is warranted. Current data do not support specific guidance indicating what magnitude of height or weight gain deceleration should trigger such a referral. Clinicians can, however, follow the medical guidelines concerning referral for short stature and consideration of growth hormone supplementation in adults and children, which are as follows (Gharib et al., 2003):

1. Height: 1.5 standard deviations (SDs) below the average of mother's and father's height;
2. Height: 2 SDs below the population mean plus 1-year height velocity 1 SD below the mean, or a 1-year decrease of 0.5 SDs;
3. 1-year height velocity 2 SDs below the mean, or 2-year height velocity 1.5 SDs below the mean.

It is important to remember that the SD charts are based on distribution of data above and below a mean value; for example, −2 SDs corresponds to ~3rd percentile.

Cardiovascular adverse events
What evidence is there to support an association between drugs used to treat ADHD and cardiovascular events?

Controlled (with placebo or untreated comparisons) studies showed possible increases in blood pressure (BP) and heart rate (HR) in the short term with use of short-acting and long-acting psychostimulants, as well as ATX (recently systematically reviewed by Hammerness, Perrin, Shelley-Abrahamson, & WiJens, 2011 and Graham & Coghill, 2008). Studies in the 1970s and 80s on MPH-IR showed dose-dependent significant increases in BP and/or HR (Hammerness et al., 2011). Subsequent controlled studies have confirmed these findings hold true for long-acting psychostimulant and ATX (Graham & Coghill, 2008). Although in most individuals, BP and HR changes are minor [average increases of 1–4 mmHg for systolic and 1–2 mmHg for diastolic pressure and 1–2 beats per minute (bpm) in HR], in a subset of patients (5–15%) increases in BP and HR may be above the 95th percentile (Hammerness et al., 2011). However, empirical evidence shows that most outlier values are sporadic and are not consistently found during treatment (Hammerness et al., 2011).

Studies extending up to 24 months have shown that these minor but statistically significant increases in BP and HR persist over time (Hammerness et al., 2011).

Summary for loss of appetite & growth delay
1. MPH and ATX are associated with loss of appetite in the short term. Further evidence is needed on the effect on appetite reduction in the mid- and long-term. More evidence is also necessary to establish possible differences in terms of appetite reduction among different drug classes, formulations and doses.
2. Psychostimulant and ATX use may be associated with delays in height and weight gain. Growth deficit is dose-dependent and reversible after treatment cessation and does not seem to differ between psychostimulant classes.
3. The management of appetite reduction includes:
   (i) Monitoring appetite, weight, height and body mass index (BMI) every 6 months.
   (ii) Differentiating between pretreatment eating problems and medication-induced eating problems.
   (iii) Giving medication after meals, rather than before.
   (iv) Encouraging the use of high-calorific snacks and late evening meals.
   (v) Possible further options such as: reducing the dose or switching to an alternative class or formulation; discontinuing medication on weekends to prevent weight loss or longer drug holidays to allow for catch-up growth.
   (vi) Referring to paediatric endocrinologist/growth specialist if height and weight values are below critical thresholds.

Limited evidence is available beyond 24 months. The 10-year follow-up of the MTA study (Vitiello et al., 2012) found no effect of psychostimulant treatment on either systolic or diastolic BP; however, use of psychostimulant medication was associated with a higher HR at years 3 and 8. In an Australian cohort of children with ADHD followed up for 14 years, psychostimulant use was associated with a significant increase in diastolic BP, but not in systolic BP and HR (Smith, Jogeling, Hartmann, Russel, & Landau, 2012)

Empirical evidence does not support an association between psychostimulant use and clinically significant changes in electrocardiographic parameters, including PR, QRS and QT intervals (Hammerness et al., 2011). A particular concern is that even
small but persistent BP and/or HR increases may lead, in the long term, to increased risk for serious cardiovascular events, including sudden cardiac death, acute myocardial infarction and stroke. In 2006, the FDA stated that no definitive conclusions could be made regarding a possible association between psychostimulant use and serious cardiovascular events, because of methodological issues and the uncertainties inherent to the AE Reporting System (Villalba & Racoosin, 2006). Apart from one study (Gould et al., 2009), with possible methodological issues (Johnson, 2010), available epidemiological studies, summarized by Hammerness et al. (2011), have not shown a significant association between ADHD drugs and serious cardiovascular events. A recent large study (Cooper et al., 2011) of 1,200,438 children and young adults between the ages of 2 and 24 years found no evidence that current use of a medication for ADHD was associated with an increased risk of severe cardiovascular events (sudden cardiac death, acute myocardial infarction, and stroke), although the upper limit of the 95% CI (=0.31–1.85) indicated that a doubling of the risk could not be ruled out. Possible underreporting and rare deaths with the initiation of the medication remain of course reasons for concern. Another large study (Habel et al., 2011) in 443,198 adults and an additional one (Schelleman et al., 2011) in 241,417 children (3–17 years) concur with the previous one (Cooper et al., 2011) confirming that ADHD drugs use is not associated with increased risk of severe cardiovascular events.

**How should I assess cardiovascular risk before and during treatment with ADHD drugs?**

The EAGG recommends that patients being considered for ADHD medication should have a clinical assessment including identification of any known heart disease, any history of syncope with exercise, and any family history of sudden unexpected death under the age of 40 years. HR and BP should be taken at baseline and repeated every 3–6 months. Both should be measured in the patient at rest. If the first measure is elevated (pulse rate >100 bpm, systolic or diastolic BP >95th percentile), it should be repeated at least twice, within 10 min. The EAGG suggests using age-adapted cuff sizes for BP measurement and height-adjusted BP percentiles as proposed by the European Society of Hypertension (Parati et al., 2008). Where persistent tachycardia (resting heart rate >110 bpm) or a history suggestive of arrhythmia or familial risk is identified, it is appropriate to request a 24-hr ECG. This should be read and reported by an experienced paediatric cardiologist.

The issue of the utility of performing an electrocardiogram (ECG) before starting treatment for ADHD has been extensively debated. In 2008, the American Heart Association (Vetter et al., 2008) recommended ECG as a routine procedure before starting treatment with an ADHD drug. However, there is no evidence that ECG screening is either cost-effective or appropriate to prevent sudden death in the paediatric population (Denchev, Kaltman, Schoenbaum, & Vitiello, 2010), and actually the recommendation by the American Heart Association was changed soon after its first release as follows:

It is reasonable for a physician to consider obtaining an ECG as part of the evaluation of children being considered for stimulant drug therapy, but this should be at the physician’s judgment, and it is not mandatory to obtain one. Treatment of a patient with ADHD should not be withheld because an ECG is not done. The child’s physician is the best person to make the assessment about whether there is a need for an ECG.

(American Academy of Pediatrics/American Heart Association, 2008)

Accordingly, the EAGG states that there is no current evidence to suggest an incremental benefit for routine ECG assessment prior to initiation of ADHD drugs. A routine ECG at baseline and during treatment is not recommended in the absence of specific indications from the personal or family history or the physical examination. This concurs with another recent recommendation from North America (Hammerness et al., 2011). We note that according to a recent survey in the US, only 15% of paediatricians declared to ask systematically for an ECG before initiating psychostimulant treatment (Leslie et al., 2012).

The EAGG points out that for ADHD patients without a known heart disease, the ADHD specialist is the appropriate individual to evaluate risk-benefit and make recommendations for pharmacological treatment. For ADHD patients with known heart disease, the ADHD specialist remains the appropriate professional to make recommendations for ADHD drugs, although consultation with a heart specialist may be required. For ADHD patients where the history or examination is suggestive of previously unrecognized heart disease and/or risk for sudden death, a referral is warranted to a heart specialist.

**How should I manage cardiovascular risk during treatment with ADHD drugs?**

Following BP measures at baseline or at follow-up (three times within 10 min, in a patient seated and at rest), if age-adjusted values are <95th percentile according to national norms, medication for ADHD can be started/continued. If BP values are >95th percentile in all three measures, the EAGG suggests using age-adapted cuff sizes for BP measurement and height-adjusted BP percentiles as proposed by the European Society of Hypertension (Parati et al., 2008). Where persistent tachycardia (resting heart rate >110 bpm) or a history suggestive of arrhythmia or familial risk is identified, it is appropriate to request a 24-hr ECG. This should be read and reported by an experienced paediatric cardiologist.

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started/continued. In the latter case, if a 24-hr BP measurement confirms hypertension [defined as systolic and/or diastolic BP >95th percentile by the National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents (2004)], further assessment with ECG and echocardiography is warranted to rule out secondary causes of arterial hypertension. Should a second 24-hr BP measurement confirms pathological (i.e., >95th percentile) values of BP, a diagnosis of hypertension should be made and an appropriate treatment for this condition should be started. If, a second 24-hr BP measurement is not pathological, treatment for ADHD can be started or continued. Whenever, following appropriate specialist treatment of hypertension, BP values are <95th percentile, treatment for ADHD can be started or continued. If BP values are still >95th percentile, medication treatment for ADHD should not be started or should be discontinued.

The EAGG also points out that occasional palpitations are not necessarily a cause for concern, but persistent tachycardia may be due to arrhythmia and needs investigation by a paediatric cardiologist. There is no evidence available to support decision-making with respect to the treatment of children with ADHD and congenital heart disease. In such cases, the EAGG recommends a full and frank discussion between the family, the ADHD specialist and a paediatric cardiologist. It is, however, the case that most children with cardiac problems, once stabilized by the paediatric cardiologist, may be treated with ADHD medications (Vetter et al., 2008).

### Sleep disturbance

**What is the evidence for an association between drugs used to treat ADHD and sleep disturbance?**

A precise answer to this question is hampered by the fact that the term “sleep disturbance” is often used to refer to different clinical conditions. Moreover, other related terms such as “insomnia” have been used without a standard and explicit definition across studies.

Considering studies investigating subjective complaints of “sleep problems”, the meta-analysis by Schachter and colleagues (2001), including selected RCTs of MPH-IR, concluded that insomnia was more frequent in those treated with MPH-IR versus those on placebo [average intergroup difference in prevalence: 17.0% (95% CI: 8.3–25.8%)]. As the studies that were included lasted, on average, only three weeks, one cannot draw evidence on possible attenuation of insomnia with time. Moreover, the included studies were rather heterogeneous in terms of dose-scheduling protocols (e.g., inclusion of a dose of medication in the early evening), which is relevant, since, in some individuals, sleep disturbance may be related to a rebound effect (i.e., increase over base-line values in ADHD symptoms when the medication wears off), rather than to medication per se (Konofal, Lecendreux, & Cortese, 2010). Although there is evidence that a third late afternoon dose of MPH-IR does not disrupt sleep in the majority of children, (Kent, Blader, Koplewicz, Abikoff, & Foley, 1995; Pelham et al., 2001; Stein et al., 1996), MPH may induce problems to fall asleep in individual cases.

No meta-analyses are currently available on the effects of long-acting MPH or other psychostimulant formulations on sleep. In a double-blind comparison of placebo, MPH-IR given three times/day, and OROS MPH once/day, no significant differences in sleep quality were seen between placebo and either drug or between the two active drugs (Pelham et al., 2001).

### Summary for cardiovascular AEs

1. In the short term, psychostimulant medications and ATX may increase BP [average increase: systolic: 1–4 mmHg; diastolic: 1–2 mmHg] and heart rate (average increase: 1–2 bpm). A minority of individuals (5–15%) may present with increases to above the 95th percentile in blood at a given assessment, although persistent elevations over several assessments are much more infrequent. Increases in BP or heart rate may, however, persist in the long term during prolonged treatment.

2. There is no evidence supporting that ADHD drugs are associated with significant changes in electrocardiographic values, including QT interval. There is no evidence to support a significant association between ADHD drugs and severe cardiovascular events (sudden cardiac death, acute myocardial infarction, and stroke).

3. Before starting an ADHD medication, the prescribing specialist should:

   (i) Conduct a clinical interview to detect any cardiovascular risk factor

   (ii) Measure baseline heart rate and BP and repeat the measure every 3 of 6 months.

   (iii) Perform an auscultation to identify any murmurs.

   (iv) Make a referral for further assessment as indicated.

   (v) A systematic electrocardiogram is not mandatory and should only be conducted when specifically indicated.

   (vi) The algorithm to manage adverse cardiovascular events suggested by the EAGG is shown in Figure 1.

   Highest level of recommendation for the management of cardiovascular risk (SIGN system): D (expert opinion).
Studies on the relationship between psychostimulants and “sleep disturbance” assessed with objective methods [such as polysomnography (PSG) and actigraphy] have reported inconsistent findings across several objective parameters (Stein, Weiss, & Hlavaty, 2012). Indeed some studies actually suggest a beneficial effect of MPH on sleep parameters (Huang, Tsai, & Guilleminault, 2011; Konofal et al., 2010). In addition, one study showed that MPH dosed four or five times daily to avoid rebound effect led to a later bedtime, later sleep onset, and reduction in sleep duration, but was also associated with more consolidated sleep (Boonstra et al., 2007). The heterogeneity in research findings on the impact of psychostimulants on sleep may be explained by several factors, including variations in the length of the trial, when the stimulant is administered, the dose of stimulant, and whether the child has just started medication, or whether they have been on medication for an extended period of time (Stein et al., 2012). Pooling the results from studies on the effect of stimulants on sleep is challenging given their heterogeneity in terms of class of drug, formulation, dose and schedule.

Looking beyond this inconsistent evidence, clinical experience suggests that the effects of psychostimulants on sleep vary considerably from patient to patient: while some patients with ADHD are able to get to sleep easily within just a few hours of taking a dose of psychostimulant, others need an interval of 6–8 hr.

As for ATX, the above-mentioned meta-analysis of RCTs in children showed that 1.9% (CI not provided) of treated cases and 1.0% of participants in the placebo arm presented with insomnia (p = 0.21); in contrast, somnolence was found in 9.9% and 4.6% of treated and placebo-assigned participants respectively (p < 0.001, significant) (Cheng et al., 2007). A head-to-head comparison study of MPH given three times/day and ATX given twice daily showed that MPH increased sleep-onset latency significantly more than did ATX (p < 0.001), considering both actigraphic and PSG data. Moreover, both child diary and parental reports indicated a better quality of sleep with ATX compared with MPH. Both medications decreased night-time awakenings, but the decrease was significantly greater with MPH (p < 0.002) (Sangal et al., 2006).

Figure 1 Recommendations for blood pressure (BP) monitoring and management in patients with ADHD before starting and/or during a treatment with ADHD medications. (Reproduced with permission of Cambridge University Press; Hamilton, Rosenthal, Hulpke-Wette, Graham, & Sergeant, 2012)
How should I monitor sleep disturbances during treatment with ADHD drugs?

Since children with ADHD may present with sleep disturbance even before treatment with medication, the EAGG guidelines recommend that sleep be carefully assessed at baseline, before medication is initiated, to avoid ascribing sleep disturbance to medication when, in fact, it is due to ADHD per se.

Based on the results of a meta-analysis that explored the nature of sleep disturbances in children with ADHD (Cortese, Faraone, Konofal, & Lecendreux, 2009), inquiry during the baseline as well as the follow-up visit should focus on: bedtime resistance, sleep-onset difficulty, night awakenings, difficulty with morning awakenings, sleep-breathing disorder and daytime sleepiness. If possible, specific sleep questionnaires for children, such as the Children’s Sleep Habits Questionnaire (CHSQ) (Owens, Spirito, & McGuinn, 2000), as well as sleep diaries completed by parents and patients, should be used to complement the clinical interview. Based on preliminary evidence pointing to a possible association between ADHD and restless legs syndrome (RLS) (Cortese et al., 2005), it is also recommended to screen RLS using the proposed criteria in children (Allen et al., 2003). Objective investigation of sleep by means of PSG is indicated if there is a suspicion of sleep-breathing disorder, episodic nocturnal phenomena, limb movements and unexplained excessive daytime sleepiness (Konofal et al., 2010).

How should I manage sleep disturbance during treatment with ADHD drugs?

The clinician should begin by reviewing the nature and history of the sleep disturbance and the efficacy of medication. Sometimes medication can be reduced or stopped; more intensive behaviour therapy may achieve good results for ADHD control even without medication. If continued medication is desirable, sleep hygiene and behaviour techniques are likely to be a first step. These may include: stimulus control (bed should be used for sleep only); adjusting bed time to the estimated sleep onset; avoiding TV, screens or bright light on settling; preventing eating around bedtime and once in bed; discouraging the use of telephones, radios, music once in bed; avoiding drinks containing caffeine; allowing the child to get up for a short period of time if unable to sleep; avoid co-sleeping; encouraging the child to use their own bed. If behavioural measures are insufficient to improve sleep adequately (or are already in use), the clinician should review the likely cause of insomnia, including RLS (monitoring ferritin levels in the evening and considering iron supplementation if needed) and periodic limb movements of sleep. If sleep difficulties appear to be related to a return of restlessness once medication effects have worn off, the clinician can consider adding a small dose of short-acting psychostimulants in the evening (Konofal et al., 2010). If the likely cause is persisting psychostimulant action, the clinician should consider reducing psychostimulant levels in the evening or switch to a shorter-acting preparation. Based on evidence from a RCT (Weiss, Wasdell, Bomben, Rea, & Freeman, 2006) and an open-label study (Tjon Pian Gi, Broeren, Starreveld, & Versteegh, 2003), melatonin (e.g., short-acting melatonin with dim light; adjusting bed time and time of dose accordingly) may represent an effective alternative to reduce sleep-onset delay associated with MPH when the clinician, the family and the patient do not wish to switch to another class or agent. Another RCT (van der Heijden, Smits, Van Someren, Ridderinkhof, & Gunning, 2007) has shown that melatonin is effective also for the treatment of sleep-onset delay in medication-naïve children with ADHD. Based on the length of treatment in the aforementioned available controlled studies, a reassessment of sleep-onset difficulties after 1 month of melatonin treatment is warranted. Alternatively, the clinician can consider substituting a nonpsychostimulant medication (ATX or guanfacine). Given the evidence that suggests that ATX may more often lead to somnolence than insomnia, switching to ATX may be warranted in cases of sleep-onset delay. In this case, ATX may be given once daily in the evening, since this schedule is associated with significantly less AEs, including somnolence, than morning dosing (Block et al., 2009).

Tics

What is the evidence for an association between drugs used to treat ADHD and tics?

Psychostimulants increase dopamine levels in the synaptic cleft. It has been suggested that increased dopamine activity in the basal ganglia underlies the pathogenesis of tics (Albin, 2006). Therefore, psychostimulants might, from a theoretical standpoint, exacerbate tic severity. However, although the Summary of Product Characteristics of several ADHD medications used to include tics as a contraindication for ADHD drugs use (Physicians’ desk reference, 2007), tics are no longer a contraindication for the use of ADHD drugs in EU, but caution is recommended (European Medicines Agency, 2010). A meta-analysis (Bloch, Panza, Landeros-Weisenberger, & Leckman, 2009) including nine double-blind, randomized, placebo-controlled trials examining the efficacy of medications in the treatment of ADHD in children with comorbid tic (total: 477 subjects) concluded that: (a) there is no evidence that MPH worsens tic severity in the short term; (b) supra-therapeutic doses of dextroamphetamine worsen tics; (c) ATX significantly improves comorbid tics. However, we point out that these conclusions

Summary for sleep disturbance

1. Sleep disturbance may be associated with use of ADHD drugs, although the precise nature of sleep disturbances and the strength of the relationship need to be established. There is no extensive evidence for differential effects on sleep of different classes or formulations.

2. The clinician is advised to screen for possible sleep disturbances, by means of clinical interview or sleep questionnaires and sleep diaries, before starting pharmacological treatment and at each follow-up visit. Objective investigation of sleep with polysomnography is indicated if there is a suspicion of sleep-breathing disorder, episodic nocturnal phenomena, limb movements and unexplained excessive daytime sleepiness.

3. The management of sleep problems during treatment with ADHD drugs should include:
   (i) Monitoring.
   (ii) Consider if it is possible to stop the medication.
   (iii) Implement sleep hygiene.
   (iv) If behavioural measures are insufficient and it is not convenient to stop medication, review the possible causes of sleep problems:
      (a) Treat RLS.
      (b) If rebound effect with psychostimulants: add small doses of short-acting psychostimulants in the evening.
      (c) If psychostimulant is the current treatment: consider reducing dose, alternative classes or formulations of psychostimulants, or ATX.
   (v) Consider adding melatonin.

Highest level of recommendation for the management of sleep-onset delay (SIGN system): A (evidence rated as 1+) for melatonin RCTs (Weiss, Wasdell, Bomben, Rea, & Fredman, 2006; van der Heijden, Smits, Van Someren, Ridderinkhof, & Gunning, 2007) and switch to ATX (Block et al., 2009); D (expert opinion) for other recommendations.

Summary for tics

Methylphenidate and dextroamphetamine may worsen tics. Atomoxetine may significantly improve comorbid tic symptoms.

The management of tics should include the following:
1. Observation of intensity of tics over a 3 months period before any decision regarding ADHD treatment.
2. Dose reduction.
3. Substitution.
4. If the previous measures are not effective, an antipsychotic (or tiapride, sulpiride or clonidine) can be added to control tics.

Highest level of recommendation for the management of tics (SIGN system): D (expert opinion).
Risk for substance use disorders (SUD) and misuse/abuse of ADHD drugs

In the literature, the relationship between use of ADHD drugs and risk for future SUDs is sometimes treated alongside, and sometimes confused, with the risk of abuse and misuse of ADHD drugs. We keep these concepts separate and provide here the following definitions to guide the reader:

1. Substance use disorder: According to the current DSM-IV criteria (American Psychiatric Association, 2000), SUD includes substance abuse and substance dependence. The former refers to a maladaptive pattern of nonmedical use of substances leading to functional impairment and/or risks over the past 12 months, while the latter implies the presence of drug tolerance, preoccupation with drug seeking and drug taking, and continued use despite knowledge of risks and despite repeated attempts to stop.

2. Misuse: the use of a drug (in this case an ADHD drug) for a purpose not consistent with legal or medical guidelines (e.g., the use of psychostimulants to achieve a ‘high’ or for other reasons, such as to stay awake or aid weight loss); use of drug dosages different than those prescribed is also referred to as misuse.

We separately consider the evidence on the relationship between ADHD drugs use and risk of future SUD (for any substance) and abuse as well as misuse of ADHD drugs.

What is the evidence for an association between drugs used to treat ADHD and a risk of future SUDs?

Before focusing on the answer to this question, we remind the reader that children with ADHD are significantly more likely to develop SUDs in adolescence and adulthood than children without ADHD (Charach, Yeung, Climans, & Lillie, 2011). Meta-analytic evidence suggests a 1.5-fold increase to develop any SUD and a nearly three times higher risk for nicotine dependence in ADHD samples (Lee, Humphreys, Flory, Liu, & Glass, 2011). Shared neurobiological influences for ADHD and SUD may, among others, comprise dysfunctional dopaminergic neurotransmission, deficits in response inhibition including abnormalities of the reward circuitry and genetic factors (Prodl, 2010; Lee et al., 2011). In addition, the relation between ADHD and SUD is very likely to be moderated by comorbid conduct and oppositional defiant disorders, but only few studies with highly variable methods have addressed this issue (Lee et al., 2011; Serra-Pinheiro et al., 2012).

There is currently no systematic empirical evidence that treatment with psychostimulants increases the risk for ADHD children to develop later SUD. Rather, meta-analytic evidence from six studies suggested that psychostimulant therapy in childhood might be associated with a reduction in the risk for subsequent drug and alcohol use disorders (Wilens, Faroone, Biederman, & Gunawardene, 2003). The pooled estimate of the odds ratio indicated a 1.9-fold reduction (95% CI: 1.1–3.6) in risk for SUD in ADHD youths who were treated with psychostimulants compared with youths who did not receive pharmacotherapy for ADHD. The effect seemed stronger when assessed in adolescence (OR: 5.8) than in adulthood (OR: 1.4). Regarding age at initiation of psychostimulant treatment, there is some evidence to suggest that early age at initiation of MPH treatment in children with ADHD may have beneficial long-term effects on later substance abuse (Mannuzza et al., 2008). A more recent 10-year prospective follow-up study in 140 boys with ADHD revealed no evidence that psychostimulant treatment increases or decreases the risk for subsequent SUD in children and adolescents with ADHD, when they reach young adulthood (Biederman et al., 2008).

What is the evidence about abuse and misuse of ADHD drugs?

Regarding misuse of ADHD drugs, a systematic review of 21 studies indicated that past year prevalence of psychostimulant misuse ranged from 5% to 9% in grade school and high school-age children and 5% to 35% in college-age individuals (Wilens et al., 2008). These data refer to the general population, not ADHD individuals in particular. Data from a controlled 10-year follow-up study (Wilens, Gignac, Swezey, Monuteaux, & Biederman, 2006) reported that 22% of the ADHD group compared with 5% of a control group, who were receiving psychotropics for reasons other than ADHD, misused their medications (including psychostimulants). In a review of the literature, the following risk factors for ADHD drug misuse were identified: conduct disorder, substance use disorder, use of an immediate-release psychostimulant and male gender (Faraone & Wilens, 2007). A further study showed that patients who had been prescribed psychostimulants for ADHD in elementary school were not at higher risk for psychostimulant or other drug misuse use during college compared with participants who were never prescribed psychostimulant medication (McCabe, Teter, & Boyd, 2004).

With respect to abuse, data from a large-scale community survey (Bright, 2008) in patients of a private ADHD treatment centre indicated that 14.3% of respondents abused prescription psychostimulants (of those, 67.9% abused a single psychostimulant; 21.4% two psychostimulants; 4.8% three psychostimulants; and 6.0% four or more psychostimulants). Almost 80% of participants who abused prescription psychostimulants abused short-acting agents; 17.2% abused long-acting...
psychostimulants; 2.0% abused both short- and long-acting agents; and 1.0% abused other medications. The most common method of psychostimulant abuse was crushing pills and inhaling/snorting (75.0%), followed by crushing and injecting (6.3%), microwaving/melting to snort (6.3%) and other methods (12.5%). After reviewing evidence on the relationship between type of administration/type of psychostimulant and potential for abuse, Wilens and Morrison (2012) concluded that, while intravenous and intranasal psychostimulant administration are associated with the highest risk for abuse, oral administration of extended-release psychostimulants is associated with the lowest abuse liability.

How should I monitor and manage misuse/abuse during treatment with ADHD drugs?

Patients with ADHD and SUD or related conditions are particularly at risk for abuse and misuse of ADHD drugs. Studies in patients with ADHD and SUD suggest that treatment of the addiction disorder needs to be addressed initially, with ADHD treatment quickly thereafter (Wilens and Morrison, 2012).

In case of current or previous substance abuse, a close monitoring of a patient’s psychostimulant use is important. Treatment decisions are uncertain and careful individual evaluation is required. The clinician is advised to choose ATX or an extended-release formulation of MPH or the amphetamine prodrug lisdexamfetamine in high-risk cases—e.g. if the patient or other members in the family are misusing illegal drugs.

Cannabis use is not known to have important interactions with ADHD drugs and does not contra-indicate psychostimulants. Nevertheless, one should discuss the dangers of cannabis responsively and consider referral to a drug misuse programme. Continuing use of cocaine is a contra-indication to psychostimulants.

Intravenous use of psychostimulant is very dangerous and immediate-release methylphenidate or dexamphetamine should not be prescribed in respective cases.

In some families there may be a misuse of the prescribed medication—for instance, for recreational use, cognitive enhancement, to achieve an undesirably high level of quietening, or to medicate other family members, or to sell to others for recreational use or cognitive enhancement. Advice and discussion are usually enough, but in extreme cases it may be necessary to stop prescribing psychostimulants and perhaps to substitute with ATX, which does not induce euphoria (Jasinski, Faries, Moore, Schuh, & Allen, 2008). In addition, close medication monitoring should be established, including pill counts where necessary.

Summary for misuse/abuse

1. There is no evidence that treatment with psychostimulants increases the risk for later SUD.
2. A subsample of individuals with ADHD and certain non-ADHD individuals may be prone to abuse and misuse of ADHD medication.
3. In patients with ADHD and SUD treatment of the addiction disorder needs to be addressed initially, with ADHD treatment quickly thereafter.
4. In case of current or previous substance abuse, an extremely close monitoring of a patient’s psychostimulant use is important. Choose an extended-release formulation of MPH, lisdexamfetamine or ATX in high-risk cases. Highest level of recommendation (SIGN system): D (expert opinion).

Seizures

What is the evidence for an association between drugs used to treat ADHD and seizures?

ADHD patients have been shown to have incidence rates of unprovoked seizures and epilepsy up to two to three times greater than non-ADHD children (Dunn et al., 2009). In contrast, among children with epilepsies, ADHD is the most frequent psycho-pathological comorbidity. Despite the clinical importance of treating both conditions properly, the evidence for ADHD treatment in children with epilepsy is limited.

In ADHD patients without epilepsy, the incidence of seizures does not differ among MPH, ATX or placebo (Wernicke et al., 2007). Despite a warning in the summary of product characteristics advising against the use of MPH in the face of seizures, the evidence to support this warning is very limited. In patients with well-controlled epilepsy and even with infrequent seizures, MPH is effective and associated with a low seizure risk (Koneski & Casella, 2010; Koneski, Casella, Agertt, & Ferreira, 2011), while for ATX, both efficacy and short-term safety has yet to be established. Available evidence does not support an increased risk of MPH in seizure-free children with rolandic (centrotemporal) spikes (Holtmann, Becker, Kentner-FIGURA, & Schmidt, 2003).

How should I monitor and manage seizures during treatment with ADHD drugs?

Treatment of ADHD in children with epilepsy requires a close collaboration between paediatric neurologists and child psychiatrists. Besides specific pharmacotherapy, symptoms of ADHD in children with epilepsy may be improved by nonspecific interventions, such as decreasing antiepileptic polypharmacy, reducing drug interactions and

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Treatment of ADHD in children with epilepsy requires a close collaboration between paediatric neurologists and child psychiatrists. Besides specific pharmacotherapy, symptoms of ADHD in children with epilepsy may be improved by nonspecific interventions, such as decreasing antiepileptic polypharmacy, reducing drug interactions and
switching to antiepileptic drugs with fewer cognitive and behavioural effects (Torres, Whitney, & González-Heydrich, 2008), which should be decided after consultation with the paediatric neurologist according to the particular needs of the patient. Before initiating pharmacotherapy for ADHD, the best possible seizure control should be sought.

In ADHD children with coexisting epilepsy, an elevated risk for seizures can be related to antiepileptic drug polypharmacy, mental retardation, neurologic deficits, metabolic diseases, congenital anomalies and other developmental disorders (McAfee, Holdridge, Johannes, Hornbuckle, & Walker, 2008). In these children, a close monitoring of treatment-related AEs is especially important.

Routine electroencephalogram (EEG) is a poor predictor of impending seizures, and variations in the EEG during MPH treatment are in most cases unrelated to seizure frequency in children with epilepsy (Gross-Tsur, Manor, van der Meere, Joseph, & Shalev, 1997). In ADHD patients without a history of seizures, EEG screening is not currently indicated in the absence of other clinical indications or before starting MPH treatment.

While increased levels of phenytoin, primidone and phenobarbital during MPH treatment have been reported in single cases, no meaningful drug-drug interactions between MPH and antiepileptic drugs have been observed in a large systematic review (Markowitz & Patrick, 2001).

Adolescents with epilepsy are at increased risk for depression and suicidal ideation (Baker, 2006). During ADHD treatment, they should therefore be monitored for the emergence of depression, irritability and suicidal ideation (see below).

## Suicidal thoughts and behaviours

**What is the evidence for an association between drugs used to treat ADHD and suicidal thoughts/behaviour?**

Suicide-related events rarely occur with ADHD drug treatment. There is little compelling evidence to suggest that rate of suicide-related events in children treated with ADHD drugs is greater than the expected rate in the general population (Bangs et al., 2008). In addition, comorbidities occurring with ADHD (such as depressive and conduct disorders) may in themselves be associated with an increase in the risk of suicidal ideation or behaviour (Agosti, Chen, & Levin, 2011). Predictors of later suicidality in children with ADHD comprise female sex, maternal depression and an early pattern of comorbid emotional and behaviour problems (Chronis-Tuscano et al., 2010).

No systematic evidence is currently available on the rate of suicidal ideation in children with ADHD following the initiation of treatment with psychostimulants. In a meta-analysis of 14 double-blind and placebo or active comparator trials, ATX has been associated with suicidal ideation in 0.37% (5/1357) of paediatric patients versus 0% (0/851) for the placebo group, while no completed suicide was reported (Bangs et al., 2008). However, these were trials for regulatory purposes. Prevalence rates found in clinical trials and particularly in regulatory trials are usually lower than those in epidemiological samples.

**How should I monitor suicidal thoughts/behaviour during treatment with ADHD drugs?**

During treatment with any ADHD medication, a psychiatric history should be taken; this should routinely include an assessment of suicidality, either via general enquiry or via a standardized suicidality rating system such as the Columbia Classification Algorithm of Suicide Assessment (Posner, Oquendo, Gould, Stanley, & Davies, 2007).

Patients being treated with medications for ADHD should be observed for the emergence of depression, irritability and suicidal ideation as part of the routine monitoring. Families and caregivers should be advised of the need to recognize any appearance of emotional change, self-injurious thinking, suicidal ideation and irritability (Graham et al., 2011).

**How should I manage suicidal thoughts/behaviour during treatment with ADHD drugs?**

Minimal research data exist to support specific pharmacotherapy recommendations for co-occurring ADHD and suicidality. In view of uncertain degrees of risk, caution is required when prescribing ADHD drugs to children and adolescents with a past history of serious suicidal attempt or current untreated severe and impairing depression (Food and Drug Administration, 2005).

In the case of ADHD and concurrent suicidal ideation in the context of a major depressive episode, the clinician should focus initially on the treatment of the disorder that is the most severe and impairing,
i.e. the depressive disorder and its potentially life-threatening complications (e.g., suicidality) (Pliszka et al., 2006). If suicidal ideation emerges during ADHD treatment, urgent psychiatric evaluation should be arranged and the patient’s evolution carefully monitored. Consideration should be given to reducing the dose and/or other changes in the therapeutic regimen, including the possibility of discontinuing the medication, especially if these symptoms are severe or abrupt in onset, or were not part of the patient’s presenting symptoms. It should, however, not automatically be assumed that any suicidal ideation or attempt is an adverse effect of medication, since a systematic review has indicated that there is a relationship between the presence of ADHD itself and suicidal attempts (Young, 2008).

**Summary for suicidal thoughts and behaviours**

1. Suicidal thoughts and behaviour rarely occur during pharmacological treatment with ADHD drugs.
2. A screening for suicidal thoughts and behaviour should be conducted during ADHD treatment, preferably complemented by standardized suicidality rating systems.
3. Focus first on the management of the psychiatric disorder underlying suicidal thoughts/behaviour. In the presence of severe suicidal thoughts/behaviour, there is no absolute contraindication for ADHD drugs, but dose reduction or discontinuation of medication is warranted.

Highest level of recommendation (SIGN system): D (expert opinion).

**Psychotic symptoms**

*What is the evidence for an association between drugs used to treat ADHD and psychotic symptoms?*

The term psychotic symptoms, as used in this paragraph, is defined at the level of symptoms and does not imply a full-blown psychotic disorder. Psychotic symptoms comprise hallucinations, delusions, but also symptoms of mania, hypomania and extreme “agitated states”. Psychotic symptoms are rarely associated with ADHD drug treatment (Goldsmith, Singh, & Chang, 2011), and there is no evidence to suggest that the observed event rate of psychotic symptoms in children treated with ADHD drugs exceeds the expected rate in the general population (for review, see Graham et al., 2011).

In a systematic review of data from postmarketing surveillance and clinical trials, Mosholder, Gelperin, Hammad, Phelan, and Johann-Liang (2009) reported a prevalence of psychotic symptoms after exposure to ADHD drugs ~1.5% (vs. 0% for placebo).

**How should I monitor and manage psychotic symptoms during treatment with ADHD drugs?**

If psychotic symptoms (such as paranoid delusions, confusion, euphoria, grandiosity, impaired judgment, hallucinations or increased aggression) do occur with therapeutic doses of ADHD drugs, they may either be a symptom of a psychotic disorder or, in very rare circumstances, represent an adverse drug reaction (Ross, 2006). Therefore, transient dose reduction or discontinuation of the ADHD drug is generally the best approach. If the psychotic or manic symptoms resolve, a re-challenge with a different class of ADHD drug may be appropriate. If not, another diagnosis and treatment with neuroleptics should be reconsidered. In cases of psychotic disorder, it is important to acknowledge the impact that untreated ADHD may have on an individual’s life and their ability to comply with treatment recommendations.

The EAGG recommends caution when prescribing ADHD drugs to children and adolescents with a past history of psychotic episodes or a family history of psychosis (Graham et al., 2011). In these patients, the potential benefits of pharmacotherapy on the child’s behaviour, family life and school functioning should be weighed against the possible risks.

**Summary for psychotic symptoms**

1. Psychotic symptoms rarely occur during treatment with ADHD drugs.
2. If psychotic symptoms occur with therapeutic doses of ADHD drugs reduce the dose or discontinue the ADHD drug.
3. Once the psychotic or manic symptoms resolve, a re-challenge with ADHD drugs may be appropriate.

Highest level of recommendation (SIGN system): D (expert opinion).

**AEs during treatment with drugs not licensed in EU for ADHD**

The EAGG guidelines did not consider drugs that are used to treat ADHD but that are not licensed for such use within the EU. However, some readers may be interested in knowing the main AEs during the use of such drugs. Therefore, in this section we provide a short overview of the main AEs and, where available, recommendations during treatment with drugs used for the treatment of ADHD not licensed in EU. In particular, we focus on clonidine and guanfacine. We
stress that the use of nonlicensed drugs does always call for close monitoring beyond the scope of this review.

**Clonidine**

**Appetite and growth:** There are no empirical data on the effect of clonidine on appetite and growth in children with ADHD.

**Cardiovascular events:** Clonidine’s primary indication has historically been in the treatment of hypertension (http://bnf.org/bnf/index.htm). It is therefore likely to be associated with some reduction in BP, and this in particular should be monitored on initiation and maintenance of treatment, including assessment for postural BP drop. Particular concerns about the safety of clonidine have arisen after case reports of sudden deaths in children treated with this drug, summarized in Daviss et al. (2008). It must be noted that these tragic events occurred in children with polypharmacy and/or congenital heart malformations. A relatively large 16-week multicentre, double-blind trial (Daviss et al., 2008) of 122 children with ADHD (without baseline cardiovascular problems) randomly assigned to clonidine (n = 31), MPH (n = 29), clonidine and MPH (n = 32), or placebo (n = 30) identified no major cardiovascular events or EEG changes in ADHD children treated with clonidine (with or without methylphenidate) versus placebo or MPH alone. However, bradycardia and drowsiness were significantly more common in children treated with clonidine compared with those not treated with clonidine. Therefore, the authors concluded that, whereas clonidine appears safe and well-tolerated in children with ADHD without polypharmacy and/or congenital heart malformations. A relatively large 16-week multicentre, double-blind trial (Daviss et al., 2008) of 122 children with ADHD (without baseline cardiovascular problems) randomly assigned to clonidine (n = 31), MPH (n = 29), clonidine and MPH (n = 32), or placebo (n = 30) identified no major cardiovascular events or EEG changes in ADHD children treated with clonidine (with or without methylphenidate) versus placebo or MPH alone. However, bradycardia and drowsiness were significantly more common in children treated with clonidine compared with those not treated with clonidine. Therefore, the authors concluded that, whereas clonidine appears safe and well-tolerated in children with ADHD without baseline cardiovascular risk, regular monitoring of pulse and BP changes is warranted. A routine ECG is not recommended.

**Sleep:** In the aforementioned trial by Daviss et al. (2008), clonidine (alone or in combination with MPH) was associated with significantly more somnolence than placebo. This result concurs with previous observational reports (Hunt, Minderaa, & Cohen, 1985). Indeed, some authors recommend using clonidine for sleep-onset delay associated with psychostimulants (Wilens, Biederman, & Spencer, 1994), although there are presently no randomized trials supporting this suggestion.

**Tics:** Although clonidine may decrease tics and some authors recommend it in children with ADHD and comorbid tic disorders, evidence also exists that it may increase tics in about a quarter of cases (Pringsheim & Steeves, 2011).

**Misuse–abuse:** Clonidine is used as (adjunctive) medication for the treatment of opioid and alcohol withdrawal. On the other hand, in very rare cases clonidine may be misused to achieve desired effects and to prolong the length of opiate’s action (Dennison, 2001). No systematic studies have been conducted regarding misuse, abuse or diversion in ADHD samples.

**Seizures:** To our knowledge, there are no prospective controlled studies of clonidine in children with ADHD and epilepsy. Therefore, any recommendations have to be regarded as preliminary. Clonidine overdose may be associated with seizures, and a possible association of clonidine with new-onset seizures has been discussed in rare cases (Feron, Hendriksen, Nicolai, & Vles, 2008). Case series seem to suggest that a cautious trial of clonidine for treatment of ADHD in a patient with epilepsy may only be justified when there is a reason not to use MPH, ATX or guanfacine (Hamoda, Guild, Gunlak, Travers, & Gonzalez-Heydrich, 2009; Torres et al., 2008). Given the narrow therapeutic index of clonidine, a close collaboration between paediatric neurologists and child psychiatrists is warranted in these cases.

**Suicidal thoughts and behaviours:** The impact of clonidine on suicidality has not been studied adequately. A review of controlled and uncontrolled studies on the relationship between affective syndromes and pharmacotherapeutic agents found no clear evidence of such a relationship with clonidine (Long & Kathol, 1993).

**Psychotic symptoms:** Since it decreases central norepinephrine activity, clonidine has been investigated as an antipsychotic in older trials (Angrist et al., 1988); some reports suggest a small beneficial effect of clonidine augmentation on psychotic symptoms (Maas et al., 1995). Regarding patients with ADHD, clonidine has not been included in a recent comprehensive review of clinical trial data, and postmarketing spontaneous reports, examining the occurrence of hallucinations and other psychotic symptoms during drug therapy for ADHD (Mosholder et al., 2009).

**Guanfacine**

**Appetite and growth:** During short-term trials, decreased appetite is seldom reported in trials of guanfacine-extended release in children with ADHD (about 5%) (Sallee & Eaton, 2010). When present, this AE did not usually lead to medication discontinuation.

**Cardiovascular:** As with clonidine, guanfacine has historical use as an antihypertensive agent. In trials of guanfacine-extended release, mean changes from baseline in systolic BP, diastolic BP and pulse (respectively −5 mmHg, −3 mmHg, and −6 bpm) were dose-dependent and normalized with taper or discontinuation. Asymptomatic decreases in both BP and heart rate persisted in long-term studies. Across
and longer trials (10 months, about 45%) of guanfacine-extended release. These events appeared to be dose-related and resulted in discontinuation in 6% of patients in short-term trials and 3% in longer trials (Sallee & Eaton, 2010).

**Sleep:** Somnolence has been the most frequently reported AEs during short-term trials (about 38%) and longer trials (10 months, about 45%) of guanfacine-extended release. These events appeared to be dose-related and resulted in discontinuation in 6% of patients in short-term trials and 3% in longer trials (Sallee & Eaton, 2010).


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Table 1: Summary of recommendations of the European ADHD Guidelines Group (EAGG) for the management of adverse events during treatment with ADHD drugs

<table>
<thead>
<tr>
<th>Areas/topics/systems</th>
<th>Monitoring</th>
<th>Managing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appetite &amp; Growth</td>
<td>Appetite, weight, height and BMI at baseline and every 6 months. Should always be plotted on standard charts.</td>
<td>Give medication after meals rather than before. Encourage the use of high-caloric snacks or late evening meal. Reduce the dose, switch to an alternative class or formulation, or discontinue medication on week-ends or during summer. Refer to paediatric endocrinologist if height and weight values are below critical thresholds [height: 1.5 standard deviation (SDs) below the average of mother’s and father’s height; or height: 2 SDs below the population mean plus 1-year height velocity 1 SD below the mean, or a 1-year decrease of 0.5 SDs below the mean or 1-year height velocity 2 SDs below the mean, or 2-year height velocity 1.5 SDs below the mean].</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>- Individual/familial cardiovascular risk factors and heart rate and blood pressure at baseline and every 3-6 months, plotted against local norms whenever possible. - Systematic (i.e., in every single case) ECG not mandatory.</td>
<td>If blood pressure measures (3 times within 10 min, in a patient at rest) &gt; 95th percentile (according to national norms): either dose reduction/drug holiday or referral to specialist. If, after dose reduction/drug holiday, 24-hours blood pressure measures are still &gt; 95th, refer to specialist. If, following treatment of hypertension, blood pressure values drop to &lt; 95th percentile, ADHD treatment can be continued.</td>
</tr>
<tr>
<td>Sleep</td>
<td>- Subjectively reported sleep problems (clinical interview, sleep questionnaires, sleep diaries filled out by parents and children) at baseline and at each follow-up visit. - Polysomnography indicated if suspicion of sleep-breathing disorder, episodic nocturnal phenomena, limb movements, and unexplained excessive daytime sleepiness.</td>
<td>If rebound effect with psychostimulants: add small (5 mg) doses of MPH-IR in the evening. If psychostimulant is the current treatment and sleep onset difficulty not due to rebound effect: alternative classes or formulation of psychostimulants or ATX. Alternative: melatonin (2-3 mg up to 6-10 mg/day).</td>
</tr>
<tr>
<td>Tics</td>
<td>Development of tic during three months before any decision regarding ADHD drugs.</td>
<td>Add antipsychotic if both ADHD and tics are impairing and discontinuation of psychostimulant would worsen ADHD.</td>
</tr>
<tr>
<td>Misuse/Abuse</td>
<td>Extremely close monitoring at each visit of possible abuse-misuse. Cannabis use is not necessarily contraindication to psychostimulants, cocaine likely is.</td>
<td>Extended-release formulation of MPH, lisdexamfetamine or ATX in high risk cases of individuals with ADHD and SUD.</td>
</tr>
<tr>
<td>Seizure</td>
<td>- EEG not mandatory before starting the pharmacological treatment in individuals without a history of seizure. - Monitor seizure at each follow-up visit.</td>
<td>Well controlled epilepsy and infrequent seizures: MPH safe and effective. Decrease antiepileptic polypharmacy. - Switch to antiepileptic with fewer cognitive/behavioural effects.</td>
</tr>
<tr>
<td>Suicidal thoughts and behaviour</td>
<td>Clinical monitoring of suicidal thoughts/behaviour at each follow-up visit by means of clinical interview and, if possible, standardized suicidal rating scales (e.g., Columbia Algorithm of Suicide Assessment).</td>
<td>Focus on the management of the psychiatric disorder underlying suicidal thoughts and behaviour. Not a contraindication to prescribe ADHD drugs but caution needed. Dose reduction or discontinuation of medication in severe suicidal thoughts or behaviours.</td>
</tr>
<tr>
<td>Psychotic symptoms</td>
<td>Clinical evaluation of psychotic symptoms at baseline and each follow-up visit.</td>
<td>Reduce the dose of psychostimulant or discontinue. After treatment of psychotic symptoms and stabilization, a re-challenge with psychostimulant is appropriate.</td>
</tr>
</tbody>
</table>
Tics: Tics have not been reported as significant events during treatment with guanfacine in children with ADHD. Indeed, a recent systematic review (Pringsheim & Steeves, 2011) has found an improvement of tics in children with both ADHD and tics treated with guanfacine, although these conclusions are based on just one study (Scahill et al., 2001).

Seizures: As with clonidine, there is a lack of prospective controlled studies in children with ADHD plus epilepsy taking guanfacine. The available information favours guanfacine over clonidine, as guanfacine is less sedating, more efficacious in treating the cognitive symptoms of ADHD, and, theoretically, less likely to promote seizures (Torres et al., 2008).

Psychotic symptoms: Besides sparse case reports (Boreman & Arnold, 2003; Luthra, Markov, & Ambrosini, 1999), we are not aware of studies specifically and systematically assessing psychotic symptoms in individuals with ADHD treated with guanfacine.

Suicidal thoughts and behaviours and misuse-abuse: We are not aware of any study specifically assessing abuse-misuse and suicidal thoughts and behaviour associated with guanfacine treatment in individuals with ADHD.

Conclusions
We have presented and discussed the empirical, peer-reviewed evidence for monitoring and managing the most common AEs during treatment with ADHD drugs. We provide in Table 1 a summary of our recommendations, which we hope will be useful for clinicians.

In conclusion, most AEs during treatment with drugs for ADHD can be managed by the clinician, so that it is not necessary to stop medication. In this way, patients with ADHD may continue to benefit from the effectiveness of pharmacological treatment. Current practice on the management of AEs during treatment with ADHD drugs is based mostly on expert consensus (many of the recommendations provided in this review are classified as D level, i.e., expert consensus, while evidence on the association between ADHD drugs and AEs is more extended). We hope that, in the future, empirical evidence will guide clinical recommendations in a more solid way, as reflected in rigorous protocols which will be useful to clinical practitioners in their day-to-day practice.

Supporting information
Additional supporting information is provided along with the online version of this article.

Appendix S1 Specific search terms for each database
Table S1 SIGN grading system (Word document)

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Involvement of the European ADHD Guidelines Group (and their main sponsors): The European ADHD Guidelines Group (EAGG) is a workgroup of the European Network for Hyperkinetic Disorder (EUNETHYDIS) and consists of the following members (listed in alphabetical order): T. Banaaschewski, D. Brandeis, J. Buitelaar, D. Coghill, S. Cortese, D. Daley, M. Danckaerts, R. W. Dittmann, M. Döpfner, M. Ferrin, J. Graham, C. Hollis, M. Holtmann, E. Konofal, M. Lecendreux, A. Rothenberger, P. Santosh, J.A. Sergeant, E. Simonoff, E.J. Sonuga-Barke, H.-Ch. Steinhausen, A. Stringaris, E. Taylor, S. van der Oord, I. Wong and A. Zuddas. The chair of the European ADHD Guidelines Group is Prof. Sir Joseph Sergeant. The members listed as authors contributed to drafting the manuscript. All members of the EAGG provided their feedback and approved the final version of the manuscript.

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Conflicts of interest disclosures: S.C. has served as scientific consultant for Shire Pharmaceuticals from June 2009 to December 2010; has received support to attend meetings from Eli Lilly and Co. in 2008 and from Shire Pharmaceuticals in 2009–2010. M.H. served in an advisory or consultancy role for Lilly, Shire, Novartis and Bristol-Myers Squibb, and received conference attendance support or was paid for public speaking by AstraZeneca, Bristol-Myers Squibb, Janssen-Cilag, Lilly, Medice, Neuroconn, Novartis and Shire. T.B. has received Speaker Bench fees from Lilly, Janssen-McNeil, Medice, Novartis, UCB; been on the Advisory Board and/or acted as a consultant to Desitin, Lilly, Medice, Novartis, Pfizer, Shire, UCB and Vifor Pharma. Research grants: Lilly, Shire and Novartis; and unrestricted grants educational: Lilly, Janssen, McNeil, Medice, Novartis, Shire, UCB. J.B. is involved in clinical trials with cognitive training and neurofeedback funded by the BrainGain grant, NWO, Netherlands; has planned studies that will be supported by Vifor; has been in the past 3 years a consultant to, member of an advisory board of and/or speaker for Janssen Cilag BV, Eli Lilly, Bristol-Myer Squibb, Shering Plough, UCB, Shire, Novartis and Servier; he is not an employee of any of these companies and not a stock shareholder of any of these companies; he has no other financial or material support, including expert testimony, patents, royalties. D.C. has received research funding from Lilly, Shire, Vifor; been on Advisory Boards for Flynn Pharma, Janssen Cilag, Pfizer, Shire, UCB, Vifor; and received honoraria for speaking at events sponsored by Flynn Pharma, Janssen Cilag, Lilly, Medice, Novartis, Shire, UCB; Consultancy: Shire. M.D. has been a speaker at conferences organized by Janssen-Cilag, Lilly, Medice, Novartis & Shire (nonproduct related talks) and has received research support from Shire.
in 2008–2011. R.W.D. is a former employee and stockholder of E. Lilly and Co. and is currently the E. Lilly Endowed Chair of Pediatric Psychopharmacology at the Central Institute of Mental Health, Mannheim, Germany; he received travel support and research funding from Ferring, Janssen-Cilag, Lilly and Shire pharmaceutical companies, public research funding from the German Research Foundation (DFG), the German Ministry of Education and Research (BMBF), the European Union / EU FP7 programme, and NIMH; he is serving on advisory boards and speaker panels of E. Lilly and Shire. J.G. has received payment for development of educational presentations including service on speakers’ bureaus for Lilly, UCB, Shire; travel/accommodations expenses covered or reimbursements from Janssen Cilag, Lilly, UCB. E.T has received consultancy expenses arising from unpaid trusteeships of child charities and publishing royalties from Blackwells, Random House, and MacKeith Press. J.S. has served on the Advisory Boards of Lilly, Shire; Speaker’s Bureau for Janssen-Cilag, Lilly, Shire; received educational grants to Eunethydis (European Network Hyperkinetic Disorders) or European ADHD Guidelines Group (EAGG) from Novartis, Janssen-Cilag, Lilly, Shire, Vifor; and undertaken a research contract for Lilly.

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Key points
- **What is known:** As with all medications, and some nonpharmacological interventions, AEs can and do occur during treatment with ADHD drugs. The management of such AEs differs among clinicians.
- **What is new:** We present a current best practice for the management of AEs during treatment with ADHD drugs based on empirical evidence or expert consensus.
- **What is clinically relevant:** There is empirical evidence to support recommendations for the management of loss of appetite/growth delay and sleep disturbances during treatment with ADHD drugs. Management of cardiovascular events, tics, abuse/misuse, seizures, suicidal thoughts and behaviours, and psychotic symptoms is mostly based on expert consensus.

References
Cheng, J.Y., Chen, R.Y., Ko, J.S., & Ng, E.M. (2007). Efficacy and safety of atomoxetine for attention-deficit/hyperactivity disorder in children and adolescents-meta-analysis and...


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Note
Several typographical and drafting errors were found in the first advanced online version of the above article published on 7 January; these have been corrected in this version, and include the following non-trivial changes:

Page 6: right-hand column, Summary of Cardiovascular AEs: box 3 (ii) should read: “Measure baseline heart rate and BP and repeat the measure every 3 of 6 months.” rather than “every 3 or 6 months.”

Page 11: left-hand column, penultimate paragraph, lines 1 and 2 should read: “... is very dangerous and immediate-release methylphenidate or dexamphetamine should not be prescribed...” rather than “... is very dangerous in the immediate-release...”