EUROPEAN GUIDELINES ON MANAGING ADVERSE EFFECTS OF MEDICATION FOR ADHD

European Guidelines Group

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Abstract

The safety of ADHD medications is not fully known. Concerns have arisen about both a lack of contemporary-standard information about medications first licensed several decades ago, and signals of possible harm arising from more recently developed medications. These relate to both relatively minor adverse effects and extremely serious issues such as sudden cardiac death and suicidality. A guidelines group of the European Network for Hyperkinetic Disorders (EUNETHYDIS) has therefore reviewed the literature, recruited renowned clinical subspecialists and consulted as a group to examine these concerns. Some of the effects examined appeared to be minimal in impact or difficult to distinguish from risk to untreated populations. However, several areas require further study to allow a more precise understanding of these risks.

Introduction

Attention-deficit hyperactivity disorder (ADHD) is one of the most common mental disorders with a worldwide mean prevalence of around 5 % in children [108] and 3 % among adults [41]. The disorder persists into adulthood in a significant proportion of the affected individuals and, most commonly, its course is complicated due to frequent comorbidities and impaired psychosocial functioning. Thus, ADHD requires continuing professional care on the level of both assessment and intervention. Guidelines serve clinicians to provide high quality care to their patients by delivering evidence-based state of the art concepts. This European guidelines group has contributed to the process through previous publications [142,10]

It is widely accepted that intervention in ADHD should be based on multimodal treatment. Amongst its various components, drug treatment is of specific value and relevance to the patients. Accordingly, methylphenidate, dexamfetamine and atomoxetine in particular are widely used in European countries and North America for the treatment of ADHD. They are effective drugs, and meta-analyses investigating their use have led to our guidelines recommending their use as part of a comprehensive treatment programme [142,9].

Their safety, however, is not fully known – for the most commonly used drug, methylphenidate, introduction and licensing came in the 1960s, before modern standards of clinical trials and post licensing surveillance were established. More recently introduced drugs for ADHD have resulted in signals of potential harm, raising the possibility that some of these adverse outcomes may also apply to methylphenidate. Public and professional concern has been raised about the potential for severe reactions, even including death, and for the generation of misuse. These uncertainties make it possible either that vulnerable children are being exposed to unreasonable hazard, if real risks go undetected, or that children are being denied the benefit of medication if perceived risks are exaggerated.

The issue of likelihood of causality is of particular relevance to examination of this area, especially in the treatment of a childhood developmental disorder with frequent comorbidity. Causality may be inferred from evidence of an excess observed (O) to expected (E) adverse event rate ratio (O>E /AE) with ADHD drugs. The higher the O:E ratio, the stronger the evidence of a causal link. Additional evidence of causality may be inferred from a dose-response relationship or recurrence of an adverse event on re-challenge with the drug (positive re-challenge).

We have therefore reviewed the published literature on adverse effects of the drugs that are licensed in Europe, and most commonly used, for the treatment of ADHD or hyperkinetic disorder. As such we have specifically examined: Immediate release methylphenidate, modified release methylphenidate, dexamfetamine and mixed amfetamine compounds, and atomoxetine. Several drugs are not licensed in Europe and are either unavailable (e.g. guanfacine), or uncommonly used (e.g. modafinil, clonidine and tricyclic antidepressants). These unlicensed drugs were not included in the review, but are referred to where relevant to understanding of the recommended medications. We have focussed on safety in children and adolescents, but the review has been additionally informed by adult data. Meta-analysis was not feasible because of heterogeneity in information reported; where quantitative data are available we have used the indices reported in the papers. In addition to addressing the published literature we requested information from the licence holders about unpublished safety information. We also consulted specialists in paediatrics, cardiology and endocrinology; and held a series of consensus conferences, examining incidence, causality and potential impact of risks, through which we have formulated advice to clinicians about the frequency and severity of each and the means of reducing harm or reacting to adverse events if they should occur. The evidence and advice will be divided into the main different areas of concern.

1. Cardiac adverse events

The cardiac safety of drugs used to treat ADHD remains of concern to many prescribers and families, following reports of sudden cardiac deaths of individuals taking drugs for ADHD. Stimulants are also well known to exert both pressor and chronotropic cardiac effects. Child and adolescent psychiatrists and paediatricians who are aware of black box advisory labels and advice to monitor cardiac parameters may remain uncertain as to the true risks in both cardionormal children and those with existing risk factors.

Frequency of cardiac adverse events in treated and untreated populations

i) Sudden death in children and adolescents

In contrast to adults, sudden death occurs only rarely in the general paediatric population. Sudden death rates range from 0.8 to 8.5/100 000 pt years [98,97,161,17,27]. The median of these published sudden death rates in children is at 1.2 to 1.3/100,000/yr. Sudden death in children and adolescents is associated with both known and previously unrecognized cardiac conditions. Among young persons with known congenital heart disease, the highest risks of sudden death (0.2% per year) occur with specific conditions such as aortic stenosis [130].

In children with ADHD, the risk of death from all causes is estimated at 58.4/100 000 patient-years [159], whereas the risk of *sudden unexplained* death is unknown. The FDA in the USA and Health Canada identified 25 sudden deaths in individuals prescribed ADHD medications from postmarketing data between 1999 and 2003, raising concerns of a possible association. However, when the number of patient-years of prescribed medication was incorporated into the evaluation, the frequency of reported sudden death per year of ADHD therapy with methylphenidate, atomoxetine or amfetamines among children was 0.2-0.5/100,000 pt-years [98]. While it is recognized that adverse events are

frequently under-reported in general (80% under-reporting is sometimes mentioned) it is likely that sudden deaths in young individuals on relatively new medications may be better reported. Death rates per year of therapy, calculated using the adverse events reporting system (AERS) reports and prescription data, are equivalent for two ADHD drugs (dexamfetamine and methylphenidate) : 0.6/100,000/yr.(40). (The accuracy of these estimates is limited, for instance because in moving from number of prescriptions to patient-year figures assumptions must be made about the length of each prescription). It seems likely, using these best available data, and assuming a 50% reporting rate, that the sudden death risk of children on ADHD medications is similar to that of children in general. Caveats to the above include the observation that 2 of the 25 sudden deaths on ADHD medication occurred with initiation of stimulant medication. Thus, as with most therapies, an exceedingly rare but real risk of sudden death cannot be completely excluded. If childhood deaths on ADHD medications are under-reported to a greater degree than we have assumed, then some incremental risk could potentially be present.

A recently published study compared stimulant use in two matched groups of 564 young people aged 7-19 years, one group who had suffered sudden unexplained death, and the other who had died as passengers in motor vehicle accidents [49]. Stimulant use was found in 10 (1.8%) of the former group versus 2 (0.4%) of the latter group. The odds ratio was reported to be 7.4 (95% CI=1.4 to 74.9); from which the authors conclude a possible association of stimulant use with sudden death. The FDA, however, has suggested caution in interpreting these findings, citing possible methodological flaws. In addition, the physical and mental health comorbidities associated with the disorder that requires stimulant treatments may themselves increase the risk of sudden death from other causes.

In another study the incidence of sudden death in children prescribed ADHD drugs was not found to be statistically different to that in the general population; but this study was limited by its sample size [90]. As sudden death in children is so rare, very large epidemiological studies are required to adequately examine this question. At the time of writing, some studies of ADHD medication risk remain pending, and practice should be reassessed in the event of any new convincing data. For example, the FDA is currently

conducting a large epidemiological study (500,000 patients) to further examine this question.

ii) Hypertension

The definition of hypertension in children (blood pressure beyond the 95th centile for age and height) suggests that about 5% of children will be hypertensive to a level requiring treatment prior to administration of stimulant drugs. In theory, every childhood population should have this number of children on antihypertensive medication in order to reduce their blood pressures below the 95th centile (and below the 90th centile if there is evidence of end organ damage)[2]. In practice, however, routine screening for and treatment of hypertension in children has not been widely implemented as a public health standard of care. The actual values for blood pressure at the various percentiles differs slightly in European countries [62,74,87,87], so local norms should be used wherever possible. The average blood pressure in children is increasing – perhaps in part due to increased prevalence of obesity [96].

All stimulant medications and atomoxetine are reported to cause elevations in blood pressure [152]. While the average increases range from 1 to 4 mm Hg systolic and 1 to 2 mm Hg diastolic, this small average change includes patients where the rise in blood pressure is more significant, and there are also data showing increases above the 95th centile in individuals taking ADHD medications. For categorically measured hypertension, controlled trial data are available for atomoxetine and indicate that elevations above the 95th percentile are seen in 6.8 % of patients (systolic) and 2.8% (diastolic) - in comparison to 3% and 0.5% respectively of patients treated with placebo [152]. Categorical hypertension data for methylphenidate are not published so far but are likely to be of a similar order of magnitude on the basis of the changes in mean pressures. The patient information leaflet for methylphenidate products in Europe indicates that the drug may increase systolic and diastolic blood pressure by more than 10 mm Hg[1].

[1] [http\\www.ema.europa.eu/htms/human/referral/article31/methylphenidate.htm]

iii) Heart Rate Increases

Stimulant and non-stimulant medications are recognised to cause a small increase in heart rate averaging 1-2 beats per minute [149,152]. The averaging of data in clinical studies can hide a small proportion where the increment is larger – indeed up to 50 beats per minute in rare cases [152].

iv) QT interval prolongation

Prolongation of the QTc interval in individuals (without a congenital long QT syndrome or previously recognised long QT interval) can be caused by a variety of medications and is a recognized risk factor for ventricular tachyarrhythmias and sudden death [162]. Thus the potential effects of ADHD medications on the QT interval are important given the concerns raised about the safety of this group of medications. The *average* QTc interval is not changed significantly by any of the drug groups (methylphenidate, mixed amfetamine salts and atomoxetine). However, as with raised blood pressure, the average changes in any study cohort may not identify significant increases in a subgroup of individuals which are averaged out by decreases in another subgroup. More important than the average change in a study cohort is the proportion with an increment in QTc to above the safe threshold (usually accepted as being above 470 to 500 msec). Such data for the various preparations is available to regulatory organizations but is not yet in the public domain. Finally, it should be noted that measurement of the QTc interval is not without difficulties, and at least 6 alternative methods of rate correction are available [151,82].

QTc prolongation (and sudden death and increased heart rate) have been reported with methylphenidate and dexamfetamine [98] and atomoxetine [30]. The assessment of sudden deaths with relation to patient-years of treatment described atomoxetine deaths at

0.5 per 100,000 patient years, and methylphenidate at 0.2 per 100,000 patient years (6). Overall, however, insufficient data exist to truly demonstrate any differential sudden death risk for different drugs. A recent retrospective study concluded that exposure to methylphenidate and amfetamine salts showed similar risks for cardiac emergency department visits [160].

Relative impact of cardiac risk, and mediating factors

Sudden death, whether occurring in children or adults, is of course a disastrous event. The aggravating of a previously unknown cardiac pathology (principally cardiomyopathy or channelopathy) by ADHD medication, with a fatal outcome, remains to be excluded as an extremely rare possible outcome.

Despite the lack of a public health approach to hypertension in younger people, it is recognised that intimal plaque formation may occur as a result of hypertension in children [16], and in the long-term even small increases of blood pressure are associated with an increased incidence of cerebrovascular disease in adults [79]. Other consequences include end organ damage such as: left ventricular hypertrophy, retinopathy, and nephropathy with proteinuria. In adults a 2 mm Hg lowering of usual systolic blood pressure would result in about 10% lower stroke mortality and about 7% lower mortality from ischemic heart disease or other vascular causes in middle age [80].

Any persistent heart rate increases seen with ADHD treatment are usually very small and unlikely to be a risk factor for exacerbation of underlying cardiac pathology, but a less common larger persistent rise in heart rate may theoretically do so. QTc prolongation to intervals above 470-500 msec result in a risk of potentially fatal arrhythmias, such as Torsade de Pointes [99].

A personal history of cardiac symptoms (e.g. syncope on exercise) and a positive family history of sudden death below the age of 40 years, or of death associated with exercise are particular risks for sudden death. This risk might potentially be increased by treatment by drugs with pressor adverse effects – although evidence is lacking – and sudden death

more commonly will be the first presentation of the underlying condition. Other risks include pre-existing arrhythmias and channelopathies (e.g. long QT syndrome).

With respect to hypertension, an elevated blood pressure before ADHD treatment or appearing in the course of treatment, a positive family history and other risk factors for cardiac disease are likely to mediate risk. Another mediator may be obesity; children with a BMI above the 95th percentile had a hypertension prevalence of 10.7% in one study – in contrast to children with a BMI below 85th percentile, who had a hypertension prevalence of only 2.6% [132].

It is not known whether children with ADHD have a coexisting increased incidence of hypertension, although there is evidence of a link [66]. The confounder is of course stimulant therapy in this population.

In the FDA post marketing reports, many of the identified subjects were receiving polypharmacy, which therefore may moderate risk of sudden death. Finally, cytochrome P450 (CYP 2D6) metaboliser status has been shown to be a modifying factor in the adverse effects of atomoxetine [92].

Management of cardiac risk

For ADHD patients without known heart disease, the ADHD specialist, whether psychiatrist or paediatrician, is the appropriate person for evaluation of benefit and risk, and the making of recommendations for medication therapy.

Congenital heart disease patients have a slightly higher incidence of ADHD [129], and those affected might well benefit from ADHD therapies - including appropriately prescribed medication. During such treatment, input from a paediatric cardiologist/electrophysiologist may be useful, although the ADHD specialist remains the appropriate individual to evaluate the benefit and risk and make recommendations for medication therapy in this case. In a setting where there may truly be a risk of sudden death (e.g. the congenital long QT syndrome), a frank discussion of these aspects

between the family, ADHD specialist and paediatric cardiologist or electrophysiologist should help to refine the acceptability for the individual patient.

Pre-treatment checking and monitoring of pulse and blood pressure are recommended with any ADHD medication in all patients with ADHD, with frequency of monitoring thereafter usually arbitrarily recommended as either three [67] or six monthly [143], but clearly this requirement may vary in individual cases. Sustained elevated blood pressure before or on treatment with stimulants requires assessment and treatment. Blood pressure should be measured prior to treatment and at each visit and converted to a centile score using the appropriate chart. If the first recording is elevated then it should be repeated at least twice and if still elevated, and above the 95th centile, then referral to a paediatric hypertension specialist is required, for 24-hour ambulatory blood pressure recordings to confirm the diagnosis and to initiate any investigations for end organ damage. In patients already treated for ADHD, alternatively, a dose reduction or drug holiday could be proposed before referring to the specialist. Further management will depend on the severity of the blood pressure elevation and in consultation with the ADHD specialist might include antihypertensive treatment in addition to the stimulants, or discontinuation of the medication. A flow chart for both the ADHD specialist and hypertension specialist is attached.

A pulse rate consistently above 120/minute should be a signal for a cardiac review. New-onset palpitations should be managed as for unmedicated patients: occasional extra beats are not necessarily a cause for concern, but persistent tachycardia could be due to arrhythmia and needs investigation. In 2008 the American Heart Association recommended ECG as a standard part of the assessment for treatment for ADHD. ECG screening is however not currently considered cost-effective or appropriate for prevention of sudden death in the general paediatric population in Europe (or the US). Our view is that there is no current evidence to suggest an incremental benefit for ECG assessment of ADHD patients prior to initiation of medication.

2. Suicide-Related Events

'Suicide-related events' are not only self-destructive acts but also include suicidal ideation, plans and beliefs in the pointlessness of life. They can be assessed by the use of ratings such as the Columbia suicide rating scale [112]; and they are not necessarily associated with a depressive disorder. Systematic review has indicated that there is a relationship between the presence of ADHD itself and suicidal attempts [163] – so it should not automatically be assumed that any suicidal thinking or attempt is an adverse effect of medication. In terms of severity and impact, most reports to the MTA have been of mild and transient symptoms that did not require hospitalisation. There were no completed suicides.

Frequency of suicidality reports

Suicide-related events are rarely associated with ADHD drug treatment. In September 2005 the United States Food and Drug Administration (FDA) added a 'black box' warning to the product labeling of atomoxetine (Eli Lilly and Co. Strattera safety information, 2006 [online]), based on an analysis of adverse-event data from the atomoxetine clinical trials database, which identified a small but statistically significantly increased risk of suicidal thoughts among atomoxetine-treated children and adolescents compared with patients in those trials taking placebo. A meta-analysis of the data showed that suicidal ideation was more frequently observed in clinical trials among children and adolescents treated with atomoxetine (5/1357) compared to those treated with placebo (0/851), with a number needed to harm (NNH) of 227 compared to the number needed to treat (NNT) of 5 to achieve remission of ADHD symptoms [12]. There was one suicide attempt in the atomoxetine treated group and no completed suicide occurred during the trials. In adults treated with atomoxetine there was no evidence of increased suicidal risk. Specific figures for stimulants are not available.

Data from population-based studies indicate that self-reported suicide-related events are common in young people who have neither been diagnosed with, nor treated for, ADHD. For example, the rate of self-harm in UK 11-15 year olds with no mental disorder was 1.2%, 9.4% in those with anxiety disorders, 18.8% in children with depression, 12.6% in those with conduct disorder and 8.5% among children with hyperkinetic disorder [91]. In contrast, the prevalence of suicide-related behaviour in children treated with ADHD drugs from RCTs is reported as only 0.4% [147]. While this low observed event rate in trials is likely to reflect the exclusion of suicidal subjects from entering trials, a short time base, and a lack of systematic assessment and reporting, there is little or no compelling evidence to suggest that the observed event rate of suicide-related events in children treated with ADHD drugs is greater than the expected (background) rate in the general population.

Causality and factors mediating risk

Various emotional and behavioural changes are occasionally described in children treated with ADHD medications including: anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania and mania. These could in principle be markers to the states of distress that can lead to suicidal acts – but no causal link between the emergence of such symptoms and the emergence of suicidal impulses has been established. Co-morbidities occurring with ADHD (such as depression and conduct disorder) may in themselves be associated with an increase in the risk of suicidal ideation and/or behaviour.

Management of suicide risk

A psychiatric history is of course routinely needed before prescription of any medication. In view of uncertain degrees of risk, caution is required when prescribing ADHD drugs to children and young people with a past history of serious suicidal attempt or depression.

Families and caregivers should be advised of the need to recognize any emergence of emotional change or self-injurious thinking; and to communicate well with the prescriber [147]. Patients being treated with ADHD drugs should be observed for the emergence of suicide-related events. If they do emerge in treatment, consideration should be given to dose reduction 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. Psychiatric evaluation (or re-evaluation) should be arranged and the patient's progress carefully monitored.

3. Growth in childhood

Poor growth is a common concern in the treatment of ADHD, especially with children already on the lower growth percentiles; but the impact of medication on growth in weight and height has remained somewhat unclear. There are remaining questions as to whether ADHD in itself is an independent risk factor for poor growth, and whether individuals showing a slowing of growth whilst on medication return to their previous growth trajectory eventually or on discontinuation of medication**.**

Evidence of impact on growth, and possible causal mechanisms

Studies providing longitudinal data suggest that treating children with ADHD with stimulant medication generally results in a reduction in both height and weight gain [35,114]. On average, the reduction in height amounts to approximately 1 cm/year during the first 1-3 years of treatment (50). The reduction in weight gain appears to be somewhat more pronounced than that for height (over a 3-year period about 3 kg less than predicted) [40,141].

Stimulant treatment does not, however, appear to markedly increase the number of children who fall below the fifth percentile of the population [34]. Effects are usually minor, but there is substantial variability: some children are completely unaffected, whereas for others treatment results in significant growth suppression. Current data indicate that the initial effect of stimulants on growth appears to attenuate over time

[39,116,141] and early studies of the adult outcomes of children treated with stimulant medications have suggested that final adult height is not affected [56,71]. Nevertheless, follow-up periods are not yet sufficiently long enough, nor the sample sizes big enough, to allow firm conclusions to be drawn.

Most studies do not suggest differences in the magnitude of growth deficits between methylphenidate and dexamfetamine [107]. Small effects were seen for atomoxetine during the first 2 years of treatment; but in those who received prolonged treatment for up to 5 years no long-term effects on growth were apparent apart from an overweight subgroup [135,136]. These two parts of the same study are probably not yet sufficient evidence for ruling out growth problems as an adverse effect of atomoxetine, and indeed there is one study describing the medication as an effective adjunct to weight loss in obese women [46].

Reduced caloric intake and suboptimal nutrition due to appetite suppression are likely causes of growth suppression. Dysregulation of receptors in the growth system could also be responsible; adaptation of receptors could contribute to tolerance to growth inhibition over time and to catch-up growth after the medication has been discontinued. Acute effects on growth hormone and prolactin have been observed, but do not yet explain persisting growth deficits [15,33,83]. A hypothesis that ADHD itself is associated with dysregulated growth, either decreased [55,133] or increased [141,140] has been put forward, but current evidence is contradictory.

It is possible that the effects of stimulants on growth are dose-dependent. Significant effects on weight and height may require average doses of methylphenidate exceeding 1.5 mg/kg/day which are given continuously [25,134]. Effects may be greater for children than adolescents, but overall there are too few studies to allow firm conclusions in either of these areas. Preschool children may be particularly vulnerable to growth effects: The National Institute of Mental Health Preschool ADHD Treatment Study reported that children between 3 and 5 years of age treated with methylphenidate had annual growth rates 20.3% less than expected for height (1.38 cm/yr) and 55.2% for weight (-1.32 kg/yr) [140].

Management of growth risks

Physicians should advise patients and their parents about the potential for growth delay with medication use and discuss the balance between these effects and the potential outcomes that may result from non-treatment. A growth chart should be used to monitor height, weight and appetite in all medication-treated children and adolescents at least 6 monthly [142]. Should growth deficits occur during treatment, various clinical strategies might be considered. Current data do not support specific guidelines indicating what magnitude of height or weight gain deceleration should trigger changes in the treatment regimen, but simple strategies to improve nutrition can be implemented. These may include coordinating the timing of doses (e.g. taking the first dose after breakfast) and meals (e.g., late evening meal) and encouraging the use of high-energy, nutritious snacks. These clinical strategies would be expected to reduce growth deficits, but no studies have yet examined this hypothesis directly. Periods of treatment cessation (drug holidays) seem to result in rebound growth for children who experienced deficits during treatment, with children seeming to return to their normal growth percentiles and trajectory [36,113]. Drug holidays, however, can also be problematic for the child and family because the ADHD symptoms will often re-emerge or worsen during the period that medication is withheld. For individual patients, physicians need to balance the risk of exacerbating the child's ADHD symptoms, by lowering the dose or switching to a different medicine, against the risks associated with growth delays. Decisions should be based on the clinical considerations of the individual patient. If there is serious concern about growth, referral to a paediatric endocrinologist is warranted. Criteria for referral can follow the medical guidelines concerning referral for short stature and consideration of growth hormone supplementation in adults and children, which are as follow [47]:

- height >1.5 SDs below the average of mother's and father's height;
- >2 SDs below the population mean plus a 1- year height velocity >1 SD below the mean or a 1-year decrease of >0.5 SD in height;
- a 1-year height velocity >2 SDs below the mean, or a 2-year height velocity >1.5 SDs below the mean.

Further research is needed into the causal mechanisms, and the long term implications of continuous treatment from childhood to adulthood for ultimate height.

4. Sleep disturbance

As is the case for several of the other adverse events, sleep disturbance is associated both with ADHD medication, and the condition of ADHD itself. A recent meta analysis [28], based on 16 methodologically sound studies published between 1987 and 2008, showed that stimulant–free children with ADHD were significantly more impaired than healthy controls in parentally reported items of problematic behaviours around bedtime and in the early morning. These children were also impaired in some actigraphic and polysomnographic measures indicating fragmented sleep and poor sleep efficiency, sleep disordered breathing, and excessive daytime sleepiness [124]. However, the pooled analysis of all data on sleep architecture gave contradictory results about any alterations in REM sleep and no alterations on percentage of slow wave sleep. Some conditions associated with ADHD (such as anxiety) can also lead to poor sleep. The effect of sleep impairment differs greatly from one individual to another, but can be distressing to both the child and the family and may give rise to behavioural and learning difficulties in the daytime [102,106]

Frequency of sleep problems and heterogeneity

Clinical experience suggests that psychostimulant medication may negatively impact on sleep, but the effects vary considerably from one patient to another. Some patients with ADHD are able to get to sleep easily within just a few hours of taking a dose of stimulant medication, others need an interval of up to 6 to 8 hours [22]. Scientific studies comparing medicated and unmedicated children [125], are inconsistent, both for polysomnographic measures and for parental reports.

A review of subjective reports indicates that medicated versus unmedicated children with ADHD did not differ in sleep disturbance in one study, but medicated children had greater sleep problems in other studies after controlling for ADHD severity [26]. In placebo-controlled studies, sleep latency was similar in children with ADHD on methylphenidate versus placebo, but total sleep duration was shorter with methylphenidate than placebo [127]. Methylphenidate does not appear to affect sleep patterns adversely and possibly normalizes them in patients with ADHD [145]. Sleep problems are primarily related to ADHD severity and comorbidity and not to medication. Among individual sleep parameters, difficulty falling asleep continues to differ significantly between children with or without medication after the severity of ADHD symptoms has been controlled for [145].

It is possible that the inconsistency in these results is linked, at least in part, to the different stimulant formulations, dose, and dose-scheduling used in the available studies - all these factors can affect the duration of pharmacological actions. Some children may have worse sleep as a result of stimulant medications whilst others may sleep better: indeed, clinical experience would suggest that this is so. In some studies, objective measures suggest that methylphenidate may reduce total sleep time but improve sleep quality by consolidating sleep (70).

Several factors that may mediate the effects of stimulant medications on sleep have been identified. In one study, depressive symptoms contributed significantly to the degree of sleep disturbance when controlling for ADHD diagnosis and methylphenidate treatment [138]. Some studies assessed the effect of stimulants given in two doses (morning and noon). It is possible that sleep problems may be linked to restlessness linked to the rebound effect more than to the direct action of stimulants [23]. Some authors have reported that a small dose of methylphenidate taken before bedtime can facilitate sleep [64,70]. Other studies, however, using a third dose did find a greater sleep onset delay in children treated with stimulants compared to untreated subjects [3,139].

Differential drug effects between stimulant and nonstimulant medications

In a randomized, double-blind, cross-over study comparing the effect of methylphenidate (given thrice daily) and atomoxetine (given twice daily) on the sleep of children with ADHD, methylphenidate increased sleep-onset latency significantly more than did atomoxetine, both considering actigraphic and polysomnographic data [125]. Moreover, both childrens' diaries and parents' reports indicated a better quality of sleep (in terms of "getting ready in the morning", "getting ready for bed", "falling asleep") with atomoxetine, compared with methylphenidate. Both medications decreased night-time awakenings, but the decrease was greater for methylphenidate. Clearly, these results from a single study need to be replicated.

Management of sleep problem risks

Given the limited number of studies and the contradictory findings, guidelines for the management of sleep disturbances associated with ADHD cannot be properly evidence-based. A history of any sleep problems should be taken before starting medication, and if this is a severe/significant issue, it may suggest atomoxetine as a first line choice. If problems arise during medication, then sleep diaries are recommended. Sleep hygiene and behaviour therapy techniques based on stimulus control, and appropriate bed-time scheduling, should be encouraged for children with sleep-onset problems and/or possible delayed sleep phase syndrome.

A switch of medication should be considered when sleep problems persist after careful dose adjustment and dose-scheduling of the original medication; for instance, patients taking a stimulant medication might switch to atomoxetine. Although Clonidine is outwith the main focus of this paper, some evidence exists to suggest it may be effective in ADHD with associated sleep problems [155]. Recent research has also shown that melatonin is effective in reducing sleep-onset problems in ADHD children and could be considered a reasonable therapeutic approach [14].

5. Tics and Tourette's syndrome

In tic disorders (TD), co-existence with ADHD can be found in about 50% of patients, while in ADHD patients a TD is seen in about 20%: Both figures are above the chance rate of combination [123].The use of licensed ADHD drugs (central nervous stimulants and atomoxetine) in the presence of tics remains debatable. Some experts describe an increase in tics when drugs are given, others do not. Several Physician's Desk References and Drug Administration Mandates still note a contraindication for the use of stimulants in patients with TD [123,110] – and even in those with only a family history of tics. Fortunately, in recent updates this is no longer the case [142,50], but taking a history of tics and close monitoring of co-existing tics are mandatory (see decision of the European Commission for a new wording of European Drug Administration Mandates being harmonized all over Europe, Homepage of EMEA 2009).
Several recent reviews [126,121,21] indicate that stimulants are adequately safe in patients with both ADHD and TD and should not be disregarded when planning treatment for ADHD in these individuals. In terms of the impact of TD, the psychosocial functioning of ADHD + TD children is usually not worsened significantly when tic exacerbation by drugs takes place, since ADHD is commonly the more impairing disorder [119,120]. Rarely, stress-sensitivity may increase, but there will usually be enough time to come to a joint treatment decision with families balancing the risk-benefit-ratio

Frequency and Causality

Dopamine-receptor antagonists may decrease tics, while drugs which increase dopamine activity may precipitate or exacerbate tics. The *precipitation* of *first-onset tics* during treatment with methylphenidate was found not to be different from placebo (range: 0-20%) [121]. The literature on *exacerbation of pre-existing tics* by stimulants indicates that about 5-10% of cases may get worse with stimulants – independent of initial tic severity. This exacerbation, if it occurs, is fully reversible after stimulant withdrawal or dose reduction [103,111]. Moreover, clinical experience suggests that with improvement of attention and self-regulation by stimulants the control of tics may itself improve. In the

controlled studies of atomoxetine, its impact on tics was either not different from placebo or even showed some positive effect on tic frequency [109,137,4]. On the other hand, a few case reports have described exacerbation of tics during atomoxetine treatment [104,105,128,76,44,77]. This might reflect dopamine imbalance in certain patients, which is in line with the theory that stimulants might lead to further activation of an already hyperactive meso-striatal dopaminergic system in TD, where higher doses of stimulant compounds may provoke a higher frequency of tics.

Management of tics during ADHD treatment

Because tics are naturally waxing and waning it is often difficult to decide if a worsening of tics is provoked by a drug. Therefore, a long-term observation of at least three months is sometimes required before a clinical decision can be made. ADHD and TD can be considered within the framework of an additive model [123,11]. It follows, that the symptoms may be treated with a separate but parallel approach, i.e. in addition to stimulants or atomoxetine for ADHD, treatment with antipsychotic medication may help to reduce tics. The latter suggestion is not evidence based, being derived from the experiences of clinical experts only, but meanwhile it has been included in clinical guidelines [122]. It can be assumed that the effect on tic-exacerbation is similar for both methylphenidate and dexamfetamine. For atomoxetine, however, the situation may be more favourable, although the negative case reports cannot be neglected. For clonidine, which is only occasionally used in Europe to treat TD and/or ADHD, but recommended by some authors (especially where TD is the predominant disorder), [118], there exists some evidence that it may reduce tics in frequency and severity, as well as improve ADHD symptoms; but on the other hand worsening of tics may be seen in about a quarter of cases [1].

6. Substance abuse, misuse and diversion

Substance use disorder (SUD) is a maladaptive pattern of non-medical use of substances leading to functional impairment and/or risks over the past 12 months. Substance dependence is differentiated from abuse by 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 (as opposed to simply use associated with various risks and actual harms). Concurrence of ADHD and SUD has been consistently observed for many years and there is an ongoing debate on the question whether medication treatment of ADHD, with stimulants in particular, changes the risk for patients to develop SUD. Concerns exist both as to the use of stimulants to achieve a 'high' or for other reasons, such as to aid weight loss (misuse), and also as to the use of medications by individuals for whom they were not specifically prescribed (diversion). Findings from preclinical research have suggested that animals exposed to stimulants become "sensitized": Subsequent administration results in more robust behavioural responses, and/or they become more likely to self-administer drugs of abuse later in development [73,72].

Co-morbid risk and estimates of frequency of abuse

Several epidemiological studies compare ADHD subjects with unaffected groups, and find hazard ratios for SUD varying from 1.2 to 3 [19,31,94] and up to 7.9 for drug dependence [68]. Even a single symptom of ADHD or conduct disorder (CD) may be associated with an increased risk for SUD [31]: hyperactivity symptoms uniquely contributed to subsequent initiation of all types of substance use, to nicotine dependence, and cannabis abuse/dependence, even after controlling for CD, whereas impulsivity predicted alcohol misuse [32]. Based on follow-up data from the Multimodal Treatment Assessment (MTA) study, significantly higher rates of child-reported lifetime substance use at age 13 were reported in ADHD patients compared to a local normative comparison group (HRs 2.3) [93]. Probands with ADHD who did not differ from those without ADHD in absolute rates of SUD, still had an earlier onset, a longer duration, and higher rates of severely impairing SUD as well as higher rates of alcohol and drug dependence

than non-ADHD children [20]. Correspondingly, the prevalence of childhood and adult ADHD in the substance-abusing population has been estimated to be about 3 times that in the general population: for instance, adults with a lifetime diagnosis of cocaine and/or opioid dependency show an ADHD lifetime prevalence of 5.2%, compared to 0.85% in individuals without SUD [6].

Whether stimulant medication adds to the risk for substance abuse is not clear; several studies suggest it does not. A meta-analytic review of six studies suggested that stimulant therapy in childhood may be associated with a reduction in risk, compared to unmedicated ADHD subjects, for subsequent drug and alcohol use disorders (HR=1.9), with a stronger effect during adolescence (HR=5.8) than adulthood follow-up (HR=1.4) [157]. The reduction in risk might be attributable to treatment rather than stimulant medication in particular: the MTA study found a reduction in risk for those patients treated with behaviour therapy; medication had no effect one way or the other [93]. No difference in substance use was observed in patients with developmental reading disorder (but without ADHD), previously treated with methylphenidate or placebo for up to 18 weeks, suggesting that neither sensitization nor protective effects can be related to stimulant treatment *per se* [84]. Other studies show either no influence of methylphenidate or a reduction of risk - in one study only when stimulant treatment had been initiated before puberty [18,38,54,65,85].With regard to potential mediating factors, gender and the presence and severity of CD/antisocial personality disorder or delinquency appear to be the moderating variables for the risk of subsequent SUD in ADHD patients; and these effects are stronger than any influence of medication [13]. In ADHD subjects, both genetic predisposition and social/environmental factors interact to determine persistence of conduct symptoms and antisocial behaviours [24,100,131], which are then important influences on substance abuse and misuse.

Euphoric properties and reinforcing effects of methylphenidate are associated only with intravenous injection or nasal inhalation and not with oral administration [150]. Euphoria is practically unknown with oral methylphenidate; though the situation with dexamfetamine is unclear, because of lack of study rather than conflicting findings. Misuse or diversion of stimulants has been reported in adolescents and young

adults in North America, either in order to improve academic performance (studying, staying awake, improved alertness) or in the context of a SUD [148,154,158].

Prevention and Management of comorbid SUD, misuse and diversion

Early recognition and treatment perhaps combined with longer-term behaviour therapy and/or longer-term/continuous medication treatment, may reduce the risk for SUD in ADHD patients. Depending on the specific situation, current or previous substance abuse in the family can be seen as either a relative contraindication for stimulant prescription, especially in the immediate release preparation, or as a reason for extremely close monitoring of a patient's stimulant use. The extended-release formulations of stimulants are less prone to diversion because these preparations cannot easily be crushed into powder for injection or snorting, and also because the once-a-day administration makes parental supervision easier to enforce. Based on preclinical, short-term clinical data and abuse liability studies, the noradrenergic compound atomoxetine does not appear to be associated with risk for substance use disorders and may well be preferred in high-risk cases [63].

Use of cannabis is not necessarily a contraindication to prescribing stimulant medication, and a pragmatic approach will be required. The other dangers of cannabis, however, should not be ignored and patients will need to be warned. Cocaine, however, is likely to be a real hazard in view of its sharing neurochemical effects with dopaminergic drugs, and the two should not be combined.

7. Epilepsy and seizures

Children with epilepsies show a three- to fivefold higher prevalence of ADHD than controls [29]. Among the various psychopathological features of the epilepsies, ADHD is the most frequent comorbidity. ADHD patients have been shown to have incidence rates of unprovoked seizures and epilepsy as many as two to three times greater than non-

ADHD children [59]. Although epileptic disorders affect ~1% of the paediatric population, the evidence base for ADHD treatment in children with epilepsies is disproportionately thin.

There are occasionally concerns that, as with other psychotropics, ADHD medications may lower the seizure threshold so as to cause seizures in previously seizure free individuals. However, in prospective trials, retrospective cohort studies and postmarketing surveillance in ADHD patients without epilepsies, the incidence of seizures did not differ between ADHD pharmacotherapy and placebo (relative risk (RR) for current vs non-use for methylphenidate: 0.8; RR for atomoxetine: 1.1 [89,153]. Methylphenidate has been shown to prolong the duration of kindled seizures in rats [7]. Amfetamine has the potential to both increase and decrease seizure risk in animals [51,69]. In rodents treated with atomoxetine, seizure induction occurred only with doses several-fold higher than the highest approved dose for humans [146].

Mediating influences

Higher seizure rates are reported from never-treated ADHD patients with epilepsy compared to ever-treated ADHD patients [89]; it is unclear whether this is due to a reluctance to administer ADHD medication to children at risk for epilepsy or to risk factors mitigated by ADHD treatment (e.g. substance abuse). An elevated risk for seizures can be associated with antiepileptic drug (AED) polypharmacy, mental retardation, neurologic deficits, metabolic diseases, congenital anomalies, and other developmental disorders [89]. Available evidence does not support an increased risk in seizure-free ADHD-children with centro-temporal (rolandic) spikes [57,60].

Differential drug effects

There is substantial evidence for short-term efficacy of methylphenidate in children with epilepsies, while no negative effects on seizures and EEG abnormalities have been observed, and indeed there is some evidence for possible beneficial impacts in some

cases [43,52,53]. A larger systematic review did not find evidence for meaningful pharmacokinetic or pharmacodynamic interactions between methylphenidate and AEDs [86]. For amfetamines, effects on comorbid ADHD and epilepsies are not yet systematically evaluated. Response rates in case series are disappointing, but these reports are biased since they included almost exclusively non-responders to methylphenidate [48,101]. Amfetamine seems to have an anticonvulsant effect in patients with nocturnal seizures and a favourable impact on drowsiness induced by AEDs [5,42,81]. In several retrospective case series in previous methylphenidate non-responders with epilepsy, atomoxetine showed disappointing response rates and high rates of discontinuation [146]. Limited evidence from prospective case series in children with epilepsy is more promising, but a seizure increase may occur in a minority of cases [58]. For ampfetamine and atomoxetine, efficacy and short term safety have yet to be established in stimulant naive patients with infrequent seizures. As with methylphenidate, preliminary evidence supports efficacy on ADHD symptoms and a low seizure risk in patients with infrequent seizures. Studies in children with more active epilepsy seem justified.

Management of seizure risks

Adolescents with epilepsies are at increased risk for depression and suicidal ideation [8]. During ADHD treatment, they should therefore be monitored for the emergence of depression, irritability and suicidal ideation. A careful evaluation of the potential benefits and risks of pharmacotherapy seems warranted in preschool ADHD children, in whom epilepsies may still be recognized during their further development. Fatal hepatotoxicity has been reported as an extremely rare event in young epileptic children with polypharmacy or inborn errors of metabolism. Regarding the combination of atomoxetine with antiepileptic agents that might increase the risk for liver toxicity, patients should be carefully monitored clinically. Elevation of liver enzymes, however, is a poor predictor of impending hepatotoxicity.

Besides specific pharmacotherapy, ADHD symptoms in epilepsy may be improved by non-specific interventions, such as a better seizure control, decreasing AED

polypharmacy, reducing drug interactions, and switching to AEDs with fewer cognitive and behavioural effects [146].

8. Psychotic Symptoms

The term 'psychosis', as a reported adverse event, is defined at the level of symptoms and does not imply a full-blown psychotic disorder. Psychotic symptoms include hallucinations or delusions occurring in clear consciousness, neither associated with fever nor transitions to or from sleep. Adverse event reporting of 'psychosis' frequently also includes symptoms of mania, hypomania and 'agitated states'. In terms of the severity of impact of these symptoms, most reports from the FDA analysis described below [95] were of mild and transient symptoms that did not require hospitalisation or treatment.

Frequency

Psychotic symptoms are rarely associated with ADHD drug treatment. The United States Food and Drugs Administration (FDA), [95], reviewed 49 RCTs of ADHD drugs in children and found a total of 11 psychosis/mania events during 743 person years of exposure with ADHD drug treatment compared to no psychosis events reported with placebo. From these data, the psychosis event rate is 1.48 per 100 person years, or one event in every 70 years of treatment with a number needed to harm (NNH) of 526.

The FDA also reviewed industry post marketing surveillance case reports in the United States for ADHD drugs prescribed in children and adults between 2000 and 2005 and found 865 reports of psychosis events (157). Half of these reports occurred in children under the age of 10 years. Although the exact denominator (prescribing frequency) is unknown for post marketing surveillance reports, if we assume a prescribing frequency of 3 per 100 school age children in the United States this results in a rate of reported psychosis events of 1 in 2,500 treated cases of ADHD.

Psychotic adverse events have been reported in association with dexamfetamine, methylphenidate, and atomoxetine. The FDA review of ADHD drug RCTs, with regard the ADHD drugs reviewed in this report, reported the highest psychosis adverse event rate with MPH (in the form of transdermal patches, not currently licensed in Europe)(13.2/100 person years) followed by dexamfetamine (2.0/100 person years) and atomoxetine (0.8/100 person years). No psychosis adverse events were reported in 11 RCTs of oral methylphenidate (immediate and modified release) and 4 RCTs of mixed amfetamine salts (Adderall XR).

Amfetamine increases synaptic release of dopamine in the mesolimbic system and is associated with increased positive psychotic symptoms in patients with schizophrenia [75]. Hence, there is a plausible neurobiological mechanism that could link stimulant drugs with psychotic symptoms. However, this evidence all comes from studies in adults and in those with a pre-existing psychotic disorder and consequent increased vulnerability to psychotic symptoms. It is unclear whether a similar risk applies to children and those without an increased biological vulnerability to psychosis. Interestingly, half of the US FDA post marketing surveillance reports occurred in young children (under age 10) who would typically be viewed as being less vulnerable to dopamine mediated drug-induced psychosis than adolescents or adults (46).

Data from population-based birth cohorts indicate that self-reported psychotic symptoms are common and may occur in up to 10% of 11-year old children [117]. In contrast, the prevalence of psychotic symptoms in children treated with ADHD drugs from RCTs is reported as only 0.19% (46). While this very low observed event rate in trials is likely to reflect a lack of systematic assessment and reporting, there is no compelling evidence to suggest that the observed event rate of psychotic symptoms in children treated with ADHD drugs exceeds the expected (background) rate in the general population. In the U.S. FDA analysis, ADHD drug overdoses did not contribute significantly to reports of psychosis adverse events.

Theoretically, at least, evidence of vulnerability to psychosis in terms of a positive family history or prior psychotic episodes may increase the risk of psychotic symptoms with ADHD drugs.

Management of risk of psychosis or mania

The evidence of an increased risk of psychotic symptoms associated with ADHD drugs is weak. Reported psychosis adverse events are rare and much less common than the expected rate of self-reported non-clinical psychotic symptoms in the general child population. The impact of reported psychosis adverse events in most cases is mild and most are self-limiting. If psychotic symptoms do occur with ADHD drugs, then they could in very rare circumstances represent an adverse drug reaction or symptom of a psychotic disorder, but consideration should be given to the more likely possibility that psychotic symptoms are common phenomena in children and in most circumstances will be unrelated to either ADHD drugs or a psychotic disorder. Nevertheless, and in view of potentially increased vulnerability to psychosis with ADHD drugs, caution would be appropriate when prescribing ADHD drugs to children and young people with a family history of psychosis or past history of psychotic episodes.

9. Drug holidays –a way of controlling adverse effects of ADHD drugs?

The structured interruption of a pharmacological treatment (often called a drug holiday) occurs when a patient stops taking medication(s) for a period of time. In general drug holidays can be very short (a few days) or very long (months or even years). Drug holidays are commonly used in a range of therapeutic domains. Clinical anecdote and informal report suggests to us that drug holidays are quite commonly used in relation to ADHD medication. Drug holidays can have various functions, and in relation to ADHD treatment these can be divided into four types.

First, drug holidays can be used to counteract waning effectiveness after a period of continuous use – perhaps by interrupting the development of tolerance and the need to

continually increase the dose over time. Second, they can be used to monitor whether medication is still effective after a period of long term treatment or whether the balance between side effects and therapeutic effects is still in favour of continued treatment. Third, they can be used to allow normal life to resume and for activities to be undertaken without the effects being apparent. Finally, drug holidays can be used to control acute adverse events (e.g., poor sleep and reduced appetite) and reduce their chronic effects (e.g., reduced growth or high blood pressure).

Despite the potential value of drug holidays and the likelihood that they are used frequently, either formally or informally, as part of ADHD medication regimen, there is very little data on issues such as the extent of their use; the factors that predict use (e.g., child characteristics, parent and clinician's beliefs, disorder progression, social structures and cultural norms); or their effectiveness in terms of either enhancing or reducing clinical effects or reducing side effects and their adverse consequences.

Systematic study of these three questions seems especially important now because not only has consideration of drug holidays been recommended on pragmatic grounds [142,115,37], but also because of their potential frequent use - especially as parents (and/or patients) may often initiate drug holidays independently without the clinical guidance or approval [156,61,88].

Evidence for drug holidays

In the only randomised controlled trial addressing the issue of drug holidays and ADHD drug adverse effects, patients were randomized to receive either BID methylphenidate seven days a week or five days a week and a weekend drug holiday when placebo was administered in a double blind design [88]. No reduction in therapeutic effects on weekends (as rated by parents) or on the following day of school (as rated by teachers) was found, but despite this, fewer sleep and appetite side-effects were reported. Observational studies have also focused on the longer term effects of drug holidays on growth. A study on the effects of long term (at least 21 months) use of OROS methylphenidate on the growth of children and adolescents reported relatively small effects of methylphenidate on overall height and weight and a slight beneficial effect of drug holidays – however these effects were not significant [134]. In a similar study

comparing amfetamine and methylphenidate in children treated for at least one year, small effects of drug dose were found on height and weight but there was no effect of the duration of treatment or the use of drug holidays (63) .

Risk-benefit balance

The risk-benefit balance of drug holidays must be taken into account, and there are risks attached to the intermittent cessation of treatment. For instance, a review of the relationship between ADHD and burn accidents reported that a high proportion of children visiting burns units had not had their usual dose of medication on the day of the visit [45,144]. Furthermore, the health economic costs per year to accident emergency departments were higher when children were not receiving their normal medication [78].

In summary to date, and despite their theoretical benefits, the evidence that drug holidays can help control side effects is very limited. The data base needs to be expanded in a number of ways. First, the Martins et al. findings of the possible benefits of 5-days-a-week administration [88] need to be replicated; second, longer term studies need to be conducted using randomized and quasi-randomized designs; third, the range of adverse effects studied in relation to drug holidays needs to be extended (to include for instance cardiac effects). Fourth, the differential impact of 'informal' parent/patient- initiated and 'formal' clinician-initiated holidays should be studied. Fifth, the predictors of drug holiday effectiveness need to be examined. Sixth, benefits and costs of drug holidays need to be assessed systematically.

10. Issues lacking evidence and future evidence sources

A recurring theme in this paper is that there is particular uncertainty about possible adverse effects that are rare and severe. The most extreme is sudden death – which, as considered above, is so uncommon that extremely large numbers of subjects will be needed to detect whether the risk is raised above the base rate in the general population. Liver failure presents a similar uncertainty for the clinician: rare cases have been reported

in people taking atomoxetine. They may well be no more common than in the population as a whole, but no conclusion is possible. The probability of under-reporting, and the lack of information about the usual prevalence of otherwise unexplained liver failure, leave real uncertainty. We can recommend only that the clinician should be vigilant for early signs of disease – which would include persistent and unexplained malaise as well as the more obvious features such as jaundice, dark urine, or itching - and investigate with liver enzyme tests if they appear. In the UK, the former Committee on Safety of Medicines has stated that families should be warned in advance of the necessity for medical advice if any of these signs should appear.

Another kind of uncertainty arises from possible problems for which good measurement has not previously been available. There could be long-term changes in the brain – for instance, in neurotransmitter levels or receptor density – but adequate techniques of investigation are only now becoming available. We do not know if such changes occur; if they do, whether they are related to medication or to the condition itself; if they are caused by medication, whether they have functional significance; and whether any changes are helpful or harmful to mental development. This is not to argue that the effects are harmful; to the contrary, our clinical experience of long-term medication has not uncovered concerns of cognitive malfunction or brain damage. Rather, it is to point to the need for research on possible subtle changes, whether for good or for ill. Neuropsychological and cognitive tests should be developed to test specific hypotheses about potentially harmful effects. New techniques are appearing that could in principle allow prediction of individuals' vulnerability to adverse effects. Pharmacogenomics, repeated monitoring of blood levels of ADHD compounds, and neuroimaging of the brain's response to medication could all earn a place in clinical practice. For the moment, however, we see them as opportunities for translational research, not recommendations for practice.

For many clinicians, the impact of risk of ADHD treatment, and the balance of that risk against possible benefits of treatment will be seen as favourable in most cases, but with a caveat that there are several areas of uncertainty about the nature of these risks. This

review should help in this regard, but as already discussed each area still requires further clarification from pharmacoepidemiology. The concept of ‘willingness to pay’ may have value when applied to the question of what level of adverse effects is acceptable for a given treatment benefit for an individual person. Responsive discussion with patients and their families is important. Monitoring should include not only the blood pressure and growth measures already mentioned, but also common symptoms such as headache, insomnia, anorexia, nausea and emotional upsets; and any specific problems emerging in the individual patient. As ever, the primary responsibility for ensuring the safety of the patient lies with the prescriber.

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