A REVIEW OF BEST PRACTICE IN THE TREATMENT OF ADHD

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This article provides an overview of various aspects of the treatment of attention deficit hyperactivity disorder (ADHD).

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Introduction

Attention deficit hyperactivity disorder (ADHD) is a heterogeneous disorder characterized by the core symptoms of hyperactivity, impulsivity and inattention, which are judged excessive for the person's age or level of overall development. The diagnosis is made on the basis of observed and reported behavioral symptoms. Two main diagnostic systems are in current use, the International Classification of Mental and Behavioral Disorders 10th revision (ICD-10) and the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5). Both systems require that symptoms are present in several settings such as school/work, home life and leisure activities. Symptoms should be evident in early life, if only in retrospect; for ICD-10, by age 7 years and for DSM-5, by age 12 years. ADHD may persist into adult life.

Prevalence rates for ICD-10 (identifying hyperkinetic disorder) are 1 to 2% in childhood. Under the previous, less stringent DSM-IV criteria, childhood prevalence rates were 3 to 9% and these may increase under the new DSM-5 criteria.

The causes of ADHD are not fully understood but several risk factors are associated with the condition. Genetic factors can have an influence, with family members frequently affected. The diagnosis

of ADHD in older family members such as parents may have previously been missed and should be considered.

Both the ICD-10 and DSM-5 require the presence of functional impairment due to symptoms of ADHD, with the symptoms adversely affecting psychological, social and/or educational/occupational functioning. The impact of ADHD may vary considerably in its severity, which is best judged by considering the level of impairment, pervasiveness, and familial and social context. For some people, symptoms may be limited to certain settings and cause minimal impairment in a limited number of domains (for example, ability to complete schoolwork, work tasks, avoiding common hazards and forming positive interpersonal relationships). In other people, multiple symptom areas (hyperactivity, inattention and impulsivity) are present in multiple settings, and this causes significant impairment across multiple domains. Symptoms and impact can also change over time. For some people, symptoms and impairment may be reduced through environmental modifications, such as a modified school curriculum or choice of employment.

Symptoms of ADHD can overlap with those of other related disorders. Therefore, care in differential diagnosis is needed. ADHD may also coexist with other disorders. Common coexisting conditions in children include disorders of mood, conduct, learning, motor control, language and communication, and anxiety disorders; in adults, they include personality disorders, bipolar disorder,

obsessive-compulsive disorder and substance misuse. Where there are coexisting conditions, it is important to try to differentiate the level of impairment due to ADHD, because this will guide the treatment plan. In addition, ADHD is under-recognized in some populations, which can mean that a lack of appropriate diagnosis and treatment adversely affects people's quality of life.

Consequences of No Treatment

Long-term follow-up, epidemiological and clinical studies have shown that adults with untreated ADHD, when compared to normal controls, experience higher rates of academic failure, low occupational status, increased risk of substance use disorders (tobacco, alcohol or drugs), accidents and delinquency, and have fewer social relationships or friends (S. J. Kooij et al., 2010). Patients diagnosed with ADHD in adulthood often complain that they did not receive treatment earlier in life and feel that their life would have been different if they had. Appropriate treatment could have prevented accidents and ongoing impairment at school, at work and in their peer and partner relationships (S. J. Kooij et al., 2010).

Treatment of adult ADHD can influence psychosocial impairment that results as a consequence of 'core' ADHD symptoms, and may lead to improvements in associated features and comorbid disorders. These include the following (S. J. J. Kooij et al., 2010):

- psychological functioning and self-confidence

- family/relationship functioning
- interpersonal (broader than family) functioning
- professional/academic functioning
- cognitive deficits
- driving performance
- risk of substance use disorder

Multidisciplinary Treatment

Treatment should happen within multidisciplinary teams or networks, including, depending on the age and stage in life of the patient, including, medical professionals, psychotherapists, educators, parents, ADHD coaches, self-help groups, HR specialists and others, while taking into account the autonomy of the patient and any confidentiality requirements.

The treatment plan and approach should be comprehensive, holistic and continuous, addressing psychological, behavioral and occupational or educational needs. The NICE Guidelines recommend taking into account (NICE, 2018):

- the severity of ADHD symptoms and impairment, and how these affect or may affect everyday life (including sleep)
- their goals
- their resilience and protective factors

- the relative impact of other neurodevelopmental or mental health conditions.

Regularly discuss with people with ADHD, and their family members or carers, how they want to be involved in treatment planning and decisions; such discussions should take place at intervals to take account of changes in circumstances (for example, the transition from children's to adult services) and developmental level, and should not happen only once.

Before starting any treatment for ADHD, discuss the following with the person, and their family or carers as appropriate, encouraging children and young people to give their own account of how they feel (NICE, 2018):

- the benefits and harms of non-pharmacological and pharmacological treatments (for
- example, the efficacy of medication compared with no treatment or nonpharmacological treatments, potential adverse effects and non-response rates)
- the benefits of a healthy lifestyle, including exercise
- their preferences and concerns (it is important to understand that a person's decision
- to start, change or stop treatment may be influenced by media coverage, teachers,
- family members, friends and differing opinion on the validity of a diagnosis of ADHD)

- how other mental health or neurodevelopmental conditions might affect treatment
- choices
- the importance of adherence to treatment and any factors that may affect this (for
- example, it may be difficult to take medication at school or work, or to remember
- appointments).

Record the person's preferences and concerns in their treatment plan.

Treatment of Children

It is important to include children and young people in any treatment discussions and recommended they should be encouraged to say how they feel. This should include their views on the aims and effect of any treatments. Since decisions around treatment can have many influences, including teachers and family, it can be helpful to ask the patient, if they want to include anyone else in the development and implementation of the treatment plan.

Evidence routinely shows the benefit of medication in this age group in improving ADHD symptoms, while there are concerns about recommending medication for ADHD and particularly the

uncertainty over the long-term adverse effects of medication in growing children. However, untreated ADHD can have far-reaching, long-lasting negative impacts on a child or young person's life, affecting

- academic performance
- interpersonal relationships
- work
- driving
- substance use
- and more

While medication may offer a more cost-effective treatment in several circumstances, it should always be part of an overall treatment package including also other therapeutic approaches. In milder cases, psychotherapy alone may be sufficient, but given the adverse consequences of an inadequately treated ADHD, one needs to keep all treatment options in mind and discuss them with the patient at intervals.

Transition into Adulthood

A young person with ADHD should be reassessed at school-leaving age to establish the need for continuing treatment into adulthood. If treatment is necessary, arrangements should be made for a

smooth transition to adult services with details of the anticipated treatment and services that the young person will require. The arrangements should usually be completed by the time the young person is 18 years. (NICE, 2018)

After transition to adult services, adult healthcare professionals should carry out a comprehensive assessment of the person with ADHD that includes personal, educational, occupational and social functioning, and assessment of any coexisting conditions, especially drug misuse, personality disorders, emotional problems and learning difficulties. (NICE, 2018)

Diagnosis

The diagnosis of ADHD is essentially a clinical diagnosis, which can benefit from the use of supportive tools, such as rating scales and a cognitive assessment. ADHD should be considered in all age groups, with symptom criteria adjusted for age-appropriate changes in behavior.

For a diagnosis of ADHD, symptoms of hyperactivity/impulsivity and/or inattention should:

- meet the diagnostic criteria in DSM-5 or ICD-10 (hyperkinetic disorder)

and

- cause at least moderate psychological, social and/or educational or occupational impairment based on interview and/or direct observation in multiple settings and be pervasive, occurring in 2 or more important settings including social, familial, educational and/or occupational settings.

Diagnosis in Females

The ADHD prevalence rates are higher among boys than girls. ADHD has repeatedly been suspected to be underdiagnosed in females, irrespective of the age. Accurate ADHD diagnosis in women and girls requires establishing a symptom history and an understanding of its gender-specific presentation. Coexisting anxiety and depression are prominent in female patients with ADHD; satisfactory academic achievement should not rule out an ADHD diagnosis. (Quinn & Madhoo, 2014)

Attitudes about ADHD among individuals with ADHD and knowledgeable informants (families, teachers, colleagues) appear to vary on the basis of the diagnosed individual's gender. Quinn and Madhoo found in a literature review that (Quinn & Madhoo, 2014):

- low index of clinical suspicion exists for girls

- girls' presentation is considered "subthreshold" because inattentiveness is more prominent than hyperactivity/impulsivity.
- anxiety and depression, common comorbidities in female patients with ADHD, can lead to missed or misdiagnosis
- if not properly diagnosed and treated, girls with ADHD experience the same negative consequences as boys, including poor academic performance and behavioral problems
- unique issues related to hormonal effects on ADHD expression and treatment response are experienced by women and girls.

It may also be that females with ADHD may develop better coping strategies than males to mask their symptoms.

Diagnosis in Adults

Adults presenting with symptoms of ADHD should be assessed, where there is evidence of typical manifestations of ADHD, such as inattention, hyperactivity or impulsiveness, that (NICE, 2018):

- began during childhood and have persisted throughout life
- are not explained by other psychiatric diagnoses (although there may be other coexisting psychiatric conditions)

- have resulted in or are associated with moderate or severe psychological, social and/or educational or occupational impairment.

At-Risk Groups

The following groups may have increased prevalence of ADHD compared with the general population (NICE, 2018):

- people born preterm (see NICE's guideline on developmental follow-up of children and young people born preterm)
- looked-after children and young people
- children and young people diagnosed with oppositional defiant disorder or conduct disorder
- children and young people with mood disorders (for example, anxiety and depression)
- people with a close family member diagnosed with ADHD
- people with epilepsy
- people with neurodevelopmental disorders (for example, autism spectrum disorder, tic
- disorders, learning disability [intellectual disability] and specific learning difficulties)
- adults with a mental health condition
- people with a history of substance misuse

- people known to the Youth Justice System or Adult Criminal Justice System
- people with acquired brain injury. [2018]

The Wider Picture

As part of the diagnostic process, include an assessment of the person's needs, coexisting conditions, social, familial and educational or occupational circumstances and physical health. For children and young people, there should also be an assessment of their parents' or carers' mental health.

The Effects of a Diagnosis

A diagnosis is usually sought because of the benefits it has. It provides information with additional insight into a patient's difficulties in life. It can also help in finding the right therapeutic approaches and provide access to them, while respecting the uniqueness and individuality of the patient.

However, there can also be negative impacts of receiving a diagnosis, such as stigma and labelling a greater tendency for impulsive behavior (NICE, 2018).

The diagnosis can also have very practical consequences, such as possible effects on driving, where the licensing office may have to be notified of the diagnosis in some countries and circumstances.

Childhood Oppositional Defiant Disorder

To evaluate the overlap between attention-deficit hyperactivity disorder (ADHD) and oppositional defiant disorder (ODD), addressing whether ODD is a subsyndromal form of conduct disorder (CD) and, if so, whether it is a precursor or prodrome syndrome of CD. Assessments from multiple domains were used to examine 140 children with ADHD and 120 normal controls at baseline and 4 years later. Of children who had ADHD at baseline, 65% had comorbid ODD and 22% had CD. Among those with ODD, 32% had comorbid CD. All but one child with CD also had ODD that preceded the onset of CD by several years. ODD+CD children had more severe symptoms of ODD, more comorbid psychiatric disorders, lower Global Assessment of Functioning Scale scores, more bipolar disorder, and more abnormal Child Behavior Checklist clinical scale scores compared with ADHD children with nonCD ODD and those without ODD or CD. In addition, ODD without CD at baseline assessment in childhood did not increase the risk for CD at the 4-year follow-up, by midadolescence. Conclusions: Two subtypes of ODD associated with ADHD were identified: one that is prodromal to CD and another that is subsyndromal to CD but not likely to progress into CD in later years. These ODD subtypes have different correlates, course, and outcome. (Biederman et al., 1996)

Consider a course of cognitive behavioural therapy (CBT) for young people with ADHD who have benefited from medication but whose symptoms are still causing a significant impairment in at least one domain, addressing the following areas:

- social skills with peers
- problem-solving
- self-control
- active listening skills
- dealing with and expressing feelings.

Dietary advice

The NICE Guidelines recommend (NICE, 2018):

- Healthcare professionals should stress the value of a balanced diet, good nutrition and regular exercise for children, young people and adults with ADHD.
- Do not advise elimination of artificial coloring and additives from the diet as a generally applicable treatment for children and young people with ADHD.
- Ask about foods or drinks that appear to influence hyperactive behavior as part of the clinical assessment of ADHD in children and young people, and:

- if there is a clear link, advise parents or careers to keep a diary of food and drinks taken and ADHD behavior if the diary supports a relationship between specific foods and drinks and behavior, offer referral to a dietitian
- ensure that further management (for example, specific dietary elimination) is jointly undertaken by the dietitian, mental health specialist or pediatrician, and the parent or carer and child or young person.
- Do not advise or offer dietary fatty acid supplementation for treating ADHD in children and young people.
- Advise the family members or carers of children with ADHD that there is no evidence about the long-term effectiveness or potential harms of a 'few food' diet for children with ADHD, and only limited evidence of short-term benefits.

Comorbidity

In the committee's experience, other mental health and neurodevelopmental conditions may affect treatment choices and how successful these are. The committee emphasized the importance of a holistic approach to managing ADHD.

Psychotherapy

Evidence indicates a benefit of non-pharmacological treatment, although this seems less than for medication (NICE, 2018). However, psychotherapy routinely shows in clinical practice to be very valuable in conjunction with medication or in relatively mild forms of ADHD by itself.

Moriyama and colleagues reviewed the literature available by searching for meta-analyses assessing pharmacological and psychosocial interventions for adults with ADHD. No conclusions about the impact of psychosocial interventions could be drawn based on meta-analyses so far. The efficacy of stimulants in reducing ADHD symptoms for adults is well documented in meta-analyses, but there is a concerning lack of meta-analysis about other treatment interventions. (Moriyama, Polanczyk, Terzi, Faria, & Rohde, 2013)

The NICE Guidelines conclude that some evidence showed a benefit of cognitive behavioral therapy (CBT) in young people with ADHD. The committee agreed that this should be considered when a young person has benefited from medication but still has symptoms that are causing a significant impairment. They used their experience to recommend areas that a program should address. (NICE, 2018)

Hesslinger and colleagues presented a structured skill training program particularly tailored for adult patients with ADHD. The program is based on the principles of cognitive-behavioral

treatment for borderline personality disorder developed by M. Linehan and contains the following elements (Hesslinger et al., 2002):

- neurobiology of ADHD, mindfulness
- chaos and control
- behavior analysis
- emotion regulation
- depression
- medication in ADHD
- impulse control
- stress management
- dependency
- ADHD in relationships
- self-respect

In an open study design, this treatment resulted in positive outcomes in that patients improved on all psychometric scales. (Hesslinger et al., 2002)

Psychodynamic Psychotherapy

In a systematic review of the literature on psychodynamic psychotherapy with ADHD children questions relevant to the practice of psychodynamic psychotherapy were the focus and included a review of psychodynamic diagnosis of ADHD, theoretical

orientations of psychodynamic psychotherapy, identification of core treatment issues, clinical examples, and theoretical perspectives on therapeutic change as well as practice techniques.. (Conway, 2012)

CBT

The COMPPAS study group follows 448 adults with ADHD. Patients are randomized to a manualized dialectical behavioral therapy (DBT) based group program plus methylphenidate or placebo or clinical management plus methylphenidate or placebo with weekly sessions in the first 12 weeks and monthly sessions thereafter. ADHD symptoms measured by the Conners Adult Rating Scale. (Philipsen et al., 2010)

Coaching

Therapy and coaching deal with feelings and beliefs but at very different levels. Coaching is not intended as a substitute for psychotherapy, nor is it likely to benefit individuals who are experiencing more severe psychiatric symptoms.

Coaching is a model intended to improve daily functioning and well-being for individuals without significant psychological impairment. There are concerns that although coaching as an adjunctive, complimentary, or supplementary treatment for ADHD has become

increasingly popular, there is little empirical data to validate the concepts and strategies of ADHD coaching.. (Goldstein, 2005)

Adults

The NICE Guidelines recommend non-pharmacological treatment for adults with ADHD who have (NICE, 2018):

- made an informed choice not to have medication
- difficulty adhering to medication
- found medication to be ineffective or cannot tolerate it.

Support Groups

Provide information to people with ADHD (and their families and carers as appropriate) in a form that: takes into account their developmental level, cognitive style, emotional maturity and cognitive capacity, including any learning disabilities, sight or hearing problems, delays in language development or social communication difficulties takes into account any coexisting neurodevelopmental and mental health conditions is tailored to their individual needs and circumstances, including age, gender, educational level and life stage.

Supporting families and carers

The NICE Guidelines recommend to encourage family members or carers of people with ADHD to seek an assessment of their personal, social and mental health needs, and to join self-help and support groups if appropriate, and to give advice to parents and carers of children and young people with ADHD about the importance of (NICE, 2018):

- positive parent– and carer–child contact
- clear and appropriate rules about behavior and consistent management structure in the child or young person's day.

Involving schools, colleges and universities

When ADHD is diagnosed, when symptoms change, and when there is transition between schools or from school to college or college to university, obtain consent and then contact the school, college or university to explain (NICE, 2018):

- the validity of a diagnosis of ADHD and how symptoms are likely to affect school, college or university life
- other coexisting conditions (for example, learning disabilities) are distinct from ADHD and may need different adjustments
- the treatment plan and identified special educational needs, including advice for

- reasonable adjustments and environmental modifications within the educational placement
- the value of feedback from schools, colleges and universities to people with ADHD and their healthcare professionals.

Children under 5 years

Offer an ADHD-focused group parent-training program to parents or carers of children under 5 years with ADHD as first-line treatment. (NICE, 2018)

If after an ADHD-focused group parent-training program, ADHD symptoms across settings are still causing a significant impairment in a child under 5 years after environmental modifications have been implemented and reviewed, obtain advice from a specialist ADHD service with expertise in managing ADHD in young children (ideally a tertiary service). (NICE, 2018)

Parents and Carers

The NICE Guidelines make the recommendation to give information about ADHD and offer additional support to parents and carers of all children aged 5 years and over and young people with ADHD. The support should be ADHD focused, can be group based and as few as 1 or 2 sessions. It should include (NICE, 2018):

- education and information on the causes and impact of ADHD
- advice on parenting strategies
- with consent, liaison with school, college or university
- both parents and carers if feasible.

Parent-training programs exist for parents and carers of children and young people with ADHD and symptoms of oppositional defiant disorder or conduct disorder.

Environment

It may not always be possible to make environmental modifications. However, sometimes even minor adjustments can be very helpful.

Medication

Results from meta-analyses suggest that stimulants are effective in decreasing ADHD symptoms on a short-term basis with a medium to large effect size. Short-acting stimulants might be superior to long-acting stimulants, but no data on difference in adherence are available for the comparison of these two types of formulation. Bupropion is superior to placebo but less effective than stimulants. (Moriyama et al., 2013) Evidence shows a clinically important

benefit for monotherapy with the stimulants methylphenidate and lisdexamfetamine compared with placebo or other drugs. Stimulants seem to work more quickly than non-stimulant drugs in clinical practice. (NICE, 2018) Results of a systematic study revealed that both prostimulant and stimulant medications, including lisdexamfetamine dimesylate, methylphenidate, amphetamines, and mixed-amphetamine salts, are effective at reducing ADHD symptoms in adolescents and adults with ADHD. (Weyandt et al., 2014)

Fredriksen and colleagues reviewed five randomized controlled trials and ten open-label extension studies of initial short-term randomized controlled trials, with total follow-up of at least 24 weeks, to find that medication was significantly more efficacious than placebo in treating ADHD in adults. The extension studies showed that this favorable effect of medication was maintained during the open-label follow-up period. A review of eighteen defined naturalistic longitudinal and cross-sectional studies also showed positive correlations between early recognition of the disorder, stimulant treatment during childhood and favorable long-term outcome in adult ADHD patients. (Fredriksen, Halmøy, Faraone, & Haavik, 2013)

Before starting medication for ADHD, people with ADHD should have a full assessment, which should also include a review of (NICE, 2018)

- presence of coexisting mental health and neurodevelopmental conditions
- current educational or employment circumstances
- risk assessment for substance misuse and drug diversion
- care needs
- a review of physical health, including:
    - a medical history, taking into account conditions that may be contraindications for specific medicines
    - current medication
    - height and weight (measured and recorded against the normal range for age, height and sex)
    - baseline pulse and blood pressure (measured with an appropriately sized cuff and compared with the normal range for age)
    - a cardiovascular assessment
    - an electrocardiogram (ECG) if the treatment may affect the QT interval.

A patient should be referred for a cardiology opinion before starting medication for ADHD if any of the following apply (NICE, 2018):

- history of congenital heart disease or previous cardiac surgery
- history of sudden death in a first-degree relative under 40 years suggesting a cardiac
- disease

- shortness of breath on exertion compared with peers
- fainting on exertion or in response to fright or noise
- palpitations that are rapid, regular and start and stop suddenly (fleeting occasional bumps are usually ectopic and do not need investigation)
- chest pain suggesting cardiac origin
- signs of heart failure
- a murmur heard on cardiac examination
- hypertensive blood pressure

General Considerations

Methylphenidate is usually recommended as a treatment for children aged 5 years and over and young people, and lisdexamfetamine or methylphenidate as a treatment for adults. (See in this regard also the NICE Guidelines (NICE, 2018)) If methylphenidate has not been effective for children aged over 5 years and young people, then lisdexamfetamine could be considered. (See in this regard also the NICE Guidelines (NICE, 2018))

Combinations

There is very little evidence to guide healthcare professionals beyond monotherapy, particularly with regard to whether there is a benefit of prescribing stimulant and non-stimulant medication together. (NICE, 2018)

Costs

The committee acknowledged the rising cost of dexamfetamine since 2008 and agreed that it should only be considered when lisdexamfetamine is effective but the longer effect profile is not well tolerated.

Treatment Naiveite

Most of the evidence to support the recommendations for medication choices for people with ADHD comes from studies in people who have previously received medication. Therefore, these studies often include a population not representative of the people with newly diagnosed ADHD. There may be differing levels of efficacy of the various treatment options in people who have received no previous medication for ADHD. (NICE, 2018)

Dosage

A careful initiation of the ADHD medication, particularly the stimulants, is crucial to identify any problems early and to find the correct dose. Slow up titration should be used for all stimulants. The optimal dose is where the patient's daily functioning, whether in a relationship, academically, socially or on the job, is maximized, while side effects, whether present or potential, in the short or long-term, is kept at a lowest level. (Haverkampf, 2018)

Children and Adolescents

The NICE Guidelines make the recommendation to offer medication for children aged 5 years and over and young people only if (NICE, 2018):

- their ADHD symptoms are still causing a persistent significant impairment in at least one domain after environmental modifications have been implemented and reviewed
- they and their parents and carers have discussed information about ADHD
- a baseline assessment has been carried out

As to the specific medication, the NICE Guidelines make the following recommendations (NICE, 2018):

- Offer methylphenidate (either short or long acting) as the first line pharmacological treatment.
- Consider switching to lisdexamfetamine if a 6-week trial of methylphenidate at an adequate dose has not derived enough benefit in terms of reduced ADHD symptoms and associated impairment.
- Consider dexamfetamine if ADHD symptoms are responding to lisdexamfetamine but the longer effect profile is not tolerated.
- Offer atomoxetine or guanfacine if:

- methylphenidate or lisdexamfetamine is not tolerated or
- symptoms have not responded to separate 6-week trials of lisdexamfetamine and methylphenidate, having considered alternative preparations and adequate doses.

Adults

There are concerns about recommending medication for ADHD and in particular the uncertainty over the long-term benefits and the adverse effects of medication. However, untreated ADHD can have a negative impact on a person's life, with lower educational attainment, and higher criminality. The NICE Guidelines recommend medication when ADHD symptoms are still causing a significant impairment in at least one domain of everyday life despite environmental modifications. (NICE, 2018)

As to the specific medication, the NICE Guidelines make the following recommendations for adults suffering from ADHD (NICE, 2018):

- Offer lisdexamfetamine or methylphenidate as first-line pharmacological treatment.
- Consider switching to lisdexamfetamine if a 6-week trial of methylphenidate at an adequate dose has not derived

enough benefit in terms of reduced ADHD symptoms and associated impairment.

- Consider switching to methylphenidate if a 6-week trial of lisdexamfetamine at an adequate dose has not derived enough benefit in terms of reduced ADHD symptoms and associated impairment.
- Consider dexamfetamine if ADHD symptoms are responding to lisdexamfetamine but the longer effect profile is not tolerated.
- Offer atomoxetine if:
    - lisdexamfetamine or methylphenidate is not tolerated or
    - symptoms have not responded to separate 6-week trials of lisdexamfetamine and methylphenidate, having considered alternative preparations and adequate doses.
    -

Atomoxetine

Atomoxetine (Strattera®) is a selective norepinephrine (noradrenaline) reuptake inhibitor that is not classified as a stimulant and is indicated for use in patients with ADHD. With its approval by the US Food and Drug Administration in late 2002, an effective non-stimulant option became available. Numerous trials have found that atomoxetine improves quality of life and emotional lability in addition to core ADHD symptoms. The median time to

response using 25% improvement in ADHD symptoms in pooled trials was close to four weeks, while the latter indicate that the probability of symptom improvement may continue to increase up to one year after treatment is initiated. (Childress, 2016)

Atomoxetine can be administered either as a single daily dose or split into two evenly divided doses, has a negligible risk of abuse or misuse, and is not a controlled substance in the US. Atomoxetine is particularly useful for patients at risk of substance abuse, as well as those who have co-morbid anxiety or tics, or who do not wish to take a controlled substance. (Garnock-Jones & Keating, 2009)

Atomoxetine appears to be significantly more effective than placebo and not to be inferior to immediate-release methylphenidate. However, it seems to be significantly less effective than extended-release formulations of both methylphenidate and mixed amphetamine salts (Garnock-Jones & Keating, 2009). A meta-analysis comparing core ADHD symptom response between atomoxetine and methylphenidate in children and adolescents found that, after 6 weeks of treatment, atomoxetine and methylphenidate had comparable efficacy in reducing core ADHD symptoms in children and adolescents. (Hazell et al., 2011) 53.6% of atomoxetine-treated patients (n = 811) had responded compared with 54.4% for methylphenidate (n = 557).

Amphetamine Formulations

In a 24-month, open-label extension of a 4-week, multicenter, double-blind, placebo-controlled, parallel-group, forced–dose-escalation study of extended-release mixed amphetamine salts in adults with ADHD, the 223 enrolled subjects started treatment at 20 mgl day for 1 week, with subsequent titration up to 60 mgl day for optimal therapeutic effects. ADHD symptoms significantly improved for all subjects, which was sustained for up to 24 months. The most common treatment-related adverse events were dry mouth (43% of subjects reporting at least one occurrence), infection (33%), insomnia (32%), anorexia/decreased appetite (32%), headache (30%), and nervousness (26%). Most adverse events were mild to moderate in intensity. (Biederman et al., 2005)

In a meta-analysis of twenty-three trials, significant differences between amphetamine and methylphenidate products were found, even after correcting for study design features that might have confounded the results. Effect sizes for amphetamine products were significantly, albeit moderately, greater than those for methylphenidate. The difference in effect size may be due to differences in the molecular mechanisms involved in facilitating the dopaminergic neurotransmission. (Faraone & Buitelaar, 2010)

Further medication choices

Atomoxetine is more widely used and that there appears to be stronger evidence for a benefit of atomoxetine compared with placebo than guanfacine compared with placebo (NICE, 2018). The NICE Guidelines recommend that in children aged 5 years and over and young people, either drug could be offered after intolerance or a lack of response to stimulants, while atomoxetine should be used in this case in adults (NICE, 2018).

Medication choice – people with coexisting conditions

The same medication choices apply to people with ADHD and anxiety disorder, tic disorder or autism spectrum disorder as other people with ADHD (NICE, 2018) For ADHD patients of any age experiencing an acute psychotic or manic episode the NICE Guidelines make the following recommendations: (NICE, 2018):

- stop any medication for ADHD
- consider restarting or starting new ADHD medication after the episode has resolved, taking into account the individual circumstances, risks and benefits of the ADHD medication.

Immediate Release

Immediate-release preparations may be suitable if more flexible dosing regimens are needed, or during initial titration to determine correct dosing levels. (NICE, 2018) As a starting point they can be increased in very small steps, such as methylphenidate by 5 mg every other day or at longer intervals. From a safety perspective, this may be superior to starting with a longer acting formulation, which stays longer in the system and often cannot be started at a very small dose.

Extended Release

Extended release formulations are often preferred by patients for several reasons, among them the convenience of not having to remember taking medication multiple times a day and a lesser need to store and transport a large number of tablets. There may also be a lower risk of diversion and abuse of longer acting stimulants.

Immediate and Extended Release Combined

While it is usually preferred to work with only one medication type and formulation, the NICE Guidelines suggest considering the use of immediate- and modified-release preparations of stimulants to optimize their effect. They give the example of a modified-release preparation of methylphenidate in the morning and an immediate-

release preparation of methylphenidate at another time of the day to extend the duration of effect. (NICE, 2018)

Emotional Symptoms

Many adults with ADHD have a hard time managing their feelings, especially when it comes to emotions like anger or frustration. Common emotional symptoms of adult ADHD include:

- Being easily flustered and stressed out
- Irritability or short, often explosive, temper
- Low self-esteem and sense of insecurity or underachievement
- Trouble staying motivated
- Hypersensitivity to criticism

To assess the medium- to long-term effects of extended release methylphenidate on emotional symptoms, Roesler and colleagues conducted a large-scale, multicenter treatment study and found that extended release methylphenidate was statistically superior to placebo in reducing emotional symptoms. The decline of obsessive-compulsive symptoms was more pronounced in treated individuals, and there was an improvement in terms of self-concept. On the other hand, symptoms of anxiety, depression, anger and hostility, phobia, paranoid ideations and psychoticism were not improved.. (Rösler et al., 2010)

Guanfacine

Guanfacine is a noradrenergic agonist. In ADHD, it probably has a beneficial effect through selective actions at α2A-adrenoceptors in the prefrontal cortex. In an up to two year open-label extension to a multi-center double-blind study with 240 children 6–17 years of age with a diagnosis of ADHD guanfacine was initiated at 2 mg/day and titrated as needed in 1-mg increments to a maximum of 4 mg/day to achieve optimal clinical response. The most common adverse events were somnolence (30.4%), headache (26.3%), fatigue (14.2%), and sedation (13.3%). Somnolence, sedation, and fatigue were usually transient. Cardiovascular-related adverse events were uncommon, although small reductions in mean blood pressure and pulse rate were evident at monthly visits. ADHD Rating Scale, Version IV, total and subscale scores improved significantly from baseline to endpoint for all dose groups. (Biederman et al., 2008)

Safety

Overall, while many safety concerns have been raised in the use of stimulants, the vast majority of treatment complications are either

quickly reversible or easily manageable with appropriate clinical care. The negative consequences of untreated ADHD clearly outweigh the risks of the stimulant medicines when used in an appropriate and careful manner. (Merkel, 2010) In children, effective drugs for ADHD appears to be safe and well tolerated. Most of the adverse events reported in randomized controlled trials are mild and transient (Clavenna & Bonati, 2017). Decreased appetite, growth decrease and the impact on sleep (insomnia for stimulants and somnolence for alpha2-agonists) are among the most common events. Concerns exist about cardiovascular and psychiatric AEs, even if the available evidence does not support an association with medications (Clavenna & Bonati, 2017).

Lisdexamfetamine

Coghill and colleagues reviewed the safety and tolerability profile of lisdexamfetamine. In short-term, parallel-group, placebo-controlled, phase III trials, treatment-emergent adverse events (TEAEs) in children, adolescents, and adults receiving lisdexamfetamine were typical for those reported for stimulants in general. Decreased appetite was reported by 25–39 % of patients and insomnia by 11–19 %. Most TEAEs were mild or moderate in severity. Gains in weight, height, and body mass index were smaller in children and adolescents receiving lisdexamfetamine than in placebo controls or untreated norms. Insomnia was a frequently reported TEAE in patients with ADHD of all ages receiving lisdexamfetamine, although the available data indicated no overall

worsening of sleep quality in adults. Post-marketing survey data suggest that the rate of non-medical use of lisdexamfetamine was lower than that for short-acting stimulants and lower than or equivalent to long-acting stimulant formulations. Small mean increases were seen in blood pressure and pulse rate in patients receiving lisdexamfetamine. (Coghill et al., 2017)

Methylphenidate

Though the absolute risk is likely to be low, the risk-benefit balance of methylphenidate should be carefully considered, particularly in children with mild ADHD. The relative risk of myocardial infarction and arrhythmias appears increased in the early period after the start of methylphenidate treatment for ADHD in children and young people. In a South Korean self-controlled case series analysis covering 1224 patients aged 17 or younger with a cardiovascular event and at least one incident prescription for methylphenidate, increased risk of arrhythmia was observed, while the risk was highest in the children who had congenital heart disease. No significant risk of myocardial infarction was observed, though risk was higher in the early risk periods between eight and 56 days after the start of treatment with methylphenidate. No significant increased risk was observed for hypertension, ischemic stroke, or heart failure. (Shin, Roughead, Park, & Pratt, 2016)

The NICE Guidelines conclude that no evidence was identified to justify different medication choices in people with ADHD and tic

disorders, a history of psychosis or mania, or emotional dysregulation. These groups are often excluded from trials. There are reasons (for example, mechanism of action of medication options, previous reports of adverse effects) to suspect that these groups may respond differently to different drugs, but a lack of trials to confirm this. Primarily there are some concerns that stimulant medication may worsen the symptoms of any of these coexisting conditions and therefore nonstimulant medication should be preferred. (NICE, 2018)

Maximum Dose

Medication guidelines frequently specify apparently arbitrary dose limitations, which could discourage clinicians from titrating methylphenidate to higher and, perhaps for some patients, more efficacious doses. At the same time this needs to be weighed off against a significant uncertainty as to the risk of higher doses, since there is relatively little data available on the titration of stimulants.

Ching and colleagues analyzed a set of 11 randomized clinical trials and 38 cohort studies. The randomized clinical trials involved 1304 participants treated with methylphenidate and 887 controls; the 38 cohort studies included 5524 participants. Maximum doses of methylphenidate ranged from 0.8 to 1.8 mg/kg/d. Common adverse effects of methylphenidate included insomnia (odds ratio, 4.66), anorexia (5.11 higher than for those who took placebo), abdominal

pain (1.9 times more likely), and headache (14% of participants). A range of maximum doses for methylphenidate was recommended in clinical studies, while no discernable scientific justification for any particular dose was given. Reports of life-threatening adverse events were absent. (Ching, Eslick, & Poulton, 2019)

Growth

Stimulant-associated growth deficits in children with ADHD have long been a concern.

Zhang and colleagues recorded changes in the weight and height of 146 school age children diagnosed with ADHD being treated with methylphenidate and 29 drug-free ADHD children, over 2–4 years. A small but significant deceleration of height velocity was identified, while the magnitude of the height deficit was related to the duration of treatment, and he deceleration of growth largest in the first year. (Zhang, Du, & Zhuang, 2010)

The NICE Guidelines suggest for patients taking ADHD medication, to measure height every 6 months in children and young people. Height and weight of children and young people should be plotted and reviewed on a growth chart. (NICE, 2018) They also suggest that if a child or young person's height over time is significantly affected by medication (that is, they have not met the height expected for their age), a planned break in treatment over school holidays to allow 'catch-up' growth may be considered. (NICE, 2018)

Weight

In the study in children by Zhang and colleagues mentioned above, methylphenidate had no significant influence on weight and BMI values. (Zhang et al., 2010) Still, the NICE Guidelines recommend measuring

- weight every 3 months in children 10 years and under
- weight at 3 and 6 months after starting treatment in children over 10 years and young people, and every 6 months thereafter, or more often if concerns arise
- weight every 6 months in adults

and in general to consider monitoring the BMI of adults with ADHD if there has been weight change as a result of their treatment and changing the medication if weight change persists. (NICE, 2018)

The NICE Guidelines recommend that if weight loss is a clinical concern, the following strategies can be considered (NICE, 2018):

- taking medication either with or after food, rather than before meals
- taking additional meals or snacks early in the morning or late in the evening when
- stimulant effects have worn off
- obtaining dietary advice
- consuming high-calorie foods of good nutritional value

- taking a planned break from treatment
- changing medication.

Emotional Lability and Stimulants

Emotional lability, or sudden strong shifts in emotion, can often be observed in youth with attention-deficit/hyperactivity disorder. An emotional lability continues in a significant number into adulthood.

Promising signals for symptom improvement have come from recent studies using stimulants in adults, children and adolescents. Similarly, neuroimaging studies have begun to identify neurobiological mechanisms underlying stimulants' impact on emotion regulation capacities. (Posner, Kass, & Hulvershorn, 2014)

Cardiovascular Side Effects

Compared to children, adults with ADHD are at greater risk for developing adverse cardiovascular related outcomes and, if treated, may be likely to carry a greater burden of exposure to stimulant medications.

Mick and colleagues critically reviewed the available literature relevant to the cardiovascular safety of CNS stimulants for adult ADHD between 1979 and 2012. Using random effects meta-analysis, they found that subjects randomized to CNS stimulant treatment

showed an increased resting heart rate (+5.7 bpm) and systolic blood (+2.0 mmHg) compared with subjects randomized to placebo, as well as an increased risk for a resting heart rate over 90 bpm (4.2% vs. 1.7%). (Mick, McManus, & Goldberg, 2013)

There is currently no indication to monitor for QTc changes when stimulants are prescribed (Graham et al., 2011).

The NICE Guidelines make several recommendations to monitor cardiovascular side effects, including also the following (NICE, 2018):

- Monitor heart rate and blood pressure and compare with the normal range for age before and after each dose change and every 6 months.
- Do not offer routine blood tests (including liver function tests) or ECGs to people taking medication for ADHD unless there is a clinical indication.
- If a person taking ADHD medication has sustained resting tachycardia (more than 120 beats per minute), arrhythmia or systolic blood pressure greater than the 95th percentile (or a clinically significant increase) measured on 2 occasions, reduce their dose and refer them to a pediatric hypertension specialist or adult physician.

- If a person taking guanfacine has sustained orthostatic hypotension or fainting episodes, reduce their dose or switch to another ADHD medication.

Tics

Clinical practice currently restricts the use of psychostimulant medications in children with tics or a family history of tics for fear that tics will develop or worsen as a side effect of treatment. One also needs to be cautious in adults with tics.

However, a recent meta-analysis of controlled trials does not support an association between new onset or worsening of tics and psychostimulant use (Cohen et al., 2015). The authors suggest that clinicians may want to consider rechallenging children who report new onset or worsening of tics with psychostimulant use, as these symptoms are much more likely to be coincidental rather than caused by psychostimulants.

The NICE Guidelines (NICE, 2018) recommend that if a person taking stimulants develops tics, one should consider whether:

- the tics are related to the stimulant (tics naturally wax and wane) and
- the impairment associated with the tics outweighs the benefits of ADHD treatment.

They recommend that if tics are stimulant related, reduce the stimulant dose, or consider changing to guanfacine (in children aged 5 years and over and young people only), atomoxetine, clonidine, or stopping medication. (NICE, 2018)

Sexual Dysfunction

In the case of atomoxetine, sexual side effects have been described. While the profiles of sexual and genitourinary treatment-emergent adverse events were not different from placebo in a meta-study of controlled studies with atomoxetine, a greater frequency was reported in adult males taking atomoxetine compared with placebo (Camporeale et al., 2013). The time to onset of the TEAEs tended to be shorter, and time to resolution tended to be longer in adult male patients treated with atomoxetine compared with those receiving placebo. The authors added that their findings are to be interpreted with caution because these side effects may have been underreported. The NICE Guidelines recommend to monitor young people and adults with ADHD for sexual dysfunction (that is, erectile and ejaculatory dysfunction) as potential adverse effects of atomoxetine. (NICE, 2018)

Seizures

If a person with ADHD develops new seizures or a worsening of existing seizures, review their ADHD medication and stop any medication that might be contributing to the seizures. After investigation, cautiously reintroduce ADHD medication if it is unlikely to be the cause of the seizures. (NICE, 2018)

However, in prospective trials, retrospective cohort studies and post-marketing surveillance in ADHD patients without epilepsies, the incidence of seizures did not differ between ADHD pharmacotherapy and placebo for current versus non-use for methylphenidate and atomoxetine (Graham et al., 2011).

Psychosis

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 (Graham et al., 2011). 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.

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 (Graham et al., 2011).

Mania

The comorbid presentation of people suffering with ADHD and BD (ADHD/BD) is associated with a more severe disease course, more severe mood disorder symptoms, and lower functional scores. Importantly, the co-segregation of these two conditions makes ADHD diagnosis challenging because its symptoms are often mistakenly assumed to be part of BD. As a result, patients with comorbid ADHD/BD are under-diagnosed and under-treated. (Klassen, Katzman, & Chokka, 2010)

Often, the safer approach is to use mood stabilizers to treat the bipolar disorder before using stimulants to treat the ADHD.

Atomoxetine may only have a modestly increased risk of (hypo)manic switches and destabilization of the mood disorder when utilized in association with mood stabilizers (Perugi & Vannucchi, 2015). Compared to baseline, bupropion treatment significantly reduced ADHD symptoms, with no evidence of mania activation (Wilens et al., 2003).

Sleep

Sleep problems associated with ADHD include restless legs syndrome, periodic limb movements in sleep, sleep-onset delay, increased nocturnal motor activity, sleep-disordered breathing, deficit in alertness, and several others which may also be linked to comorbid conditions. (Konofal, Lecendreux, & Cortese, 2010) Stimulant medication has been shown to lead to longer sleep latency, worse sleep efficiency, and shorter sleep duration in children and adolescents (Stein, Weiss, & Hlavaty, 2012), and the authors recommended that pediatricians carefully monitor sleep problems and adjust treatment to promote optimal sleep. The NICE Guidelines recommend in general that changes in sleep pattern should be monitored, for example, with a sleep diary, and the medication be adjusted accordingly (NICE, 2018).

Behavior

Methylphenidate, dexamfetamine and mixed amphetamine formulations all showed beneficial effects on children's on-task behavior and academic work completion. Atomoxetine was examined in two studies, and was found to have no significant effect. (Prasad et al., 2013)

The NICE Guidelines recommend to monitor the behavioral response to medication, and if behavior worsens adjust medication and review the diagnosis (NICE, 2018).

Stimulant Diversion

Healthcare professionals and parents or carers should monitor changes in the potential for stimulant misuse and diversion, which may come with changes in circumstances and age.

A systematic study suggested that individuals with ADHD may have higher rates of stimulant misuse than individuals without the disorder, and characteristics such as sex, race, use of illicit drugs, and academic performance are associated with misuse of stimulant medications. Results also indicated that individuals both with and without ADHD are more likely to misuse short-acting agents than long-acting agents. (Weyandt et al., 2014)

Compliance

Various issues can lead to non-adherence to treatment in individuals with ADHD. Some are as follows:

- time management and forgetfulness; problems remembering to order and collect medication.
- worries that medication or non-pharmacological treatment might lead to a change in personality
- misunderstandings and misconceptions about the effects of treatment
- worries about adverse effects

- the attitudes of people close to a person with ADHD can influence adherence

Information

Ensure that people are fully informed of the balance of risks and benefits of any treatment for ADHD and check that problems with adherence are not due to misconceptions (for example, tell people that medication does not change personality).

The committee provided examples of how healthcare professionals might encourage people to follow strategies that support adherence (for example, following clear instructions and using visual reminders).

The committee agreed that it was important that although children and young people should take responsibility for their own health (including taking medication), parents and carers should oversee them.

Medication

Encourage the person with ADHD to use the following strategies to support adherence to treatment:

- being responsible for their own health, including taking their medication as needed
- following clear instructions about how to take the medication in picture or written

- format, which may include information on dose, duration, adverse effects, dosage
- schedule (the instructions should stay with the medication, for example, a sticker on the side of the packet)
- using visual reminders to take medication regularly (for example, apps, alarms, clocks, pill dispensers, or notes on calendars or fridges)
- taking medication as part of their daily routine (for example, before meals or after brushing teeth)
- attending peer support groups (for both the person with ADHD and for the families and carers).

Encourage parents and carers to oversee ADHD medication for children and young people.

Supporting adherence to non-pharmacological treatments

Non-Pharmacological Treatment

Support adherence to non-pharmacological treatments (for example, CBT) by discussing the following (NICE, 2018):

- the balance of risks and benefits (for example, how the treatment can have a positive effect on ADHD symptoms)
- the potential barriers to continuing treatment, including:
    - not being sure if it is making any difference
    - the time and organisational skills needed to commit to the treatment

- the time that might be needed outside of the sessions (for example, to complete homework)
- strategies to deal with any identified barriers (for example, scheduling sessions to minimise inconvenience or seeking courses with child care provision)
- a possible effect of treatment being increased self-awareness, and the challenging impact this may have on the person and the people around them
- the importance of long-term adherence beyond the duration of any initial programme (for example, by attending follow-up/refresher support to sustain learned strategies).

Review of medication and discontinuation

ADHD medication should be reviewed at least once a year and discussed with the person with ADHD (and their families and carers as appropriate) whether medication should be continued. (NICE, 2018) The review should include a comprehensive assessment of the (NICE, 2018):

- preference of the child, young person or adult with ADHD (and their family or carers as appropriate)

- benefits, including how well the current treatment is working throughout the day
- adverse effects
- clinical need and whether medication has been optimised
- impact on education and employment
- effects of missed doses, planned dose reductions and periods of no treatment
- effect of medication on existing or new mental health, physical health or neurodevelopmental conditions
- need for support and type of support (for example, psychological, educational, social) if medication has been optimised but ADHD symptoms continue to cause a significant impairment.

Consider trial periods of stopping medication or reducing the dose when assessment of the overall balance of benefits and harms suggests this may be appropriate. If the decision is made to continue medication, the reasons for this should be documented. (NICE, 2018)

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