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Autism spectrum disorder: Consensus guidelines on assessment, treatment and research from the British Association for Psychopharmacology

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Abstract

An expert review of the aetiology, assessment, and treatment of autism spectrum disorder, and recommendations for diagnosis, management and service provision was coordinated by the British Association for Psychopharmacology, and evidence graded. The aetiology of autism spectrum disorder involves genetic and environmental contributions, and implicates a number of brain systems, in particular the gamma-aminobutyric acid, serotonergic and glutamatergic systems. The presentation of autism spectrum disorder varies widely and co-occurring health problems (in particular epilepsy, sleep disorders, anxiety, depression, attention deficit/hyperactivity disorder and irritability) are common. We did not recommend the routine use of any pharmacological treatment for the core symptoms of autism spectrum disorder. In children, melatonin may be useful to treat sleep problems, dopamine blockers for irritability, and methylphenidate, atomoxetine and guanfacine for attention deficit/hyperactivity disorder. The evidence for use of medication in adults is limited and recommendations are largely based on extrapolations from studies in children and patients without autism spectrum disorder. We discuss the conditions for considering and evaluating a trial of medication treatment, when non-pharmacological interventions should be considered, and make recommendations on service delivery. Finally, we identify key gaps and limitations in the current evidence base and make recommendations for future research and the design of clinical trials.

Keywords

Autism, treatment, guidelines, neurodevelopmental, aetiology

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Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder with an estimated lifetime prevalence of at least 1% (Baird et al., 2006; Brugha et al., 2011). Core symptoms include deficits in social communication and the presence of restricted and repetitive interests or activities and sensory anomalies, beginning in the early developmental period (American Psychiatric Association, 2013). The assessment and management of ASD is complex, due to its multifactorial aetiology, persistence into adulthood, presence of co-occurring mental and physical disorders and attendant disability. The total cost, including accommodation, treatment, loss of earnings and health care for individuals over their life span has been estimated to range between £0.92 m and £1.5 m for someone without or with an intellectual disability, respectively (Buescher et al., 2014). ASD-related difficulties are lifelong and often require on-going support. Many people with ASD are prescribed psychotropic medications at some point in their lives. According to a recent study in the UK, using a representative primary care database, psychotropic drugs are prescribed to 29% of people with ASD (Murray et al., 2014). In this study, the most commonly prescribed categories of drugs for ASD were sleep medications (9.7%), psychostimulants (7.9%) and antipsychotics (7.3%) (Murray et al., 2014). In particular, the use of psychostimulants and antipsychotics in ASD is much higher than in the general population (Murray et al., 2014). Similar rates of prescribing psychotropic drugs have also been reported in the USA and Canada. For example, a recent study of over 2800 children from the Autism Treatment Network in North America reported that 27% of children and adolescents with ASD are prescribed at least one psychotropic medication (Coury et al., 2012). Stimulants were most often prescribed (13%), followed by selective serotonin re-uptake inhibitors (SSRIs) (8%) and atypical antipsychotics (8%) (Coury et al., 2012). Evidence also indicates that prescription rates have increased, with a more than three-fold increase in antidepressant drug prescriptions for people with ASD in the USA between 1992–2001 (Aman et al., 2005b). Sixty per cent of adults with ASD have concerns about taking medications, particularly due to side-effects and lack of effectiveness (Wallace et al., 2013). This, and the commonplace use of drugs in ASD, suggests there is a need for comprehensive guidance on the assessment and management of ASD, which incorporates advice on the use of psychotropic medications. However, it should be recognised that some people with ASD do not want treatment for the core aspects of ASD. As such, discussion about treatment should take into consideration individual preferences.

In view of the uncertainties, the British Association for Psychopharmacology (BAP) coordinated the development of this consensus guideline to review and make recommendations for the assessment and management of ASD with a focus on drug treatments. We first review the aetiology of ASD to provide a

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framework to understand the diagnostic assessment of ASD and treatment targets. Subsequently we address the management of core symptoms, the management of common co-occurring conditions, non-pharmacological treatments and the implications for service provision, before discussing future directions for clinical research.

Method

A consensus meeting was held with the support of the BAP involving a group of experts on ASD in children, adolescents and adults. The group consisted of psychiatrists, psychologists, researchers in the field and service user representatives. Members of the group gave presentations summarising each topic discussed in this paper, followed by discussion on the nature and quality of the evidence and its implications. Following the consensus meeting, a further literature review was conducted to support the consensus points. Drafts of the review and the recommendations were circulated to the expert group for comments, which were then revised by the expert group to derive the final version of the guidelines.

The evidence in each area was rated using the criteria by Shekelle et al. (1999) (Supplementary Table 1), which rank meta-analyses of randomised controlled trials (RCTs) and large, representative observational studies as the best evidence. Our recommendations were graded based on the strength of the evidence supporting them using the grading criteria described in previous BAP guidelines (Bolea-Alamañac et al., 2014). Thus, recommendations were rated A to D to reflect the evidence (see Supplementary Table 1), with grade A indicating the recommendation is supported by the highest quality evidence. Although, some of the recommendations were based on weaker evidence (B, C, D), this does not necessarily reflect their clinical importance. The category S corresponds to a standard for clinical care, which comprises a consensus on good clinical practice in the absence of other evidence. In summarising the pharmacological evidence, we have focused on the primary end-points of studies but, where this is not the case, we have indicated that the evidence is based on a secondary end-point. We have reported the doses used or, where the dose was variable, we have reported the mean dose used or range if the mean dose was not reported. We also summarise key aspects of the design of the study (whether the raters were blind to intervention, and whether the sample was randomised to a placebo or other comparator) and sample size (using the intention to treat sample) so that readers can gauge the strength of evidence.

Aetiology

Genetic risk factors

Genetic factors play a substantial role in the aetiology of ASD. Recent studies have shown about 80% heritability for ASD (Lichtenstein et al., 2010; Ronald and Hoekstra, 2011). However, within families, no one pattern of inheritance (e.g. autosomal dominant or recessive) is observed. With the exception of a small number of rare genetic variants (recently estimated at 71 variants; (Sanders et al., 2015)), the effect of more common individual risk variants so far identified is small. Monogenetic syndromes with high rates of overlapping disorders which often include ASD as part of their behavioural phenotype include Phelan–McDermid syndrome (PMS), fragile X syndrome (FXS) and tuberous sclerosis (Ghosh et al., 2013). These constitute about 10–15% of all cases of ASD.

In the majority of cases, the genetic risk for ASD is polygenic, involving multiple single nucleotide polymorphisms (SNPs), each of minor effect (Anney et al., 2012; Clarke et al., 2015; Gaugler et al., 2014; Klei et al., 2012). In addition to SNPs and monogenic disorders, a number of de novo suspected single gene loss of function mutations and copy number variants (CNVs; such as microdeletions or microduplications) spanning multiple genes have been reported to increase the risk of ASD and (often substantially), intellectual disability (de la Torre-Ubieta et al., 2016). Breakpoints consistently associated with ASD include the SHANK3 deletion, 1q21, 3q29, 7q11.23, 15q11.2-13.1, 15q12, 15q13, 16p11, 17q12, 22q11.2 and Xq (Vorstman et al., 2006).

The genetic risk variants for ASD implicate a number of key neurobiological pathways that are potential targets for drugs. Specific examples include the N-methyl-D-aspartate (NMDA) 2B glutamate ionotropic and gamma-aminobutyric acid (GABA) receptors (including GABARA3 and GABARB3), cell adhesion molecules, scaffolding proteins such as SHANK1, SHANK2, SHANK3 ankyrin repeat domain proteins (Bourgeron, 2015), and neuron-glia signalling and microglial activation (de la Torre-Ubieta et al., 2016). An improved understanding of the nature of the disruption in these pathways in ASD is needed to help develop targeted molecular therapies.

Environmental risk factors

A number of prenatal, perinatal and neonatal factors, including significant prematurity, perinatal hypoxia, maternal pre/perinatal infections, maternal vitamin D deficiency, higher paternal age, gestational valproate exposure, maternal obesity and very low birthweight (<1500 g), have been associated with an increased relative risk of ASD (for further details see reviews and meta-analyses: Eyles et al., 2013; Gardener et al., 2009, 2011; Mandy and Lai, 2016). Maternal use of SSRIs before or during pregnancy has also been identified in some studies, but significant questions have been raised about the causality of this association (Man et al., 2015). Interestingly, preclinical work shows that some of these environmental risk factors impact on the same pathways implicated by the genetic association studies (Basil et al., 2014; Richetto et al., 2014), suggesting risk factors may converge on common pathways at the molecular or higher-level brain circuit levels (Voineagu et al., 2011).

Biology of ASD

Brain structural differences in ASD have been identified early in life. The first studies examined head circumference and discovered that this proxy measure of brain size increased more in individuals with ASD than in controls and their unaffected siblings during the first years of their life (Constantino et al., 2010; Courchesne et al., 2003; Elder et al., 2008; Redcay and Courchesne, 2005). This is thought to be explained by a greater volume of both grey and white matter, with especially pronounced overgrowth in the frontal and temporal cortex (Schumann et al., 2010). Early brain overgrowth may include an increase in cortical thickness in ASD at ages 3–4 years old, but seems to be followed by accelerated cortical thinning (Zielinski et al., 2014). Overall, the growth trajectory rate flattens in ASD such that, by the ages of 10–15 years old, average brain size in ASD is similar to typically developing children. Subsequently grey and white matter volumes may decrease in ASD in adulthood (Lange et al., 2015). However, it is noteworthy that not all head circumference or magnetic resonance imaging (MRI) volumetric studies support this model (Hansen et al., 2008; Raznahan et al., 2013a,b; Rogers, 2004). It is therefore possible that early brain overgrowth and subsequent growth trajectory flattening is present in only a subset of individuals with ASD (Lenroot and KaYeung, 2013).

Neurochemical alterations are also reported in ASD. One system which is repeatedly implicated is the serotonin system, which is thought to underpin some anatomical features of ASD. The serotonin system has a role in neurite outgrowth (Fricker et al., 2005), synaptogenesis (Faber and Haring, 1999; Mazer et al., 1997), differentiation and neurogenesis (Kesterson et al., 2002) and therefore its contribution to the early developmental aberrations reported in ASD is highly plausible. Serotonergic abnormalities in ASD include elevated serotonin levels in whole blood and platelets in upwards of 25% of affected individuals (Gabriele et al., 2014; Hanley et al., 1977) and alterations in the developmental trajectory of brain serotonin synthesis activity (Chugani et al., 1997). Together this evidence has provided a theoretical rationale for exploring the effect of serotonergic medications in ASD (Veenstra-VanderWeele et al., 2012) (see section 'serotonergic agents').

More recently, evidence for a pivotal role of the excitatory (E) glutamate and inhibitory (I) GABA systems in ASD has accumulated. An influential review by Rubenstein and Merzenich (2003) proposed that ASD is caused by an increased E/I ratio leading to pathological hyper-excitability within cortical circuits. Some preliminary support for the model comes from a positron-emission tomography (PET) study using a tracer that is relatively selective for the GABA-A alpha-5 receptor sub-type, showing elevated GABA receptor availability in ASD, potentially indicating reduced GABA transmitter levels (Mendez et al., 2013).

Criticisms of the model include that it may be overly simplistic and not specific to ASD, as E/I imbalance has been implied in epilepsy and schizophrenia. E/I balance is likely to differ depending on the brain region and cell-type studied (Nelson and Valakh, 2015; Rothman et al., 2011, 2012; Sibson et al., 1998). Furthermore, evidence from magnetic resonance spectroscopy (MRS) studies of glutamate and GABA in ASD has not been consistent. For example, a recent review of MRS studies reported that out of the 12 studies in frontal cortical regions, four studies failed to report any differences between individuals with ASD and healthy controls; four studies (three in childhood and one in adolescence) reported increased levels of glutamate and the combination of glutamate and glutamine (Glx), and one study reported reduced levels of Glx (Naaijen et al., 2015). In addition, three studies reported decreased levels of GABA in frontal regions (Naaijen et al., 2015). There are fewer studies in the thalamus, hippocampus and striatum, although the results are similarly inconsistent (Naaijen et al., 2015). However, although informative, MRS is limited as it is an overall measure of tissue glutamate and/or GABA which means intra-cellular levels may mask changes in synaptic levels. Thus, these inconsistencies may simply be a product of the current constraints of technology available to examine these neurotransmitters in the living human brain. However, they may also reflect the highly heterogeneous nature of ASD and/or pronounced differences between brain regions or developmental stages.

In contrast, preclinical studies have generated a much more consistent picture of E/I disruption in the perinatal period in rodent models relevant to ASD. In brief, animal models of ASD reveal an increase in spontaneous activity in sensory cortices in early life (Gonçalves et al., 2013; Gutierrez et al., 2009; Peixoto et al., 2016). This may, at least, be partly a consequence of a 'delay' in the switch in GABA responses in brain from excitatory, during prenatal life, to inhibitory, during postnatal life, in ASD and related conditions (Ben-Ari et al., 2012).

Animal and clinical studies have shown that the neuropeptide oxytocin regulates social bonding and recognition, suggesting alterations in the oxytocin system could contribute to manifestations of ASD or its treatment (Baumgartner et al., 2008; Domes et al., 2007; Ferguson et al., 2000; Insel and Shapiro, 1992). This has led to a number of clinical trials (see section on treatment of core symptoms). Furthermore, oxytocin modulates the switch from excitatory GABA to inhibitory function and is therefore an important regulator of E/I balance during the perinatal period (Tyzio et al., 2006, 2014). It is likely that oxytocin continues to have a modulatory effect on E/I later in postnatal life. Hence, oxytocin could serve as a target to modulate E/I balance in ASD.

Lastly, increasing evidence from animal and clinical studies has confirmed that a role for maternal and postnatal immune dysregulation in the aetiology of ASD cannot be overlooked. Taking into account the regulatory role that the immune system has on neuronal cells at every stage of brain development, it is plausible that immune dysfunction, caused by genetic mutations or environmental factors, could alter brain development and function (Estes and McAllister, 2015). Dysfunction of microglial cells, the resident brain immune cells, is one immune mechanism implicated in the pathogenesis of ASD. Data suggest that aberrant microglial function may lead to altered synaptic pruning, which may subsequently contribute to the pathogenesis of ASD (Koyama and Ikegaya, 2015). However, not all in vivo evidence finds support for immunologic dysregulation (Pardo et al., 2017).

Summary

In conclusion, ASD is a complex neurodevelopment disorder that, in the majority of cases, shows multifactorial, polygenic inheritance, although de novo mutations and CNVs are currently estimated to play an important role about 10–20% of patients. Environmental factors, in particular early insults (prenatal, perinatal and postnatal factors), also contribute to an increased risk of developing ASD. Brain development is disrupted from early childhood and shows alterations into adulthood. Key systems implicated in the pathophysiology of ASD are increasingly being identified and provide targets for clinical trials. These include (but are not limited to) the serotonin and oxytocin systems, the immune system and GABA/glutamate interactions.

Diagnostic criteria

Diagnostic and Statistical Manual, version 5 (DSM-5)

The DSM-5, published in 2013 (American Psychiatric Association, 2013), has the latest revision of the diagnostic criteria for ASD, and a number of changes have been made to reflect recent research. The International Classification of Disease (ICD) version-10 (World Health Organization, 1992) is currently under review with a new revision, ICD-11, planned to be published in 2018. It is not yet clear to what degree ICD-11 will be aligned with DSM-5 – but it is likely there will be substantial agreement on core ASD characteristics.

The main features of the DSM-5 criteria for ASD are summarised in Supplementary Table 2. One key change is that the term 'autism spectrum disorder' is used rather than the term 'autism' and its related categories used in DSM-IV (1994) and ICD-10 (e.g. Asperger syndrome, pervasive developmental disorder – not otherwise specified (PDD-NOS), atypical autism). This shift acknowledges the lack of distinct neurobiological profiles between the different subtypes (Noterdaeme et al., 2010) and the inconsistency in their use (Lord et al., 2012a). The DSM-5 also includes a new category – social (pragmatic) communication disorder (SCD) – to describe individuals with deficits in social verbal and non-verbal communication, but who do not otherwise meet the criteria for a diagnosis for ASD because they do not show repetitive and restricted behaviours. As SCD was only recently introduced, its diagnostic reliability and validity, prognosis, and common features are still to be determined (Norbury, 2014).

The DSM-5 diagnostic criteria for ASD are broader than the DSM-IV criteria for autism. The previously separate domains of social interaction and communication under the DSM-IV classification have been unified as one domain in the DSM-5 (social communication). Hence, the DSM-5 classification of ASD covers two domains; social communication difficulties and repetitive and restricted behaviours (Supplementary Table 1), and include abnormal sensory responses as a cardinal symptom (restored from the DSM-III).

An important addition to the DSM-5 is the inclusion of severity specifiers to indicate the impact of symptoms on adaptive functioning (Supplementary Table 3). Adaptive functioning encompasses communication, occupation and daily living skills (Bal et al., 2015). As shown in Supplementary Table 3, there are three categories for each of the two core symptoms, indicating the level of support the affected individual requires, depending on his/her adaptive functioning. This addition is undoubtedly crucial, as the severity of core symptoms and deficits in adaptive functioning may vary considerably between individuals with the disorder (Constantino and Charman, 2015). Another modification in the DSM-5 is that the new diagnostic criteria offer the option to diagnose co-occurring psychiatric disorders.

Another important change is that the DSM-5 does not specify an age of onset, which has instead been revised to 'symptoms must be present in the early developmental period (but may not fully manifest until social demands exceed limited capacities, or may be masked by learned strategies in later life)' (American Psychiatric Association, 2013: 50-51). This recognises that ASD may not become fully apparent until later in life, and enables the diagnosis of ASD in adulthood (Howlin and Moss, 2012). In addition, the DSM-5 does not require all symptoms to be currently present but rather specifies that they should have occurred at some point in the lifetime. This takes account of the observation that some symptoms are more common at certain time points and also that they may be less evident when the individual is in an optimal environment.

A final change in the DSM-5 is the introduction of clinical specifiers to be noted alongside the ASD diagnosis. These include the presence or absence of the following components: (a) intellectual impairment, (b) language impairment, (c) known medical or genetic condition or environmental factor, (d) neurodevelopmental, mental or behavioural disorder, (e) catatonia (American Psychiatric Association, 2013).

Recent studies indicate that the overall prevalence of ASD may be lower under the DSM-5 compared to the prevalence of autism and related disorders based on the DSM-IV criteria (Maenner et al., 2014). This appears to be mostly due to ~20% of the individuals previously meeting the DSM-IV criteria for PDD-NOS not qualifying for a diagnosis of ASD according to the DSM-5 criteria (Maenner et al., 2014; Mazefsky et al., 2013; Wilson et al., 2013; World Health Organization, 1992).

In summary, the DSM-5 criteria may be particularly useful for diagnosis as they enable diagnosis of adults whose symptoms were not impairing in childhood, and it highlights the importance of co-occurring disorders and functional impact.

Consensus recommendations for diagnosis

- ASD is a complex neurodevelopmental disorder. Its diagnosis requires a neurodevelopmental history and, where possible, a multi-disciplinary approach. (B)
- It is recommended that established diagnostic criteria are used for diagnosis. (D).
- Consider using the DSM-5 criteria as they enable diagnosis in adults and the diagnosis of co-occurring disorders. (D)
- Further studies are required to evaluate the reliability and validity of the Social Communication Disorder diagnosis as a distinct disorder from ASD. (D)

Assessment and diagnosis

Making a diagnosis of ASD is a multi-stage process. It requires the multidisciplinary assessment of current symptoms, acquisition of a developmental history from a primary caregiver and the exclusion of alternative diagnoses by the clinician (National Institute for Health and Clinical Excellence, 2013) (evidence level IV).

Symptoms can manifest and be interpreted differently depending on the environmental context. Thus, evaluation of symptomatology in different environments (home, school, community, in addition to the clinic) should be an expectation. The clinician should consider whether impairment in adaptive function is exclusively due ASD or an additional psychiatric or medical disorder (Constantino and Charman, 2015). The high prevalence of co-occurring disorders in ASD indicates that medical and psychiatric disorders, including intellectual ability, should be routinely screened for in individuals presenting with ASD (Kielinen et al., 2004; Simonoff et al., 2008). In addition, cognitive, language and neuropsychological assessments may be considered, as they can provide valuable information about the individual's strengths and weaknesses and inform the management plan (Charman and Gotham, 2013; Ozonoff et al., 2005).

Reaching a diagnosis of ASD, particularly in adults, may be challenging for a variety of reasons. One of the key pillars of the diagnostic process is the acquisition of a developmental history, preferably from a primary caregiver. However, informants for adults with a potential diagnosis of ASD may not be able to recall the developmental history in detail. In some instances, the primary caregivers may not be alive, so clinicians will need to rely on a history that they obtain from other informants, and additional sources of information (such as school reports). Careful consideration should be given to the accuracy of retrospective recall and specific examples of behaviour should be elicited. Where no informant is available, diagnosis should be based on the history and current circumstances (including the current assessment, and reports from employment or school) (Lai and Baron-Cohen, 2015). Similarly, the assessment of a non-verbal child with suspected ASD is also challenging with respect to accurate estimation of intellectual ability, social understanding, and co-occurring disorders.

Instruments and diagnostic tools

More than 20 screening and diagnostic tools for ASD have been developed over the last two decades (Charman and Gotham, 2013). The aim of screening tools is to identify individuals who are in need for further diagnostic assessment and evaluation. In the next section, we briefly summarise the most commonly used instruments used in childhood and adolescence (Supplementary Tables 4 and 5), and in adulthood (Supplementary Table 6).

Children. In Supplementary Table 4, we provide a list of the most frequently used screening instruments for children who may have ASD. Supplementary Table 5 summarises the structured diagnostic instruments for children who may have ASD based on a screening instrument or other information. The structured instruments vary from observational measures (e.g. Autism Diagnostic Observation Schedule (ADOS); Lord et al., 2012b) to caregiver interviews (e.g. Autism Diagnostic Interview Revised (ADI-R); Lord et al., 1994).

Adults. In Supplementary Table 6, we summarise the most common screening instruments for ASD in adults. Diagnostic tools for adults are summarised in Supplementary Table 5. The most robust observational measure for ASD diagnosis in adulthood is the ADOS (module 4) (Lord et al., 2000). However, it has limitations, including its relatively low sensitivity when used to diagnose higher functioning adults with ASD and low specificity in individuals with severe intellectual disability (when used without ADI-R) (Bastiaansen et al., 2011). Also, it may not fully capture repetitive behaviours and/or intense preoccupations (Kim and Lord, 2010).

The development of assessment tools for ASD has helped increase the identification of ASD and aided accuracy of diagnosis both in clinical and research settings (Johnson and Myers, 2007). Clinicians and researchers should be aware of the strengths and limitations of the instruments. For example, being screened positive on one of the screening instruments does not mean that the individual meets a diagnosis for ASD; in the same way, being screened negative does not exclude the diagnosis of ASD. Results of the instruments differ depending on the setting, the presence of other mental disorders, the sample characteristics and the purpose of the screening (Charman and Gotham, 2013) (evidence level II). Other limitations include the requirement for trained administrators and raters and the time taken to administer them; which can be several hours. One should also take into consideration that most of these tools have not been extensively validated in individuals with ASD and intellectual disability or non-western cultures (Rudra et al., 2014).

Despite the acknowledged limitations of individual instruments, the use of a structured diagnostic instrument is still highly recommended in the evaluation of an individual with suspected ASD to ensure a comprehensive and systematic assessment.

Diagnostic challenges

Individuals with ASD may present to services with co-occurring psychiatric disorders, and ASD may be overlooked if it is not considered during the assessment (Lai and Baron-Cohen, 2015). Adults with ASD may develop adaptive mechanisms to manage social situations, for example by mimicking the gestures and conversational style of others (Lai et al., 2011) (evidence level II). This can mask the presentation and make the diagnosis more challenging (Lai et al., 2011). Another complication is that some studies have shown that core symptoms may be manifested differently in females than in males (Van Wijngaarden-Cremers et al., 2014), which may delay diagnosis in females (Wilson et al., 2016). For example, females with ASD may have restricted interests that involve people (literature, pop bands) rather than objects, such as collection of stamps or trains, as seen in males with ASD. They also may have fewer stereotyped behaviours and have more socially accepted interests (Mandy et al., 2012; Van Wijngaarden-Cremers et al., 2014) (evidence level III). Females with ASD may be more likely to have developed coping strategies to manage social situations that mask the degree of their social isolation from peers (Dean et al., 2016). Females in particular may demonstrate overt shyness or bossiness and being perfectionist. These characteristics constitute the so-called 'female phenotype' (Lai and Baron-Cohen, 2015) (evidence level III), however they do not constitute core autistic symptoms and, importantly, may be present in people without ASD.

Consensus recommendations for the diagnostic process

- A multidisciplinary approach is recommended for the diagnosis of ASD. (D)
- The diagnostic process should involve a direct clinical assessment of the individual and, wherever possible, a detailed interview with the caregiver or other informants, reports from school and employment, and assessment of cognitive and language skills and a medical examination. (D)
- Screening instruments are useful in aiding diagnosis, but should not be used exclusively to make or exclude the diagnosis. (B)
- Diagnostic challenges are more pronounced when diagnosis is made in adulthood, and extra care should be made to rule a diagnosis out. (B)
- It is recommended that ASD is routinely considered in the differential diagnosis when an individual presents to mental health services with a psychiatric disorder. (D)
- Clinicians should be aware of the so-called female phenotype and a careful assessment in females is recommended. (C)

Prevalence of co-occurring mental health difficulties in ASD

Co-occurring psychiatric disorders are highly prevalent in ASD and are more common in ASD than in the general population (Croen et al., 2015). Between 69–79% of individuals with ASD experience at least one additional psychiatric condition during their lifetime (Buck et al., 2014; Lever and Geurts, 2016), compared to rates of lifetime psychiatric disorder of approximately 40% in the general population (Bijl et al., 1998).

Co-occurring difficulties in children with ASD

Irritability, self-injurious behaviour and temper tantrums are amongst the most common co-occurring symptoms in children with ASD, seen in around 85% of both high and lower functioning children with ASD (Mayes et al., 2011). Anxiety is also common, and anxiety disorders are seen in children with ASD with prevalence rates of between 42–55% (de Bruin et al., 2007; Simonoff et al., 2008). Of these, specific phobia (prevalence in ASD of between 9–44%) and social phobia (prevalence in ASD of between 8–29%) are the most common disorders (de Bruin et al., 2007; Leyfer et al., 2006; Simonoff et al., 2008). Attentional/hyperactive and behavioural difficulties are also common in ASD. Between 28–53% of children with ASD meet criteria for attention deficit/hyperactivity disorder (ADHD) and between 7–37% meet criteria for an oppositional defiant disorder or conduct disorder (de Bruin et al., 2007; Leyfer et al., 2006; Salazar et al., 2015; Simonoff et al., 2008; Sinzig et al., 2009). Bipolar disorder and psychotic disorders are less common in ASD, but occur at rates above those of comparison groups (Croen et al., 2015). Mood disorders also often occur in children with ASD (de Bruin et al., 2007; Leyfer et al., 2006; Simonoff et al., 2008). This constellation of problems might also contribute to the sleeping difficulties, which parents report are a concern in 50–80% of children (Richdale and Schreck, 2009). What it is not clear, however, is to what extent these are part and parcel of an ASD diagnosis, or a component of the other conditions that children with ASD may experience. Moreover, the underlying mechanisms may be different to those in people without ASD, which would have implications for using treatments developed for these difficulties in people without ASD (Maskey et al., 2013).

Co-occurring difficulties in adults with ASD

Mood and anxiety disorders are also common in adults with ASD (Wigham et al., 2017). Between 26–57% of adults with ASD experience a mood disorder at some point (Croen et al., 2015; Hofvander et al., 2009; Joshi et al., 2013; Lever and Geurts, 2016; Roy et al., 2015), and anxiety disorders, particularly social phobia, are similarly common (Croen et al., 2015; Hofvander et al., 2009; Joshi et al., 2013; Lever and Geurts, 2016; Roy et al., 2015). ADHD is also frequently reported in adults with ASD, with prevalence rates of between 11–43% (Croen et al., 2015; Hofvander et al., 2009; Joshi et al., 2013; Lever and Geurts, 2016). However, older adults with ASD have been reported to have lower rates of co-occurring psychiatric disorders than younger adults with ASD, and social phobia in particular appears to be significantly less common in this group (Lever and Geurts, 2016). Tic disorders and Tourette syndrome are also frequently reported co-occurring problems in adults with ASD. Between 20–22% of children and adults with ASD meet the criteria for a tic disorder (Canitano and Vivanti, 2007; Hofvander et al., 2009).

There is a lack of validated screening instruments for the detection of co-occurring conditions in ASD. However, a recent study demonstrated the validity of the Strengths and Difficulties Questionnaire (SDQ) in screening for emotional disorders and hyperactivity in adolescents and adults with ASD (Findon et al., 2016).

Together, these co-occurring disorders have a marked impact on functional impairment and caregiver burden, comparable to that reported by persons caring for individuals with a brain injury (Cadman et al., 2012). Thus, identifying and treating co-occurring disorders in adults with ASD is critical; and this has been identified as a priority by health services and agencies (such as the UK Department of Health and the US Agency on Healthcare Research and Quality).

Pharmacological treatment of core symptoms of ASD

In this section, we will initially summarise the results from studies of pharmacological treatments for the core symptoms of ASD (deficits in social communication and interaction, and restricted and repetitive interests or behaviours). We will then discuss the limitations of the evidence and, finally, proceed with recommendations.

Two main approaches have been taken to develop pharmacological agents for ASD. One is re-purposing treatments from other psychiatric disorders that have symptoms in common with ASD. The second approach is to target the putative neurobiological processes underlying ASD, in some instances by targeting potentially more homogenous sub-populations, such as those with rare genetic abnormalities who have ASD, for example individuals with FXS.

In the following sections, we summarise results from the pharmacological studies grouped by the system primarily targeted, in children first and then adults. In this and the section on co-occurring conditions and symptoms, studies with less than 20 participants in the intention to treat analysis are described as small, studies with 20–45 participants are described as medium, and those with more than 50 participants are described as large. An overview of study designs and findings is given in Supplementary Table 7.

Serotonergic agents

A number of trials of SSRIs have been undertaken but all bar one have involved small sample sizes and demonstrated mixed results (Supplementary Table 7).

A small study of fenfluramine was conducted in children with ASD (Barthelemy et al., 1989) (evidence Ib). Core symptoms were assessed using the Behavior Summarized Evaluation scale (Barthélémy, 1986). There was no significant difference from baseline or between the treatment and placebo groups. Reported side effects included withdrawal and sadness, and weight loss (Barthelemy et al., 1989). Fenfluramine is no longer marketed due to serious adverse effects and it is not recommended for use in ASD.

One large study of citalopram evaluated its effect on repetitive behaviours in children with ASD and failed to demonstrate any significant improvement on the Clinical Global Impression (CGI) Improvement subscale, or on any secondary outcomes including the Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) modified for pervasive developmental disorders (King et al., 2009) (evidence Ib). In addition, children on citalopram experienced significantly more adverse events than children given placebo, particularly increased energy levels, impulsiveness, decreased concentration, hyperactivity, increased stereotypy, diarrhoea, initial insomnia, dry skin and, in one case, a prolonged seizure (King et al., 2009). Citalopram is therefore not recommended for the treatment of core symptoms in children with ASD (evidence Ib). A medium-sized study of liquid fluoxetine was conducted in children and adolescents with ASD (Hollander et al., 2005). Using a low dose of fluoxetine, significant improvement was reported in repetitive behaviours as measured by the CY-BOCS, with an effect size of 0.76, but the overall reduction in repetitive behaviours was <10%. No significant differences between fluoxetine and placebo were reported for side effects (Hollander et al., 2005) (evidence Ib). However, another large completed but unpublished study registered on Clinicaltrials.gov of children and adolescents with ASD treated with fluoxetine was reportedly negative (evidence level Ib) (Neuropharm: clinicaltrails.gov, 2012).

In contrast with studies in children, the studies in adults have been more consistent. A small study of fluoxetine in six adults with ASD showed improvement in the CGI scale in three subjects (Buchsbaum et al., 2001) (evidence IIb double down-graded because of the small sample size). In addition, two small studies showed benefits for fluvoxamine and fluoxetine on measures of repetitive behaviours for adults (Hollander et al., 2012; McDougle et al., 1996). However, the benefits were small relative to placebo and the evidence is limited by the small sample sizes (evidence Ib). Therefore, there is not sufficient data to support the recommendation for fluvoxamine or fluoxetine.

A recent Cochrane review concluded that there is no evidence to support the use of serotonergic agents in children, whereas there are data to support their use in adults, particularly for repetitive behaviours (Williams et al., 2013) (evidence Ia). Fluoxetine seems the best tolerated of the serotonergic agents, but it should be noted that there have been no head-to-head comparisons of fluoxetine against other agents.

Glutamatergic agents

1. Metabotropic glutamate receptor 5 (mGLuR5) antagonists: animal models of fragile X syndrome (FXS) have shown that in the absence of fragile X mental retardation protein (FMRP), encoded by the *FMR* gene, there is an elevation of mGluR5 receptor levels (Dolen and Bear, 2008). Animal behaviours analogous to ASD symptoms are improved by mGluR5 antagonists (Silverman et al., 2014). Based on these findings, trials in FXS have focused on mGluR5 antagonists, such as AFQ056. The first small-sized study of AFQ056 did not find any statistically significant effect on the Aberrant Behaviour Checklist (ABC-C) (evidence level Ib), although a post-hoc analysis suggested an improvement in the ABC-Social Avoidance subscale for a subgroup of patients based upon level of *FMR1* methylation (Jacquemont et al., 2011) (evidence level IIb). Moreover, recent results from two large studies failed to demonstrate any efficacy in the primary endpoint, the ABC-C, (Berry-Kravis et al., 2016) (evidence level Ib) regardless of *FMR1* methylation status. Although the authors of these studies suggested that further trials in a younger population with longer treatment duration are needed in order to fully test the mGluR5 theory (Berry-Kravis et al., 2016), the current evidence does not support the use of AFQ056 and the value of targeting mGluR5 in ASD appears in doubt, at least for people with FXS.
2. Memantine is an uncompetitive NMDA antagonist that has been used in dementia (Reisberg et al., 2003). Preclinical studies have shown that when synaptic glutamate levels are high, memantine blocks NMDA receptors, whereas it has the opposite effect when synaptic glutamate levels are low (Parsons et al., 2007). A small study of memantine (Erickson et al., 2007) suggested promising effects, as measured with the CGI scale, however a subsequent large study (Aman et al., 2017) in children with ASD did not demonstrate any efficacy in either primary or secondary outcomes (evidence level Ib). Overall, the evidence does not support the routine use of memantine.
3. D-cycloserine is a partial agonist at the glycine$_b$ site on NMDA receptors. Several studies have indicated that it is beneficial for the treatment of the negative symptoms of schizophrenia (Tsai and Lin, 2010). Based on the overlap between negative symptoms in schizophrenia and social withdrawal in ASD, Posey et al. (2004) conducted a small study in children with pervasive developmental disorder (PDD). Results showed a significant improvement on the CGI and social withdrawal subscale of the ABC (Posey et al., 2004) (evidence level Ib). A recent medium-sized study in children with ASD reported that D-cycloserine with adjunctive social skills training was superior to placebo at reducing Social Responsiveness Scale scores at 22 weeks (Wink et al., 2017), but not 11 weeks (Minshawi et al., 2016) (evidence level Ib). Thus, while there are some promising results, the current evidence does not currently support the routine use of d-cycloserine.
4. CX516 is an allosteric positive modulator of AMPA receptors that has been trialled in FXS (Berry-Kravis et al., 2006). CX516 binds to the AMPA receptor complex, and is thought to slow down the rate of receptor closing to promote long-term potentiation (LTP) in the hippocampus (Arai et al., 1996). However, a medium-sized study in adults with FXS reported no significant effects on cognitive and behavioural outcome measures (Berry-Kravis et al., 2006) (evidence level Ib). Thus, the evidence does not currently support the use of CX516.

GABAergic agents

GABA$_b$ agonists. GABA$_b$ agonists such as arbaclofen activate GABA and preclinically inhibit the release of glutamate. Theoretically this should restore the balance of E/I neurotransmission in ASD. Three trials have been conducted with arbaclofen to date, one in individuals with FXS and two in individuals with ASD. The first was a medium-sized study in individuals with a full mutation of the *FMR* gene (Berry-Kravis et al., 2012). Although there was no difference in the primary outcome (ABC-Irritability subscale) (evidence level Ib), post hoc analysis showed significant improvements with arbaclofen in the ABC-Social Avoidance subscale (evidence level IIb). The second study was a medium-sized study in children and young people with either ASD, PDD or PDD-NOS (Erickson et al., 2014). The results showed significant improvement on the primary outcome, ABC-Irritability scale, as well as in the Lethargy/Social Withdrawal subscale (Berry-Kravis et al., 2012; Erickson et al., 2014) (evidence level IIb). In a recent large study in children and young people with ASD (Veenstra-VanderWeele et al., 2016) (evidence level Ib), there was no significant change in the primary outcome, the ABC-Social Withdrawal Scale, but there was an improvement in secondary outcomes including on the CGI Severity and Improvement scale, and the Socialization and Communication subscales of the Vineland Adaptive Behavior Scale (VABS) (Veenstra-VanderWeele et al., 2016).

Overall, there is insufficient evidence to recommend the routine use of arbaclofen. Further studies are needed to evaluate this further and examine sub-groups (Brondino et al., 2016).

Pregnenolone is a neurosteroid that acts as a positive allosteric modulator of $GABA_A$ receptors to enhance $GABA_A$ receptor function (Hosie et al., 2006). A previous functional neuroimaging study in healthy volunteers reported that compared to placebo, administration of a single oral dose of 400 mg pregnenolone was associated with increased connectivity between the amygdala and medial prefrontal cortex, and reduced self-reported anxiety (Sripada et al., 2013). Subsequently a small study was conducted in adults with ASD (Fung et al., 2014). Among the secondary outcome measures, there was a significant improvement in the ABC-Lethargy/Social Withdrawal Scale (evidence level IIb). However, the study has a number of limitations, including the small sample size, open-label design and absence of a placebo group (Fung et al., 2014), which means it is premature to base recommendations on this study. Therefore, large scale, placebo-controlled randomised trials are necessary to test the benefit of pregnenolone further before it can be recommended in clinical practice. Until then, pregnenolone is not recommended.

Dopamine receptor blockers (antipsychotics)

1. Risperidone is a D2 dopamine receptor subtype antagonist and is one of the only two approved medications by the European Medicines Agency/Food and Drug Administration (FDA) for the treatment of irritability in ASD. Several trials have also measured core symptoms of ASD. Secondary analysis on participants selected for high irritability (McDougle et al., 2005) from the Research Units on Pediatric Psychopharmacology (RUPP) study ((McCracken et al., 2002) has shown significant decreases in repetitive behaviours with moderate effect sizes (Cohen's d=0.55), as measured with CY-BOCS scale, and paralleled by decreases in ABC-Stereotypy subscale scores with large effects (Cohen's d=0.8) (evidence level IIa (downgraded from Ib because it is based on secondary analyses). In a post hoc analysis of RUPP and RUPP2 (Aman et al., 2009; McCracken et al., 2002) risperidone studies, significantly greater decreases in ABC-Lethargy/Social Withdrawal and Hyperactivity subscale scores were observed in the risperidone- versus placebo-treated subjects (Scahill et al., 2013) (evidence level IIb). Common side effects reported in the studies included weight gain, elevated prolactin levels and sedation (seen in 37% of subjects), although sedation subsided after eight weeks of treatment (Aman et al., 2005a).
2. Aripiprazole is a D2 dopamine receptor subtype antagonist with some partial agonist properties (Kim et al., 2013). It is FDA-approved for irritability in ASD. It has been examined in ASD primarily to treat irritability, but secondary analyses have investigated effects for core symptoms. A recent Cochrane review of aripiprazole for ASD concluded that evidence from two RCTs suggested that it was effective as a short term medication for some behavioural aspects of ASD (Hirsch and Pringsheim, 2016). Significant improvements on the ABC-Stereotypy scale and CY-BOCS were reported from a large study in children and adolescents with ASD (Marcus et al., 2009) (evidence level IIa) (down-graded because this was not the primary outcome measure). In addition, a post hoc analysis that combined this study with another study (Aman et al., 2010; Owen et al., 2009) showed a significant improvement in the ABC stereotypic behaviour subscale scores, with greatest change on the item for repetitive hand, body or head movement (Aman et al., 2010) (evidence level IIa). The most common side effects reported were sedation (20%) and somnolence (10%) (Aman et al., 2010).

Taken together, the studies of dopamine receptor blockers provide evidence that these agents may be beneficial for the treatment of repetitive behaviours in ASD (evidence level IIa). However, there are some caveats: the outcome measures used do not differentiate between compulsions and stereotyped behaviours, the observed differences versus placebo were modest (20%), and the trials were short, hence there is no evidence to indicate if benefits are maintained. Furthermore, the level of clinical benefit due to reduction in these behaviours was not determined and the patient populations were all selected because of high levels of irritability, rather than high levels of repetitive behaviours. Overall, in view of the potential risk of adverse effects, it is not recommended that they are routinely used to treat repetitive behaviours. If they are used, a clear treatment goal should be agreed and a plan to measure this put in place; the risks and benefits should be carefully re-evaluated at regular intervals to ensure the balance continues to favour treatment. Furthermore, dosages should start small and build up over time.

Other approaches

Methylphenidate. Jahromi and colleagues conducted a four-week randomised, double-blind crossover sub-study of placebo in children with PDD and high levels of ADHD symptoms (Jahromi et al., 2009), as a part of a larger methylphenidate ASD trial (see below). Observational measures assessing social communication and self-regulation were recorded at each medication dose.

Sub-analysis of data from a larger methylphenidate ASD trial (Research Units on Pediatric Psychopharmacology (RUPP) Autism Network, 2005) in children with symptoms of ADHD reported dose-dependent improvements in joint attention and self-regulation (Jahromi et al., 2009). There was a moderate effect size

(Cohen's d=0.49) benefit for the best dose versus placebo for joint attention initiations and a moderate-large effect size (Cohen's d=0.61) for regulated affective state scores (Jahromi et al., 2009) (evidence level Ib). It is unclear whether these results are mediated by improvement in ADHD symptoms. Moreover, there is no theoretical reason to expect these findings generalise to individuals with ASD who do not have high levels of ADHD symptoms.

Oxytocin. Evidence from genetic and preclinical studies suggests that oxytocin plays a role in social recognition, attachment and stereotyped behaviours (Carter, 1998; Insel et al., 1999).

A small pilot study of intranasal oxytocin was conducted in adults with ASD (Anagnostou et al., 2012). This study reported no significant changes in the primary outcome measure (the Diagnostic Analysis of Nonverbal Accuracy and Repetitive Behaviour Scale Revised). However, there were significant changes in secondary outcomes, specifically the Reading the Mind in the Eyes Test, a measure related to social communication, and a quality of life questionnaire (Anagnostou et al., 2012). A further small study in adults with ASD reported a significant improvement in social reciprocity, as assessed by the ADOS. The effect size was large (Cohen's d=0.78), and improvement was correlated with increased functional connectivity between the anterior cingulate cortex and medial prefrontal cortex (Watanabe et al., 2015) (evidence level Ib). Results from studies in children and young people are also inconsistent. Guastella et al. (2015) conducted a medium-sized study in adolescent male individuals with ASD (evidence level Ib). Results did not suggest any clinical efficacy in primary outcomes including change in the Social Responsiveness Scale as rated by caregivers and the clinician rated CGI-Improvement scale. (Guastella et al., 2015) (evidence level Ib). A recent medium-sized study with intranasal oxytocin in young children showed significant improvement in the primary outcome of caregiver-rated social responsiveness (Yatawara et al., 2016) (evidence Ib).

In summary, the evidence for oxytocin shows some promise, but also inconsistencies, with the largest study failing to find clear benefits. Moreover, direct replications are lacking due to studies using different outcome measures. There are also few findings of improvements that directly relate to real world function. Additionally, little is known about the side effects of longer-term exposure to oxytocin (Okamoto et al., 2016). In sum, further studies are required to fully investigate oxytocin before it can be recommended for routine use.

Recommendations

Overall, the evidence is currently too limited to support the routine use of any of the agents discussed above for the core symptoms of ASD. Although risperidone and aripiprazole have both shown modest efficacy for the management of repetitive behaviours (evidence level IIa), these studies focussed on individuals with high levels of irritability and it is unclear whether the findings would generalise to the wider ASD population. Furthermore, side effects should be carefully considered. Oxytocin has shown some encouraging preliminary results for deficits in social cognition (evidence level Ib), although large scale randomised clinical trials for assessment of benefits for clinical outcomes and functioning and side effects of long-term exposure are warranted.

Clinical trials for ASD core symptoms in progress

There are at least 12 active studies of oxytocin currently underway and there is also one large phase 2 study of vasopressin in children with ASD (NCT01962870). Insulin growth factor-1 (IGF-1) is another promising target. Based on findings from preclinical studies, where it has been shown that IGF-1 ameliorates synaptic and behavioural deficits in SHANK3 deficient mice (Bozdagi et al., 2010, 2013), Kolevzon et al. conducted a small-scale feasibility study of IGF-1 treatment in nine children with PMS. Interestingly, this showed a statistically significant improvement in social impairment and restrictive behaviours (Kolevzon et al., 2014). Currently a large study on IGF-1 is taking place in children with ASD (NCT01970345), and the results of this, and further work on the potential long-term effects of IGF-1, are awaited.

Consensus recommendations of pharmacological management of core symptoms

- Evidence from clinical trials to date has not demonstrated clear efficacy for the use for any agent in the routine management of ASD core symptoms. (S)
- There is some evidence for the use of risperidone and aripiprazole in the management of repetitive behaviours but, in view of the potential adverse effects, routine use is not recommended for treating repetitive behaviours. If used, clinicians should weigh up the risks and benefits and re-evaluate these regularly. (B)

In the next sections, we summarise the results from studies of pharmacological treatments for co-occurring conditions and symptoms in ASD, discuss the limitations of the evidence, and finally, proceed with recommendations. As many co-occurring conditions and symptoms vary by age, we discuss findings in children separately (in the following section) from findings in adults (in the subsequent section). An overview of study designs and findings is given in Supplementary Table 8.

Pharmacological treatment of co-occurring conditions and symptoms in children with ASD

Treatment of depression in children with ASD.

SSRIs and other antidepressants are widely prescribed for people with ASD (Coury et al., 2012). However, there have been no rigorous studies that have investigated the role of SSRIs in treating mood disorders in children with ASD. Given the lack of direct evidence for SSRIs in ASD, the use of SSRIs to treat depression is therefore based on extrapolation from trials in patients without ASD (see BAP guidelines on major depression for recommendations; Cleare et al. (2015)). An additional consideration is the evidence of increased sensitivity to side effects of SSRIs (see chapter on pharmacological treatments of core symptoms) seen in children with ASD (King et al., 2009) (evidence level Ib). We therefore recommend that SSRIs should be used in low doses and titrated up gradually and monitored carefully for side-effects.

Treatment of anxiety and OCD in children with ASD

Although pharmacological treatment of anxiety disorders has not been studied specifically in ASD, symptoms of obsessive-compulsive disorder (OCD) and anxiety have been investigated in a number of trials.

Risperidone. A medium-sized trial in participants with ASD and high levels of irritability (but not necessarily anxiety) at two dose ranges (lower=0.125–0.175 mg/day; higher=1.25–1.75 mg/day) found improvement in OCD symptoms only in the high-dose group (Kent et al., 2013) (evidence level IIa). Similarly, a large study reported significant, albeit modest, improvements in OCD symptoms after risperidone treatment at 2 mg/day (McDougle et al., 2005).

In addition to improving symptoms of OCD, there is also evidence that risperidone may be effective at treating general symptoms of anxiety in ASD too. A medium-sized trial of risperidone in participants with ASD and high levels of irritability reported significant improvement relative to placebo on the insecure/anxious scale of the Nisonger Child Behavior Rating Form (N-CBRF) (parent version) (Shea et al., 2004) (evidence level IIa). However, it should be noted that a 16-week open-label study of 26 ASD child responders to risperidone reported increased anxiety in the mild-moderate range as a side-effect of treatment (Troost et al., 2005) (evidence level IIa).

Clomipramine. One small study that investigated clomipramine in children with ASD reported a significant improvement in OCD symptoms (Gordon et al., 1993) (evidence level IIa). However, cardiovascular side effects of clomipramine can be significant, and reports of treatment-emergent seizures have been noted (Alldredge, 1999; Pacher and Kecskemeti, 2004).

SSRIs. Two large studies have reported no effect of SSRIs (citalopram and fluoxetine) on obsessive-compulsive symptoms (Hollander et al., 2005; King et al., 2009). Neither drug was effective at reducing symptoms of OCD (evidence level IIa).

Overall, there is little or no evidence for treating anxiety or OCD symptoms with risperidone, clomipramine or an SSRI. The studies of risperidone are limited to participants with high levels of irritability and did not select participants on the basis of clinically significant anxiety or OCD symptoms. Hence it is unclear whether any positive effects are clinically meaningful or pertain to those with co-occurring anxiety/OCD. The same applies to studies of SSRIs, although here the combined evidence failed to identify an effect on anxiety or OCD symptoms. In view of the limited evidence, we recommend cautiously following the BAP guidelines for treating anxiety and OCD (Baldwin et al., 2014).

Treatment of sleep problems in children with ASD

Melatonin. A meta-analysis of five small studies supports the use of melatonin for sleep disorder in ASD (Rossignol and Frye, 2011) (evidence level Ia). Sleep duration was increased (the mean increase was 73 min versus baseline and 44 min versus placebo) and sleep onset latency decreased (mean decrease of 66 min compared with baseline, and in comparison with a 39 min decrease with placebo). However, there were no changes in night-time awakenings in children with ASD (Rossignol and Frye, 2011). The length of melatonin usage in these studies ranged from 14 days to over four years. Melatonin use was associated with minimal to no side effects. A further large study reported a small increase in total sleep time (by a mean of 22 min) and an improvement in sleep onset (with a mean improvement of 38 min), though waking times became earlier too (Gringras et al., 2012). There is also evidence that melatonin combined with cognitive-behavioural therapy (CBT) is superior to melatonin only, CBT only and placebo in reducing symptoms of insomnia (Cortesi et al., 2012). The combination group also had a greater proportion of treatment responders reaching clinically significant improvements and fewer dropouts after 12 weeks (Cortesi et al., 2012) (evidence level Ib). Thus, overall, melatonin has proven to be an effective and well-tolerated drug in treating sleeping problems in children with ASD. Adding a behavioural intervention may be of additional value, at least in the short-term.

Treatment of irritability in children with ASD

Common irritability symptoms seen in children with ASD include severe tantrums, aggression or self-injurious behaviours. It is important to note that irritability is more common in individuals with ASD and a co-occurring mood or anxiety disorder (Mayes et al., 2011). It is therefore important to consider and treat, if warranted, any co-occurring mood or anxiety disorder.

Risperidone was the first antipsychotic to receive approval by the USA FDA for irritability in ASD (Food and Drug Administration, 2006). It has been widely studied, with evidence from 10 RCTs reporting its efficacy (evidence level Ib). Several small studies have reported reductions in irritability with large effect sizes (0.7–1.03; Kent et al., 2013; Shea et al., 2004). Similarly, a large multi-site study reported a 57% reduction in irritability (effect size=1.2; McCracken et al., 2002). The most commonly reported side effects of risperidone were weight gain, increased appetite, fatigue, drowsiness and drooling. Long-term (six months) use of risperidone has been investigated by two small studies. Risperidone appears to be tolerated reasonably well but long-term (six months) use was associated with persistent side-effects, including increased appetite, weight gain, mild sedation, hypersalivation and hyperprolactinaemia (Luby et al., 2006; Nagaraj et al., 2006) (evidence level Ib). Hyperprolactinaemia, which is potentially caused by a blockade of dopamine receptors in the tubero-infundibular system (Howes et al., 2009), may normalise over the long-term (Findling and McNamara, 2004), however there is also evidence of increased prolactin after six months of treatment (Luby et al., 2006). In comparison to haloperidol, risperidone seems to be better tolerated with a smaller sedative effect and a lower risk of extrapyramidal symptoms (Miral et al., 2008).

Aripiprazole has also been approved by the FDA for the treatment of irritability in children with ASD (Waknine, 2010) and its effects studied in several RCTs. This evidence has been meta-analysed by Douglas-Hall et al. (2011) which reported a significant reduction in irritability relative to placebo with an effect size of 0.64 after eight weeks of treatment (evidence level Ib; downgraded because this study included only two RCTs (total *n*=316, dose range=2–15 mg/day). Similar to risperidone, side-effects of aripiprazole included sedation, fatigue and increased appetite. Vomiting was also reported by some children. It is also noteworthy that no increase in serum prolactin was observed in the aripiprazole studies and reductions were seen in some children. This suggests that aripiprazole is preferable to risperidone in cases with concerns regarding hyperprolactinaemia. A line-item analysis of the ABC-I from the two RCTs revealed that aripiprazole had no effect on self-injurious behaviour, which was attributed to low baseline rates (Aman et al., 2010). Thus, although the construct of irritability includes self-injury, aripiprazole may not be helpful specifically for this symptom. A similar item analysis has not been performed for risperidone so it is unclear how this drug compares for self-injury.

A large long-term study of aripiprazole reported that the benefits of aripiprazole on irritability were maintained over the study period (Marcus et al., 2011). However, discontinuation due to side effects occurred in about 10%, with aggression and weight increase being the most commonly reported. No additional safety concerns were identified besides those evident in short-term exposure. Therefore, both risperidone and aripiprazole appear to retain most of their initial benefits on irritability seen in acute studies, and both agents are suitable for longer periods of treatment, with appropriate routine safety monitoring.

In conclusion, there is a reasonable body of evidence indicating that risperidone and aripiprazole are effective at treating irritability in ASD with moderate to large effect sizes. However, their potential benefits should be weighed against the risk of side effects. Behavioural and/or educational interventions should be considered prior to prescribing these drugs, given their side-effect profiles. It is recommended that if an antipsychotic is started, treatment targets should be set and progress against these regularly evaluated, and weighed against side-effects (including relevant medical assessments and laboratory tests) during treatment reviews. In view of the risk of persistent side-effects, we also recommend periodic attempts to reduce the daily dosage and discontinue to either confirm the necessity for on-going exposure, or establish that the need for the drug has resolved.

Other approaches to treating irritability in children with ASD

Minocycline has been investigated in an open-label add-on pilot study of individuals with FXS (Paribello et al., 2010). Minocycline significantly reduced irritability ratings and improved secondary outcome measures, including the CGI-I (average score ‘mildly improved’) and a visual analogue scale (VAS) for behaviour (Paribello et al., 2010) (evidence level IIb). The most common side effects were dizziness and diarrhoea. A medium-sized trial also in subjects with FSX reported a modest improvement (2.49 versus 2.97, minocycline versus placebo respectively) on CGI-I ratings, but not in any of the secondary outcomes including the ABC–C scale (Leigh et al., 2013) (evidence level Ib). Overall, minocycline’s potential benefit for reducing irritability needs additional study before routine use can be recommended, particularly in non-FSX ASD populations.

Arbaclofen has been studied in children with ASD for irritability with inconsistent findings to date. One open-label study reported significant improvement on irritability ratings (Erickson et al., 2014) but two medium and large controlled trials reported no change on irritability ratings (Berry-Kravis et al., 2012; Veenstra-VanderWeele et al., 2016) (evidence level Ib).

Amantadine is a non-competitive NMDA antagonist. Despite encouraging case reports and small open-label studies, a small controlled trial by King et al. (2001) reported no effect of amantadine on responder rate or irritability ratings (evidence Ib). However, there were significant (albeit, modest) differences in clinician ratings for hyperactivity (amantadine reduction of –6.4 versus placebo reduction of –2.1) and inappropriate speech (amantadine reduction of –1.9 versus placebo reduction of 0.4) (King et al., 2001) (down-graded to evidence level IIa as a secondary analysis). No parent-reported measures were identified as being significantly different. Thus, current evidence does not support the use of amantadine for irritability.

In view of the limited data available for minocycline, randomised, double-blind controlled studies are required before recommendations can be made. The current evidence does not support the use of arbaclofen or amantadine for irritability.

Treatment of ADHD and hyperactivity symptoms in children with ASD

Methylphenidate has been reported as an effective treatment for ADHD in children with ASD by a meta-analysis of four studies (effect size=0.67) (evidence level Ia, but note this is based on only four studies) (Reichow et al., 2013). A variety of different ADHD outcome measures were used in these studies and the duration of exposure ranged between 1–4 weeks (see Supplementary Table 8). There is also evidence that the response rate to methylphenidate in individuals with ASD and ADHD is lower than in individuals with ADHD without ASD. For example, one medium-sized study reported a response rate of 50% in ASD subjects with symptoms of ADHD (Research Units on Pediatric Psychopharmacology Autism Network, 2005) compared to response rates of 70–80% in children with ADHD without ASD (Jensen, 1999). The severity of side-effects may also be greater in individuals with ASD and ADHD compared to individuals with ADHD without ASD. Discontinuation rates due to side effects were much higher in the ASD study (18%) compared to the non-ASD study (1.4%) (Jensen, 1999; Research Units on Pediatric Psychopharmacology Autism Network, 2005). The most commonly reported side effects in children with ASD were decreased appetite, sleeping difficulties, abdominal discomfort, social withdrawal, irritability and emotional outbursts, mostly similar to those seen in the treatment of ADHD for people without ASD. Taken together, these findings suggest that, although effective, methylphenidate may not be as effective in people with ASD as in people with ADHD and that individuals with ASD are more likely to experience side-effects.

Atomoxetine, a non-stimulant drug for ADHD is an alternative to methylphenidate. Evidence from one small and one medium study demonstrate improvement in symptoms of hyperactivity but not inattention (Hedge’s g=0.83, effect size d=0.90) (Arnold et al., 2006; Harfterkamp et al., 2012) (evidence level Ib). The most common side effects were nausea, fatigue and sleeping difficulties (Arnold et al., 2006). A further large study investigated individual and combined-effectiveness of atomoxetine and parent training (PT). Atomoxetine, (both alone and combined with PT) significantly reduced ADHD symptoms (Handen et al., 2015). The authors conducted a 24-week extension study demonstrating that atomoxetine combined with PT was superior at reducing ADHD symptoms than atomoxetine alone (Smith et al., 2016). The effect sizes reported in the atomoxetine studies (0.59–0.98) are similar to the effect size reported for methylphenidate in children with ASD (0.67) (Research Units on Pediatric Psychopharmacology Autism Network, 2005), suggesting equivalent efficacy.

The α2A receptor agonist antihypertensive-drugs clonidine, guanfacine and lofexidine have also been examined as treatments for ADHD in children with ASD.

Clonidine. Two small studies have reported improvements in symptoms ADHD – in particular, symptoms of hyperactivity (Fankhauser et al., 1992; Jaselskis et al., 1992) (evidence level IIa down-graded because of the small sample sizes). Reported side-effects included sedation, drowsiness, fatigue and decreased activity. Guanfacine appears to be less sedating than clonidine with promising evidence for its efficacy according to two studies (one small, one medium) (Scahill et al., 2006, 2015) (evidence level Ib). The study authors report a response rate of 50%, which is comparable to the group's earlier methylphenidate response rate of 48% (Research Units on Pediatric Psychopharmacology (RUPP) Autism Network, 2005). Notable side-effects included drowsiness, irritability, reduced blood pressure and bradycardia. There is some preliminary evidence for lofexidine based on one small, non-randomised study, which reported significant improvement in ADHD (in particular, hyperactivity) (Niederhofer et al., 2002), but this is insufficient evidence to support routine use (evidence level Ib).

In summary, there is good evidence that methylphenidate is an effective treatment for co-occurring ADHD in children with ASD. Atomoxetine should be considered as a good alternative to methylphenidate. There is also promising evidence for α2A receptor agonists, which should also be considered as alternatives amongst those who are not responsive or intolerant to this class of medication. Reports suggest that risperidone and aripiprazole significantly improve scores on the ABC-H relative to placebo, suggesting these drugs may also be useful. Further studies are required in samples of ASD+ADHD to confirm their effectiveness, since the samples were not selected for ADHD and the ABC-H was not the primary outcome measure. Treatment effect sizes are generally lower in ASD than typically developing populations, and, at least for stimulants, levels of adverse effects are higher. Close periodic monitoring of side effects (including relevant medical assessments) is thus of high importance where these treatments are used in ASD.

Pharmacological treatment of co-occurring conditions and symptoms in adults with ASD

Treatment of depression in adults with ASD

The evidence for treating mood disorders in adults with ASD is very limited. Only one SSRI (fluoxetine) has been studied in adults with ASD (Buchsbaum et al., 2001). This small study reported no change in depression relative to placebo (Buchsbaum et al., 2001) (evidence level IIa). Secondary analysis of risperidone in a trial for repetitive behaviours demonstrated significant reductions on a VAS for mood in a non-clinically depressed group (McDougle et al., 1998). The efficacy of risperidone for clinical depression in ASD remains to be tested.

Given the limited evidence-base of studies in ASD groups, we recommend following the BAP guidelines for treating depression in ASD (Cleare et al., 2015). These should be applied cautiously given the apparent increased propensity for behavioural activation associated with antidepressants in youth with ASD and that these guidelines are not specific to people with ASD (Vasa et al., 2014).

Treatment of anxiety and OCD in adults with ASD

Evidence for treating anxiety in adults with ASD is also limited and studies have been mainly focused on obsessive/compulsive symptoms.

1. Fluoxetine has been studied for anxiety in ASD in two small studies. One reported a significant improvement in obsessions but not compulsions (Buchsbaum et al., 2001) (evidence level IIa) and the other reported a significant reduction in self-reported compulsions (Hollander et al., 2012) (evidence level Ib). No change in compulsions was found in ratings by independent observers.
2. Fluvoxamine has been reported to reduce symptoms of both obsessions and compulsions by one small study at eight and 12 weeks (McDougle et al., 1996) (evidence level Ib). Apart from nausea and mild sedation in a few patients, fluvoxamine was well tolerated.
3. Risperidone was reported to reduce symptoms of anxiety/nervousness on a clinician-rated VAS and self-reported compulsions in a study of repetitive behaviours in ASD (McDougle et al., 1998) (evidence level Ib). The participants all scored above 10 on the Y-BOCS compulsion subscale at entry, indicating at least mild severity at baseline.

In summary, benefits have been reported in small studies using SSRIs as a treatment for anxiety disorders, predominantly OCD, in adults with ASD. Although SSRIs are generally well tolerated, the beneficial effects are modest, and the evidence is limited. There is currently insufficient evidence to recommend risperidone. In view of the limited specific evidence in ASD, we therefore recommend following the BAP guidelines for treating anxiety (Baldwin et al., 2014), but, as with the treatment of mood disorders, we would recommend proceeding cautiously.

Treatment of sleep problems in adults with ASD

Despite the evidence for its effectiveness in children with ASD, there are currently no published clinical trials of melatonin in adults with ASD. One small (n=6) retrospective study reported that melatonin was effective in reducing sleep onset latency and nocturnal awakenings and improved total sleep time (Galli-Carminati et al., 2009) (evidence level III). Effects remained after six months and no side effects were noted during the therapy.

Table 1. Consensus recommendations: Pharmacological treatment of co-occurring conditions and symptoms in children and adults with ASD.

	Children	Adults
Mood disorders	Decision on treatment needs to be made on a case-by-case basis. Follow the BAP guidelines for treating depression. (S)	Decision on treatment needs to be made on a case-by-case basis. Follow the BAP guidelines for treating depression. (S)
Anxiety disorders	Consider a cautious trial of an SSRIs followed by risperidone if poor response. Monitor for worsening of anxiety in some children. (B)	Decision on treatment needs to be made on a case-by-case basis. Follow the BAP guidelines for treating anxiety. (S)
Sleep disorders	Melatonin, if possible, in combination with a behavioural intervention. (A) Prolonged use of benzodiazepines and related GABA agonists is not recommended. (S)	Melatonin, if possible, in combination with behavioural intervention (extrapolation from findings in children). (S) Prolonged use of benzodiazepines and related GABA agonists is not recommended. (S)
Irritability	Risperidone or aripiprazole but only when behavioural or educational approaches have failed. (A)	Decision on treatment needs to be made on a case-by-case basis. Aripiprazole or risperidone or an SSRI should only be considered cautiously and after considering alternatives. (S)
ADHD	First line: methylphenidate. Second line: atomoxetine, or α2A receptor agonist. Children with ASD may experience more side-effects and show less response than non-ASD patients with ADHD. (A)	Decision on treatment needs to be made on a case-by-case basis. Follow the BAP guidelines for treating ADHD. (S)
Tic disorders and Tourette syndrome	Decision on treatment needs to be made on a case-by-case basis. (S)	Decision on treatment needs to be made on a case-by-case basis. (S)

ADHD: attention deficit/hyperactivity disorder; ASD: autism spectrum disorder; BAP: British Association for Psychopharmacology; GABA: gamma-aminobutyric acid; SSRI: selective serotonin re-uptake inhibitor.

Given the limited evidence, recommendations must be made by extrapolation from studies in children and adults without ASD. We recommend following the BAP guidelines on sleep disorders (Wilson et al., 2010) with the same general caveats discussed for mood and anxiety disorders. In addition, it is worth considering an early trial of melatonin, in view of the benefit in children, and its favourable side-effect profile. We do not recommend the prolonged use of benzodiazepines and related GABA-agonists due to the risk of tolerance and side-effects, in line with the BAP guidelines on sleep disorders.

Treatment of irritability in adults with ASD

Treating irritability has been less well studied in adults than it has been in children with ASD.

Risperidone was reported to significantly reduce symptoms of irritability and aggression in a small study after 12 weeks (McDougle et al., 1998) (evidence level IIa). The same group also investigated fluvoxamine in a small study that reported a reduction in aggression after 12 weeks of treatment (McDougle et al., 1996) (evidence level IIa). In both these studies, irritability and aggression were not the primary outcome measures. A small study of fluoxetine reported no effect on irritability, although this was not the primary outcome of this (Hollander et al., 2012) (evidence level IIa). A small study of pregnenolone reported significant improvement in irritability (Fung et al., 2014) (evidence level IIb).

In summary, there is limited evidence to guide the treatment of irritability in adults with ASD. A dopamine blocker such as risperidone or SSRI could be tried cautiously and side-effects should be carefully monitored (including relevant medical assessments and laboratory tests). Alternatives such as behavioural approaches should also be considered first (see section on non-pharmacological approaches below). Further studies on pregnenolone are warranted.

Treatment of ADHD in adults with ASD

There have not been any RCTs that have investigated the role of stimulant or non-stimulant medications in treating ADHD in adults with ASD. In view of this we recommend cautiously following the BAP guidelines for treating ADHD (Bolea-Alamañac et al., 2014), with the same general caveats discussed above for mood and anxiety disorders.

Treatment of tic and Tourette syndrome in ASD

No current studies are available for treating tic disorders in children or adults with ASD specifically. A recent review (Whittington et al., 2016) on tic disorders in the absence of ASD reported evidence favouring the use of the a2-adrenergic receptor agonists clonidine and guanfacine (standardised mean difference= −0.71; 95% confidence interval (CI) −1.03 to −0.40; evidence level Ia). This was based on four trials with a total n=164. As there are no studies on treating tic disorders in ASD we would recommend that the decision on using α2A receptor agonists with ASD is made on a case-by-case basis.

Summary

Most RCTs in ASD have centred on children and adolescents, and have overwhelmingly been focused on symptoms, not co-occurring disorders. There is some limited evidence to suggest that both treatment response and side effects to pharmacological interventions differ from the general population, suggesting extrapolation from findings in non-ASD populations should be made cautiously (evidence level IIb). Currently the best studied medication classes include dopamine blockers to target irritability and drugs targeting ADHD symptoms (methylphenidate, atomoxetine, α2A receptor agonists). Secondary data analyses suggest the antipsychotics have modest benefits on repetitive behaviours. However, there remain very significant gaps in knowledge particularly with respect to some of the most common co-occurring conditions (e.g. anxiety and mood disorders) and some of the most widely prescribed drugs (e.g. antidepressants).

Consensus recommendations of pharmacological treatment of co-occurring conditions and symptoms in children and adults with ASD can be found in Table 1.

Non-pharmacological approaches for core symptoms of ASD in children

A full analysis of psychological interventions for ASD is beyond the scope of these guidelines. However, we summarise key elements of the evidence to provide context for the other aspects of management discussed, particularly drawing on recent National Institute for Health and Clinical Excellence (NICE) (National Institute for Health and Clinical Excellence, 2013) and US Agency for Healthcare Research and Quality (AHRQ) (Weitlauf et al., 2014) reviews of behavioural interventions.

Social-communication interventions

Individual focused interventions can be delivered to young children. They are commonly mediated by parents, teachers or peers and can be combined with joint-attention approaches and applied behaviour analysis (ABA). These interventions typically include developing patterns of communication that are directed by the child's interest in activities, repeating back or expanding on what the child says, sitting close to the child and making eye-contact and using mirroring/imitation of the child's actions. Parent-mediated interventions use parent-training programmes to improve parental sensitivity and responsiveness to child communication through techniques such as therapist-lead instruction and video feedback. Most programmes available for parents of children with ASD have been developed specifically for young preschool children with ASD. The effectiveness of such programmes has been assessed by NICE (National Institute for Clinical Excellence, 2012). This found there was evidence of efficacy for some of these programmes over treatment as usual (TAU) at reducing symptoms of social interaction impairment including communication acts, parent–child joint attention and joint engagement. However, these effects were small and often not clinically meaningful. For example, Green et al. (2010) compared the Preschool Autism Communication Trial (PACT) to TAU. ADOS-G scores were reduced by 3.9 points in the PACT group and 2.9 points in the TAU group, representing a between group effect size of –0.24. However, both parent synchrony and child initiations were improved in the short-term by the PACT treatment (Green et al., 2010) and recent long-term follow-up has reported reduced ASD symptoms as measured by the ADOS and sustained increases in child initiations six years after treatment ended (Pickles et al., 2016). Similarly, a RCT of Hanan's 'More Than Words' intervention versus TAU found no main effect of treatment on child outcomes immediately or at five months after treatment (Carter et al., 2011). However, there were gains on child communication at nine months which were moderated by baseline object interest (lower object interest=greater gains). Two further RCTs of parent-mediated interventions published after the NICE and AHRQ reviews indicate improvements in parent–child interactions (Kasari et al., 2014; Wetherby et al., 2014).

Peer-mediated social-communication interventions can be delivered to school-aged children. These typically involve free-play sessions between a child with ASD and typically-developing children who have undergone preparatory training. There is evidence (level Ib) of the effectiveness of such interventions on the core feature of reciprocal social communication and peer–child joint engagement from four RCTs and one non-randomised trial (see recent review by Chang and Locke (2016)). However, most of these studies were conducted with high functioning children with ASD. Hence there is a need for further research to establish the effectiveness of peer-mediated interventions in other age and functional groups with ASD.

There is also evidence (level Ib) of modest gains on the quality and frequency of social play after the parent-assisted 'Children's Friendship Training (CFT)' social skills group training programme (Frankel et al., 2010). This programme has also shown effectiveness on social skills in children with ADHD (Frankel et al., 1995, 1997) and children with foetal alcohol spectrum disorders (O'Connor et al., 2006). The CFT and other similar social skills interventions (Koenig et al., 2010; Lopata et al., 2010) typically involve mixed clinical groups with or without typically developing peers and the teaching of social skills through instruction, modelling, rehearsal, role-play, performance feedback and homework. The CFT programme has been adapted for adolescents and found to have beneficial effects on social skills among teens 13–17 years of age (Laugeson et al., 2009).

Behavioural interventions

Although not explicitly recommended in the NICE guidelines, the AHRQ review found evidence that a number of interventions based on high-intensity ABA applied over an extended time-frame had a positive effect on cognitive functioning and language skills (Weitlauf et al., 2014). These interventions include the Learning Experiences and Alternative Program for Preschoolers and their Parents (LEAP), the Lovaas Model and the Early Start Denver Model (ESDM). Of the 10 studies included in the AHRQ review, only two were RCTs and both were conducted in the USA (Dawson et al., 2010, 2012; Strain and Bovey, 2011), where health and education services may not readily generalisable to other settings. There is also evidence (level Ib) for combined joint attention training and ABA-based interventions. Two studies reviewed by NICE (Kasari et al., 2006; Landa et al., 2011) showed large effects (standardised mean difference [SMD]=1.11) of additional joint-attention training for the child responding to joint attention during child–examiner interactions, moderate to large effects

(SMD=0.55–0.69) on the duration of child-initiated joint attention during mother–child interaction and moderate effects (SMD=0.69) on pointing during examiner–child interaction. However, there is criticism that ABA does not generalise beyond the skills trained and thus should be combined with other interventions to promote the use of skills across settings (Smith, 2001). Hence, the effectiveness of ABA may be limited to the specific skills taught.

Alternative interventions

A number of alternative therapies, such as exclusion diets, secretin, chelation and hyperbaric oxygen therapy, have been tried for ASD. The evidence available indicates that exclusion diets such as gluten- or casein-free diets should not be routinely used for the management of core features of ASD (National Institute for Health and Clinical Excellence, 2013). Moreover, the available evidence indicates that secretin treatment is not effective (Sandler et al., 1999). Chelation and hyperbaric oxygen therapy are potentially harmful with little evidence of benefit and should not be used to manage ASD in any context (Davis et al., 2013; Goldfarb et al., 2016; National Institute for Clinical Excellence, 2012).

Recommendations

We recommend considering a specific social-communication intervention for the core features of ASD in children and adolescents that includes play-based strategies with parents, carers and teachers to increase joint attention, engagement and reciprocal communication. These interventions may also support the parents', carers', teachers' or peers' understanding of, and sensitivity and responsiveness to, the child or young person.

Consensus recommendations of non-pharmacological approaches for children and adolescents

1. A specific social-communication intervention should be offered to children and adolescents according to their developmental level. (A)
2. Social skills training should be offered to adolescents in either group or individual sessions. (A)
3. Exclusion diets and secretin, chelation and hyperbaric oxygen therapy should not be used for the management of ASD in children or adolescents. (D)

Psychological approaches to ASD in adults

A full analysis of psychological approaches for adults with ASD is beyond the scope of these BAP guidelines. In the following section, we summarise the key points to provide context for other aspects of management considered, drawing on the NICE guidelines and AHRQ review.

Social learning programmes

NICE guidelines recommend group- or individual social learning programmes for adults with ASD without a learning disability (LD) or with a mild to moderate LD, who have problems with social interaction. Social learning programmes to improve social interaction deficits apply behavioural therapy techniques within a social learning framework, such as using video modelling, peer/individual feedback, imitation and reinforcement to teach conventions of social engagement. There is evidence (level III) from observational studies in adults with ASD that suggest social skills groups may be effective at improving social interaction (Hillier et al., 2007; Howlin and Yates, 1999). However, the only RCT of social skills training found no positive treatment effect of emotion recognition training on general emotion recognition (Golan and Baron-Cohen, 2006), suggesting that social interaction programmes may only be effective when they include a more general social learning component.

Behavioural and life-skills interventions

Adults with ASD of all ranges of intellectual ability who need help with activities of daily living can be offered a structured, predictable training programme based on behavioural principles. However, the evidence (level Ib) of the effectiveness of these programmes is indirect and largely reliant on studies of adults with a learning disability (Matson et al., 1981).

In adults with ASD without LD or with mild to moderate LD who are socially isolated or have restricted social contact, interventions should focus on the acquisition of life skills based on the specific need of the individual. In recent years, there has been increased interest in providing structured leisure activities for people with ASD. There is evidence (level Ib) of the effectiveness of these programmes on overall quality of life and emotion recognition from two RCT's (see review by National Institute for Clinical Excellence, 2012).

Cognitive-behavioural interventions

CBT can help adults with ASD across a range of domains. Principally, CBT is effective at treating anxiety and OCD, and supporting adults who have difficulties with victimisation and obtaining or maintaining employment. Evidence (level II) from a systematic review demonstrates the effectiveness of CBT for anxiety in ASD (Lang et al., 2010). However, there is also evidence that anxiety management performs just as well as CBT in reducing symptoms of OCD in individuals with ASD (Russell et al., 2013).

Cognitive-behavioural interventions can be implemented to support individuals with ASD who are at risk of victimisation by teaching decision-making and problem-solving skills. Evidence (level Ib) from two RCTs suggests that CBT in adults with LD is effective at increasing skills to deal with victimisation (Khemka, 2000; Khemka et al., 2005). However, these studies are limited by including cases without ASD. Individual support programmes can be used to improve employment and job retention. Studies of supported employment programmes are consistently positive despite methodological concerns including lack of randomisation in one study.

Facilitated communication

Facilitated communication uses a facilitator to support the arm movement of an individual with ASD to point at letters on an alphabet board, keyboard or similar device. Positive reports of its effectiveness are almost exclusively based on anecdotal evidence (Biklen, 1990; Biklen et al., 1992, 1995; Biklen and

Schubert, 1991; Clarkson, 1994; Crossley and Remington-Gurney, 1992; Heckler, 1994; Janzen-Wilde et al., 1995; Olney, 1995; Sabin and Donnellan, 1993; Sheehan and Matuozzi, 1996; Weiss et al., 1996). There is no evidence of positive effects from any scientific study (Bebko et al., 1996; Beck and Pirovano, 1996; Bomba et al., 1996; Braman et al., 1995; Crews et al., 1995; Eberlin et al., 1993; Edelson et al., 1998; Hirshoren and Gregory, 1995; Hudson et al., 1993; Klewe, 1993; Konstantareas and Gravelle, 1998; Montee et al., 1995; Myles and Simpson, 1994; Myles et al., 1996; Oswald, 1994; Regal et al., 1994; Simon et al., 1996; Simpson and Myles, 1995a; Smith and Belcher, 1993; Smith et al., 1994; Szempruch and Jacobson, 1993; Vázquez, 1994; Wheeler et al., 1993). In addition to the lack of empirical support, there is evidence that facilitated communication can lead to significant harm. For example, there have been unsubstantiated claims of sexual abuse against family members made when using facilitated communication (Rimland, 1992; Simpson and Myles, 1995b). For these reasons, NICE strongly recommends that facilitated communication is not used (National Institute for Clinical Excellence, 2012).

Recommendations

It is recommended that adults with ASD are offered psychological interventions to optimise personal functioning, including developing the skills necessary for access to public transport, employment and leisure facilities. Interventions should focus on supporting access to community activities and increasing the individual's quality of life. Furthermore, psychological approaches can be used to help with acceptance of their difficulties, treat co-occurring conditions and to teach life skills specific to the needs of the individual.

Consensus recommendations of psychological approaches with adults

1. For adults with problems with social interaction, consider a group or individual social-learning programme. (A)
2. Do not provide facilitated communication for adults with ASD. (D)
3. For adults who need help with activities of daily living, consider offering training programmes based on behavioural principles. (A)

Service provision

The NICE guidelines published in 2011 recommend the development of multi-agency teams for people with ASD that include representatives from child health and mental health services, education, social care and the voluntary sector. However, service provision varies greatly and in many settings is significantly weighted towards diagnosis and children's services rather than treatment and support or adult care. In particular, there are unmet needs around common co-existing conditions including feeding problems, sleep problems, anxiety, hyperactivity and sensory problems (Maskey et al., 2013). Unfortunately, there has been very little health service research that has focused on ASD. In view of this, we review the available evidence below and make recommendations for service provision for children and adults, but it should be appreciated that these are largely based on the expert opinion of the working group.

Diagnostic services

Timely and valid diagnosis is important as early diagnosis and provision of appropriate management services is likely to improve long-term outcome (Magiati et al., 2014; Oono et al., 2013). Referral and diagnostic pathways for ASD vary, but in most cases, the initial concerns raised by parents or professionals will be directed to a general practitioner (GP), speech and language therapist or an educational psychologist. These will undertake an initial assessment and decide to refer the patient to children's health or mental health services for a full assessment. A full assessment should be made by professionals who are trained in the assessment, diagnosis and treatment of ASD using a combination of diagnostic tools, assessments and clinical experience (level IV). In general, diagnosis should not be formulated by one single professional and should involve a multi-disciplinary team (MDT) (Penner et al., 2017). This should ideally consist of a speech and language therapist, a clinical psychologist, paediatrician or child psychiatrist, and an occupational therapist. However, there is significant variation in service provision. For example, 47% of teams surveyed in the UK do not have access to a clinical psychologist (Palmer et al., 2010).

It is noteworthy that studies from some settings report a correlation between lower socioeconomic status and later diagnosis (Goin-Kochel et al., 2006), suggesting that there are social impediments to referral and diagnosis. However, studies in settings where there is universal free healthcare (such as the UK) do not show this relationship, or even show the opposite relationship (Brett et al., 2016). Other factors reportedly associated with earlier age of diagnosis in the UK include a 'core' ASD diagnosis (as opposed to broader ASD), language regression or delay, and greater degree of support needed (Brett et al., 2016). Furthermore, there is evidence of a sex bias in referral and diagnosis even in settings such as the UK, suggesting a delayed recognition of the disorder in young girls (Brett et al., 2016; Rutherford et al., 2016). Moreover, within the UK there is regional variation in the diagnostic services available (Gray et al., 2015; Palmer et al., 2010; Parr et al., 2013) (level IV).

Given these findings, there is a need for clear referral pathways that ensure adequate assessment is available to all who need it (Buckley, 2016). This needs to be coupled with increased training to raise awareness of ASD among GPs and healthcare visitors (level IV).

Management/treatment services

Given the complexity of ASD, its treatment and monitoring should be conducted by professionals who are trained and experienced in treating and monitoring ASD (S). For patients with severe symptoms, a structured multi-disciplinary approach that includes regular reviews of the overall care package, such as the care programme approach, is indicated (S). Ideally, treatment should be managed by a specialist MDT with experience in ASD and related disorders. Where this is not possible, services should consider a consultation-liaison model where recommendations are made by a specialist team but implemented by general health services such as general psychiatrists, paediatricians or GPs, with further liaison depending on response (S).

Individuals with ASD who are in child and adolescent services should be reassessed around 14 years of age to establish the need for continuing treatment into adulthood (S) (National Institute for Health and Clinical Excellence, 2013). Where ongoing treatment is required, arrangements should be made for a smooth transition into adult services and the individual kept informed about the treatment and services available to them (S) (National Institute for Health and Clinical Excellence, 2013). Information about adult services should be provided to the young person, and their parents or carers, including their right to a social care assessment at age 18 (S).

Finally, there is a clear need for health services research to evaluate diagnostic and treatment service models, both in terms of clinical outcomes and cost-effectiveness.

Improving services

Given the importance of timely diagnosis, early identification and referral is a priority. GP initiatives and specialist training for health visitors are recommended to improve early identification (S). Diagnostic and treatment services should be led by MDTs that consist of a minimum of a psychiatrist (or paediatrician where appropriate), a speech and language therapist, and a psychologist. Treatment recommendations should be made alongside diagnosis and followed up by a team experienced in treating ASD, using a structured care approach, such as the Care Programme Approach, particularly for people with severe and complex needs. There is a possibility that referral rates for ASD will increase given the greater public awareness and diagnostic service availability. This poses a challenge to services that are trying to provide a valid and timely diagnosis. It is therefore important to use screening tools in order to target service resources. Finally, it is important to consider costs when assessing current services or developing new ones. Services should be audited regularly to ensure quality and accessibility of care for patients.

Recommendations

There is large variation in services between settings and little research on the optimum service provision or cost-effectiveness. There is a need for well-designed studies to evaluate models of service provision, and RCTs developed to test these using patient experience, functional outcomes in addition to standard clinical measures (strength of recommendation: D). Finally, it is important to consider costs when assessing current services or developing new ones, and future studies of service provision should include cost-analysis (strength of recommendation: D). Services should be audited regularly to ensure quality and accessibility of care for patients (strength of recommendation: D).

Consensus recommendations for service provision

1. Reassess individuals with ASD in children's services during adolescence well in advance of the transition date to establish the need for continuing treatment. (S)
2. If continuing treatment is necessary, make arrangements for a smooth transition to adult services or GP and give information to the young person about the treatment and services they may need. (S)
3. For young people and adults whose needs are complex or severe, use the care programme approach or similar structured approach to coordinate their needs and to aid the transfer between services. (S)
4. Involve the individual with ASD in care planning and, where appropriate, their parents or carers. (S)
5. Provide information about adult services to the young person, and their parents or carers, including their right to a social care assessment at age 18 years. (S)

Future directions

The earlier sections have highlighted that there are a number of limitations and areas of uncertainty, particularly for core ASD symptoms. The following section discusses these and makes recommendations for future research.

Future design of clinical trials

Many studies are open-label and/or small scale, or lack an adequate placebo group. Hence, there is a general need for positive findings from these initial exploratory and proof-of-concept studies to be followed-up with large-scale randomised placebo-controlled trials. This presents a number of challenges for the field. First, as some potentially useful treatments are off-patent, the field will not be able to rely on the pharmaceutical industry to fund studies of these compounds. Thus, funding will need to be sought from other sources, including government funded agencies, and charities and foundations. Second, the field will need infrastructure for large-scale trials across many settings. This will also involve centres developing the capacity to screen and recruit people with ASD to clinical trials, and is likely to benefit from the involvement of support groups and charities (Warnell et al., 2015) (strength of recommendation: D).

One major limitation of the literature to date is that only a small number of clinical trials have included participants below the age of five years. Interventions that begin before the age of five years may have the most dramatic effect (Aman et al., 2015) as ASD symptoms start emerging and brain plasticity is at its peak during this period. However, there are important safety considerations regarding the use of pharmacological interventions in paediatric populations (Kearns et al., 2003). Consequently, it will be necessary to develop and trial interventions in this period both to prevent the onset of ASD and minimise its effects on brain and cognitive development (strength of recommendation: D). Another general limitation of studies to date is that individuals with ASD who have an intellectual disability are usually excluded, despite the fact that over a third of people with ASD have an intellectual disability (Baio, 2012). Thus, to be representative, future studies should include people with ASD and intellectual disability, and need to adopt designs that facilitate this (strength of recommendation: D). Clearly both these issues will involve overcoming the ethical and practical challenges of enrolling young children and people with intellectual disability into clinical trials. This may be helped by wider engagement with individuals and their families regarding the design of clinical trials. Another issue that needs addressing is the duration of trials, which have mostly been weeks or at most a few months to date. Given the long-standing and pervasive nature of core symptoms, it is highly unlikely that core symptoms will improve in a few weeks or months and, where there is change, it is necessary to show that this is sustained (strength of recommendation: D).

Non-pharmacological interventions and service provision

There is a lack of large-scale, multicentre RCT's investigating the effectiveness of social-communication interventions, ABA, behaviourally-based life skills training and anti-victimisation CBT. Studies are required to assess the effectiveness of these interventions across a range of outcome measures including cost-effectiveness and quality of life (strength of recommendation: D). Similarly, models of service provision are under-tested and require empirical evaluation (strength of recommendation: D). These studies should use patient experience and functional outcomes in addition to standard clinical measures of improvement.

Future outcome measures

Another critical issue that needs to be addressed is the lack of agreement on the outcome measures to be used in trials to accurately capture changes in core ASD symptoms over time (Aman et al., 2004). An optimal tool needs to be reliable and suitable for repeated administration. Current functioning should also be a focus. Aman and colleagues provide a comprehensive review of potential instruments and also point out that other aspects such as language, intellectual level and adaptive behaviour should be incorporated in the outcome measures (Aman et al., 2004) (strength of recommendation: D). Another obstacle that needs to be considered in pharmacological studies is that in the absence of objective psychometric measures, evaluation of symptom change in children depends on the parent-report measures, which are prone to expectancy bias (Aman et al., 2015). Thus, blinding and placebo control is important, and findings from open-label studies should be treated with caution. Last, but not least, the perspective of individuals with ASD and their carers should be taken into account when deciding on outcome measures. A recent systematic review highlighted the disparity in the outcomes identified as important by parents and those identified by health professionals: parents highlighted the importance of social participation and emotional well–being, whereas health professionals concentrated on the content of the available instruments they have (McConachie et al., 2015). A tool that indexes the quality of life of individuals with ASD that should be included as an outcome measure in future clinical trials (strength of recommendation: D). Furthermore, monitoring of adverse effects should not be limited to studies of pharmacological interventions. Adverse effects should be monitored when studying psychological and other interventions too.

The challenge of biological heterogeneity

On top of these difficulties in designing clinical trials, another challenge is the genetic and neurobiological heterogeneity seen in ASD, which means that it is unlikely that any single drug will be effective for all patients. It is clear that we need better understanding of the neurobiology underlying ASD to identify key molecular and system pathways that are disrupted, and the determinants of heterogeneity. This will enable the development of treatments that target key components of the neurobiology. Coupled with this we need biomarkers to identify sub-types that will respond to particular approaches (Loth et al., 2016b). A considerable amount of work is currently on-going to develop imaging, genetic, proteomic and other biomarkers for this purpose (e.g. Loth et al., 2017). To date there is no independently validated biomarker for stratification of patients, and trials have rarely attempted to include biomarkers that would enable stratification. Thus, it is largely unknown if there are sub-groups that showed better or worse response in past trials.

Syndromic types of ASD with a defined genetic basis can be used in the absence of biomarkers. Pathophysiological changes are likely to more homogenous in syndromic ASD (e.g. FXS). As discussed earlier, open-label studies on FXS using lithium (Berry-Kravis et al., 2008) and minocycline (Paribello et al., 2010) have shown encouraging results, suggesting the potential of this approach, although studies need to be replicated in randomised, double-blind controlled studies. This highlights two over-riding issues; first of all, the level of complexity in the neurobiology of ASD (Ghosh et al., 2013) and secondly the importance of either conducting the studies in a clinically and biologically homogenous groups or including biomarkers to stratify heterogeneous groups.

So far, the identification of putative subgroups has been limited by small sample sizes, which limits the power of studies to test the influence of stratification by sub-groups on treatment response. Small discovery studies need to be followed by larger studies with the power to test the clinical utility of the potential biomarkers they identify (strength of recommendation: D). Therefore, in the future, large-scale, multicentre studies where patients are stratified according to their biological subtype are necessary in order to test whether stratification by particular biomarkers corresponds to improved response in a sub-group (strength of recommendation: D). In these studies, subgroups may be identified according to their genetic or molecular profile and then subsequently compared in terms of cognitive, neuroimaging and biochemical measures (Loth et al., 2016a). These advances will hopefully make it possible to identify biomarkers which, in the future, can be used to treat individuals with ASD more effectively and with a more personalised approach.

Consensus recommendations for future research directions

- Studies should include biomarkers to identify potential sub-groups in order to support stratification in future clinical trials where possible. (D)
- Clinical trials should ideally be multicentre, large-scale and include biomarkers where possible. This will ensure results are more generalisable and offer the opportunity to test whether a change in outcome measures is associated with change in biomarkers. (D)
- Clinical trials should include younger children and individuals with ASD and intellectual disability to ensure generalisability to the whole population of people with ASD. (D)
- Longer-term clinical trials lasting at least six months are required. (D)

- There is a need to develop objective outcome measures that can reliably capture changes of core symptoms over time. (D)
- Clinical trials should also include measures of quality of life of individuals with ASD. (D)
- Large-scale, multicentre, RCTs are needed to assess the effectiveness of social-communication interventions and applied behavioural analysis on a range of outcome measures. (D)
- All interventional studies, including those investigating psychological and social interventions, should include measures of adverse effects (D)
- Studies are needed to examine the effectiveness of behaviourally based daily life skills in adults with ASD. (D)
- Studies are needed to examine the effectiveness of anti-victimisation CBT in adults with ASD. (D)
- Studies are needed to evaluate models of service provision using patient experience and functional outcomes in addition to standard clinical measures (D).

Summary of guidelines and conclusions

These guidelines present recommendations based on the current literature and expert opinion for the diagnosis and management of ASD in children and adults. Our review of the evidence is not intended to be exhaustive, but to highlight key findings and also place them in a clinical context, drawing from the practical experience of the contributors. We hope that this balance will help the clinician who draws on the guidelines to place the evidence and our recommendations in the individual context of the person with ASD in front of them.

Current evidence does not support the routine use of any pharmacological treatment for the core symptoms of ASD. The evidence base is growing, particularly for co-occurring symptoms and disorders, yet much of the evidence is relatively nascent, particularly for core aspects of ASD. Aripiprazole and risperidone have shown some benefit for repetitive behaviours but are recommended only on a case-by-case basis in view of the risk of side-effects. There are a number of treatments for co-occurring conditions with a reasonable evidence base, although the evidence is still largely limited to symptomatology and mainly limited to children. In children, melatonin is recommended for sleep disorders, risperidone and aripiprazole may be cautiously used in the management of irritability if behavioural approaches are not possible, and methylphenidate is recommended for ADHD symptoms. There is very limited evidence for treatments for other co-occurring symptoms or disorders and in adults. Consequently, treatment is guided by extrapolation from studies in people without ASD. As treatment response and side-effect profiles in ASD may differ from the general population, treatment guided by extrapolation from studies in people without ASD must be cautious. Therefore, each treatment for an individual with ASD should be approached as an n=1 trial with careful evaluation of both benefits and side-effects.

In children and adolescents, social-communication interventions should be offered to increase joint-attention, engagement and reciprocal communication. In adults, psychological interventions should focus on the acquisition of life skills, access to community activities and quality of life.

ASD is a common and pervasive condition with a high health burden, and complex pathoaetiology involving a number of brain systems. The impact of ASD on the individual, their family and wider society is substantial, but may be reduced by timely diagnosis, the use of effective treatments, and avoiding inappropriate treatment. We recommend that service providers ensure people with ASD have timely access to diagnostic and treatment services with specialist expertise in ASD. Research into the genetics and neurobiology of ASD indicates that there is significant genetic and neurobiological heterogeneity. This is likely to lead to heterogeneity in the response to treatment and differential sensitivity to side-effects. It also highlights the need for biomarkers that can be used to guide the development of new treatments for core symptoms and co-occurring conditions, and help identify sub-groups who may respond better. Our analysis of the current evidence also highlights particular key gaps and limitations, and makes recommendations to address these. There are a number of studies of promising treatments being developed and we hope our recommendations will inform the development of studies. Finally, it is important to appreciate that we do not see these guidelines as set in stone. Indeed, we look forward to the evidence base growing, and anticipate revising these guidelines in the light of future developments.

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Supplementary material

Supplementary material is available for this article online.

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