2020 surveillance of autism (NICE guidelines CG128, CG142 and CG170)

Surveillance proposal

We will not update the following guidelines on autism:

- Autism spectrum disorder in under 19s: recognition, referral and diagnosis (NICE guidance CG128).
- Autism spectrum disorder in adults: diagnosis and management (NICE guideline CG142).
- Autism spectrum disorder in under 19s: support and management (NICE guideline CG170).

We are consulting on:

- The importance practitioners place on scores from the Autism Spectrum Quotient test (AQ-10) when trying to identify autism in adults, in order to assess the impact of new evidence on recommendation 1.2.3 in autism spectrum disorder in adults: diagnosis and management.
- Amending recommendation 1.7.7 in autism spectrum disorder in under 19s: support and management to include advice that melatonin can be considered as a medication to aid sleep.

Reasons for the proposal

Most of the new evidence and information identified during surveillance was assessed as being consistent with exiting recommendations in the 3 included guidelines, inconclusive, or their conclusions were limited by small study populations or methodological issues.

For further details and a summary of all evidence identified in surveillance, see the summary of evidence from surveillance.

We identified new evidence about:

- Risk factors associated with increased prevalence of autism, including: parental age; cardiovascular conditions during pregnancy; familial risk factors; exposure of children to pollutants; and maternal mental health
- Checking for the presence of coexisting conditions, including functional, medical, genetic, behavioural and neurodevelopmental
- Identifying possible autism using screening tools in adults and children, including: the 'Autism Detection in Early Childhood' tool and 'Autism Spectrum Screening Questionnaire (ASSQ)' for children; and the 'Autism Quotient test (AQ-10)' for adults
- Diagnostic accuracy of tools used to assess autism, including: the 'Autism Diagnostic Interview (ADI)' and 'Autism Diagnostic Observation Schedule (ADOS)' tools for children; and the 'Diagnostic Behavioral Assessment for autism Spectrum disorders-revised (DiBAS-R)' tool for adults
- Diagnosing autism in girls that investigated underdiagnosis and described the characteristics of autism in this group
- Medical investigations to identify autism or coexisting conditions, including; genetic; biomedical and computerised techniques, including the use of machine learning to interpret diagnostic data
- Excess mortality, its prevalence and association with coexisting conditions
- Psychosocial interventions for the core features of autism and behaviour that challenges including applied behaviour analysis; educational interventions; and social skills training. For adults we also identified employment interventions and cognitive behavioural therapy
- Drug treatments for the core features of autism and behaviour that challenges, including antidepressants, antipsychotics, stimulants, and oxytocin
- Drug and non-drug interventions for managing of sleep disorders, including melatonin, carnosine and behavioural interventions
- Interventions to improve the variety of diet in children with autism
- Dietary supplements and complimentary therapies for the management of the core features of autism and behaviour that challenges, including vitamin D, folinic acid, omega fatty acids, and acupuncture

- Training interventions for parents, carers and teachers of children with autism.

We identified 2 new pieces of evidence which are discussed below. One about the effectiveness of AQ-10 for screening adults for autism, and one about the use of melatonin to treat sleep disorders in children. We are consulting with stakeholders for their views about the potential impact of this new evidence on the guidelines.

Autism spectrum quotient (AQ-10) test

Autism spectrum disorder in adults: diagnosis and management recommendation 1.2.3 recommends considering AQ-10 for adults with possible autism who do not have a moderate or severe learning disability and if they score above 6, or based on clinical judgement, offer a comprehensive autism assessment. This recommendation was based on a study that reported sensitivity and specificity greater than 88% for AQ-10 for correctly diagnosing autism.

A new study (Ashwood, K.L. et al. 2016) that evaluated the AQ-10 in 476 adults reported it performed poorly at correctly identifying people with autism, producing a 64% false negative rate. Topic experts commented that this finding makes recommendation 1.2.3 out of date.

Although recommendation 1.2.3 is a 'consider' recommendation and recommends AQ-10 should be used alongside clinical judgement, the new study highlights that it may potentially miss many cases of autism. Therefore, we are consulting with stakeholders about the impact of this new evidence on recommendation 1.2.3. by asking to what extent they rely on AQ-10 when making decisions to offer a full autism assessment.

Melatonin

We identified one systematic review (Parker, A 2016) and 2 studies from one RCT population (Gringas, P 2017 and Maras A. 2018) that reported melatonin improves time to sleep onset and wakefulness. Since the last surveillance review of autism spectrum disorder in under 19s in 2016, melatonin has been

licensed for use for insomnia in children aged 2 to 17 years with autistic spectrum disorder, where sleep hygiene measures have failed (see the BNF for Children entry for melatonin). NICE guidance on challenging behaviour and learning disabilities recommendation 1.11.2 recommends considering melatonin if medication is required to aid sleep. This guideline covers many conditions that co-exist with autism and uses evidence that includes populations with autism. We are therefore proposing amending the wording of recommendation 1.7.7 to include the following sentence taken from NICE guidance on challenging behaviour and learning disabilities: 'If medication is needed to aid sleep, consider melatonin.'

We are consulting with stakeholders about the validity of this proposal.

Based on these finding we do not plan to update any of the 3 guidelines but are consulting on amending recommendations about the use of AQ-10 in adults and the use of medication in children with sleep disorders.

Overview of 2020 surveillance methods

NICE's surveillance team checked whether recommendations in the following guidelines remain up to date:

- Autism spectrum disorder in under 19s: recognition, referral and diagnosis (NICE guidance CG128).
- Autism spectrum disorder in adults: diagnosis and management (NICE guideline CG142).
- Autism spectrum disorder in under 19s: support and management (NICE guideline CG170).

The surveillance process consisted of:

- Feedback from topic experts via a questionnaire.
- A search for new or updated Cochrane reviews and national policy.
- Consideration of evidence from previous surveillance.
- Examining related NICE guidance and quality standards and National Institute for Health Research (NIHR) signals.

- A search for ongoing research.
- Examining the NICE event tracker for relevant ongoing and published events.
- Literature searches to identify relevant evidence.
- Assessing the new evidence against current recommendations to determine whether or not to update sections of the guideline, or the whole guideline.
- Consulting on the proposal with stakeholders, except if we propose to update and replace the whole guideline (this document).

For further details about the process and the possible update proposals that are available, see ensuring that published guidelines are current and accurate in developing NICE guidelines: the manual.

Evidence considered in surveillance

Search and selection strategy

We searched for new evidence related to the 3 NICE guidelines on autism in children and adults.

We found 191 studies in a search for systematic reviews, randomised controlled trials and diagnostic studies published between 27 January 2016 and 1 November 2019.

We also included:

- 5 out of 166 relevant studies and policies identified by topic experts.
- 4 studies from previous surveillance reviews to provide a context for new studies identified (on therapeutic horseback riding, use of atomoxetine, use of guanfacine and parent training versus parent education)
- 1 study considered during development of autism spectrum disorder in children (NICE guideline CG170) to provide context for new studies identified (on parent-mediated social communication treatment (PACT)).

From all sources, we considered 201 studies to be relevant to the guideline.

See the summary of evidence from surveillance for details of all evidence considered, and references.

Selecting relevant studies

Diagnostic studies were only eligible for inclusion if they met the criteria set by the original guideline development group of at least 80% sensitivity and specificity. There were no specific inclusion criteria for RCTs or systematic reviews.

Ongoing research

We checked for relevant ongoing research; of the ongoing studies identified, 16 were assessed as having the potential to change recommendations. Therefore, we plan to regularly check whether these studies have published results and evaluate the impact of the results on current recommendations as quickly as possible. These studies are:

- Can exercises involving movement and the senses improve behavior and life skills in non-speaking children with severe autism?
- ComAlong Toddler - Parental course to help the child to communicate.
- PALACES – Parenting for autism, language, and communication evaluation study.
- Improving autistic children's social communication with parents in everyday settings..
- ADIE to prevent development of anxiety disorders in autism.
- An investigation of the frequency of social communication problems are among adults admitted to acute mental health ward.
- Sleeping Sound with Autism Spectrum Disorder (ASD).
- Managing repetitive behaviours parent group study.

- A primary school research study to establish whether Social Stories™ can improve social and emotional health in children with autism spectrum disorder.
- A trial of sensory integration therapy versus usual care for sensory processing difficulties in autism spectrum disorder in children.
- Reducing suicidality in autism-spectrum patients using dialectical behaviour therapy.
- An evaluation of LEGO-based therapy in school for children with autism.
- A trial of Acceptance and Commitment Therapy for caregivers.
- The Secret Agent Society: Operation Regulation intervention - transdiagnostic trial.
- Behavioural and cognitive behavioural therapy for obsessive compulsive disorder (OCD) in individuals with autism spectrum disorder (ASD) (Cochrane review).
- Pivotal Response Treatment for autism spectrum disorder (ASD) (Cochrane review).

Intelligence gathered during surveillance

Views of topic experts

We considered the views of topic experts who were recruited to the NICE Centre for Guidelines Expert Advisers Panel to represent their specialty. For this surveillance review, topic experts completed a questionnaire about developments in evidence, policy and services related to the guidelines.

We sent questionnaires to 26 topic experts and 4 patient groups. We received responses from 13 topic experts and 3 patient groups.

Topic experts comprised: a consultant child and adolescent psychologist; a consultant speech and language therapist; a consultant in paediatric neurodisability; a professor of clinical child psychology; a professor of adult and child psychology; a social care provider with a special interest in autism and behaviour that challenges; a nurse consultant with special interest in learning disabilities, autism and behaviour that challenges; an autism lead practitioner; a GP with special interest in autism and ADHD; an improvement manager with special interest in autism, learning disabilities and mental health in children and young people; an occupational therapist specialising in neurodisability; a child and adolescent psychiatrist and a consultant psychiatrist.

Patient group responses were received from the National Autistic Society, Autistica and the National Autistic Taskforce.

Topic experts and patient groups raised the issue of the validity of AQ-10 as a screening tool, discussed in the reasons for the proposal section above. They also highlighted several areas where lack of service capacity was acting as a barrier to the implementation of guideline recommendations, discussed in the implementation issues section below. Topic experts and patient groups also highlighted that people with protected characteristics need specific consideration when providing autism services. This is discussed in the equalities section below.

Views of stakeholders

Stakeholders are consulted on all surveillance reviews except if the whole guideline will be updated and replaced. Because this surveillance proposal is to not update the guideline, we are consulting with stakeholders.

Implementation issues

Service capacity issues were highlighted as barriers to implementing recommendations by 9 of 13 topic experts and the 3 patient groups consulted. Similar concerns were highlighted during previous surveillance reviews.

These capacity issues were felt by experts to impact implementation of recommendations in the following areas:

Diagnosis and assessment

Capacity issues made it difficult to carry out assessments and diagnoses within specified timescales. Concerns were raised that the overall diagnosis process takes too long and that there is underdiagnosis in adults.

Organisation of services

Lack of capacity acted as a barrier to working with other departments to manage coexisting conditions.

Experts highlighted that transition from children to adult services is often not joined up or sufficiently forward planned. It is noteworthy that NICE have published transition from children's to adults' services for young people using health or social care services (NICE guideline NG43) which makes recommendations which aim to help young people and their carers have a better experience of transition in health and social care by improving the way it's planned and carried out. NICE have also produced a quality standard based on this guideline that is designed to enable service providers and commissioners to improve quality in areas identified as high priority for improvement.

Concerns were raised about the training and competencies of healthcare staff including specialists, and about the lack of 'autism-friendly' environments in health care facilities.

Experts noted that there is insufficient community care resulting in inappropriate inpatient admissions.

Autism without learning disability

Experts commented that there is insufficient implementation of recommendations with people who have autism but who do not have a learning disability.

The findings of the government's Autism self-assessment framework which reviews progress in implementing the autism strategy in England are consistent with the issues highlighted by topic experts and patient groups. The government has started a review of the 2014 Autism Strategy which has not yet published. The revised strategy is expected to support the NHS Long Term Plan which includes initiatives to improve outcomes relevant to people with autism. We discussed planned investment in autism services with NHS England who noted that evaluations of new services could inform this surveillance review. However we did not identify any evidence of this type; and the government reports and policies identified support existing recommendations. We acknowledge that there are concerns around the implementation of some recommendations. We will monitor the progress of the review of the 2014 autism strategy and assess its impact on the guidelines covered by this surveillance review on publication.

For further details and a summary of all evidence identified in surveillance, see the summary of evidence from surveillance.

Other sources of information

We considered an enquiry about pathological demand avoidance (PDA) that suggested PDA is not adequately addressed by the guidelines and that there is a failure to distinguish between PDA and oppositional defiance disorder. Experts in this area informed us that PDA is not a recognised diagnosis in ICD-11 or DSM-V but its characteristics are considered to be part of the autistic spectrum disorder of diseases. There was no new evidence identified about PDA and clinical opinion is very mixed about its status as a distinct developmental condition. We therefore assessed this enquiry as having no impact on recommendations.

Equalities

Topic experts and patient organisations indicated that transgender people and women may have a higher risk of autism. Additionally, the need to further engage hard to reach groups was highlighted, as well as concerns that uptake of specialist services was low among black and minority ethnic groups.

We identified new evidence that does indicate an underdiagnosis in girls and women. However, no evidence for gender-specific diagnostic criteria were identified, and new evidence suggests that high-quality diagnostic assessment may reduce this disparity. CG128 research recommendation 1 Training professionals to recognise signs and symptoms of autism includes addressing underdiagnosis in girls and we will highlight this to the NIHR as an area where research is needed.

No new evidence was identified addressing the needs of any other specific groups, a finding consistent with previous surveillance reviews. Several vulnerable and hard to reach groups were identified in the scopes of the included guidelines and a small amount of evidence for specific subgroups was identified and considered during development of the guidelines. These resulted in autism spectrum disorder in under 19s and diagnosing and managing autism in adults making recommendations 1.1.5 and 1.8.3, respectively about promoting and organising care for specific subgroups.

In the absence of new evidence, we have concluded that these service organisation recommendations are still valid, and that clinical recommendations about specific healthcare interventions remain applicable to all groups.

Overall proposal

After considering all evidence and other intelligence and the impact on current recommendations, we are proposing that no update is necessary.

We are also proposing that recommendation 1.7.7 in autism spectrum disorder in under 19s: support and management should include advice that melatonin can be considered as a medication to aid sleep.

Appendix A: summary of evidence from surveillance

2020 surveillance of autism – NICE guidelines CG128, CG142 and CG170

Overview of methods

Overall approach

This surveillance review covers the theme of autism and considers evidence and intelligence relevant to the following 3 guidelines:

- Autism spectrum disorder in under 19s: recognition, referral and diagnosis (NICE guidance CG128).
- Autism spectrum disorder in adults: diagnosis and management (NICE guideline CG142).
- Autism spectrum disorder in under 19s: support and management (NICE guideline CG170).

Brief references to recommendations from these guidelines are given in the text in the form: guideline number - recommendation number. For example, CG128-1.1.1 refers to recommendation 1.1.1 in the guideline on diagnosing autism in children and young people.

Document structure

We structured the surveillance review based on the evidence and intelligence identified using the structure of the guidelines as a starting point. Although the guidelines have a clear divide between adults and children, we noted that most of the studies were in children and young people, but a notable proportion were in mixed aged groups or the abstract did not report the age of the participants. Therefore, we have presented results for adults and children together where necessary.

Overall the content covers 3 broad areas:

- Implementing the guidelines, service capacity and equality issues
  - Autism service capacity and implementing the guidelines

- Diagnosis and screening for autism in children and adults
  - Factors associated with an increased prevalence of autism
  - Assessing coexisting conditions in the autism diagnostic assessment
  - Identifying possible autism
  - Autism diagnostic assessment
  - Autism in girls
  - Diagnostic stability in toddlers
  - Medical investigations in people with autism
  - Excess mortality in people with autism

- Interventions for managing autism in children, young people and adults
  - Exercise interventions for autism
  - Psychosocial interventions for children with autism
  - Psychosocial and employment interventions for adults with autism
  - Drug treatments for children and young people with autism
  - Drug treatments for adults with autism
  - Interventions for sleep disorders in children with autism
  - Increasing dietary variety in children with autism
  - Dietary supplements and complementary therapies for children with autism
  - Training interventions for parents, carers and teachers of children with autism

Evidence synthesis

Studies identified in literature searches were summarised from the information presented in their abstracts.

Non-research evidence

Feedback from topic experts and any relevant policy documents were considered alongside the evidence to reach a view on the need to update each section of the guideline.

Guideline surveillance and updates to the autism guidelines

Evidence from previous surveillance and Evidence Updates for the autism guidelines was also considered. Evidence updates were previously produced by NICE to highlight new evidence relating to published NICE guidelines (see table: previous surveillance of autism guidelines).

In this surveillance review, we checked the findings of previous surveillance to see whether any areas are showing a weight of cumulative evidence. Throughout the document we refer mostly to the 2016 surveillance evidence reviews because this considered the cumulative evidence from all previous surveillance. However, the findings of previous surveillance have not been fully described with this surveillance review because full details can be found in the previous surveillance reports (see Table 1).

Table: surveillance history of autism guidelines

Guideline title	Guideline number	Previous surveillance	Link to publication	Outcome
Autism spectrum disorder in under 19s support and management	CG170	2016	2016 surveillance report	No areas of the guideline were identified as needing an update.
Autism spectrum disorder in adults: diagnosis and management	CG142	2016	2016 surveillance report	No areas of the guideline were identified as needing an update.
Autism spectrum disorders in children and young people: diagnosis and management	CG128	2016	2016 surveillance report	An update to the sections of the guideline dealing with risk factors for autism and coexisting conditions associated with an increased risk of autism was undertaken. References to the Diagnostic and Standard Manual version IV (DSM-IV) were updated to the latest version (DSM-5). Updated recommendations were published in December 2017.
Autism spectrum disorder in adults: diagnosis and management	CG142	2014	2014 surveillance report	No areas of the guideline were identified as needing an update.
Autism spectrum disorders in children and young people: diagnosis and management	CG128	2014	2014 surveillance report	No areas of the guideline were identified as needing an update.
Autism spectrum disorder in adults: diagnosis and management	CG142	2013	2013 evidence update	No areas of the guideline were identified as needing an update.
Autism spectrum disorders in children and young people: diagnosis and management	CG128	2013	2013 evidence update	No areas of the guideline were identified as needing an update.

Autism service capacity and implementing the guidelines

Background

All 3 of NICE's guidelines on autism have broad recommendations about the organisation and delivery of services for diagnosing and managing autism spectrum disorder. See recommendations on:

- Local pathway for recognition, referral and diagnostic assessment of possible autism in the guideline on diagnosis in children and young people (CG128-1.1.1 to CG128-1.1.10).
- General principles of care – structures for the organisation and delivery of care and interventions (CG142-1.1.12 to CG142-1.1.14) and organisation and delivery of care (CG142-1.8.1 to CG142-1.8.10) in the guideline on diagnosis and management in adults.
- General principles of care – organisation and delivery of services in the guideline on management in children and young people (CG170-1.1.2 to CG170-1.1.7).
- Transition to adult services in the guideline on management in children and young people (CG170-1.8.1 to CG170-1.8.9).

Topic expert and stakeholder feedback on previous surveillance reviews shows gradually increasing concerns about the ability of services to implement recommendations in the NICE guidelines on autism.

Evidence and intelligence review

Service capacity effects on implementing the guidelines

Feedback from topic experts, patient groups and NHS England

As part of this surveillance review, we received detailed feedback from 13 topic experts and 3 patient groups. Several issues related to service capacity and the ability to implement current recommendations were raised by 9 topic experts and all three patient groups, including:

- Lack of capacity to conduct diagnostic assessments within recommended timeframes, and concerns about the overall length of the diagnostic process taking too long.
- Underdiagnosis of autism in adults.
- Difficulties in providing joined-up care with other specialties for differential diagnosis or managing coexisting conditions.
- Concerns about training and competencies of health care staff, including the autism team.
- Insufficient implementation of recommendations on managing autism, particularly for people who do not also have a learning disability.
- Lack of availability of autism-friendly environments.
- Incomplete transition from children's services to adult services.
- Inappropriate inpatient admissions because of insufficient community care services.

Comments received during this surveillance review highlighted that transition from children's to adult services is a problem and the recommended 'care programme approach' for transition (CG170-1.8.6) needs clarification. A patient group commented that they thought this recommendation was being widely disregarded due to service and financial pressures.

Topic experts and patient groups highlighted several references that are directly relevant to service capacity and service delivery but did not meet inclusion criteria for this surveillance review. This included news articles and other reports published by the patient groups and other organisations. Additionally, care for people with autism has been highly publicised in the media over the past year, including widespread coverage of the Joint Committee on Human Rights' report on the detention of young people with learning disabilities and/or autism (see inpatient mental health services and suicide later in this document).

We also discussed the planned investment in autism services with NHS England, who noted that evaluation of new service models may provide

evidence that could inform an update to the NICE guidelines, but we did not identify any published studies, or ongoing research in this area.

Government reports and policies

Several recent government reports and policy documents provide overarching context for the current state of services and direction for the future. We considered these as the main evidence on service capacity and implementation of the guideline in this surveillance review.

The government's Autism self-assessment framework reviews progress in implementing the autism strategy in England. The published results were consistent with the feedback we received on service capacity and implementation of the guidelines from topic experts.

- Fewer than half of responding authorities have a multi-agency autism training plan, which was noted as being 'almost unchanged since 2016', and only 21% reported 'satisfactory' specific autism training for staff conducting statutory assessments (see Autism self-assessment exercise 2018 executive summary section 4, training) (1).
- Although all local authorities reported having an autism pathway, only 17% rated themselves as 'green' (meeting requirements). Many 'amber' (progressing towards meeting requirements) ratings were due to not meeting the 3-month waiting time limit recommended in the NICE guideline on diagnosis of autism in children and young people (recommendation 1.5.1). The median waiting time is 30 weeks, which has increased from 16 weeks in 2016. This increase was attributed largely to a 40% increase in the population-based rate of diagnosis (see Autism self-assessment exercise 2018 executive summary section 5, diagnosis and overview of results section 7, diagnostic services).
- Generally, access to diagnostic services was reported to be better for people with learning disabilities than for those diagnosed with autism who do not have learning disabilities (see Autism self-assessment exercise 2018 executive summary section 5, diagnosis).

- 74% of respondents reported that individuals diagnosed with autism had difficulty in subsequently getting access to mental health services (see Autism self-assessment exercise 2018 executive summary section 6, care and support).

The government started a review of the 2014 Autism Strategy with a public consultation calling for evidence in Spring 2019. The revised strategy is expected to support the NHS Long Term Plan (2), which notes 'Across the NHS, we will do more to ensure that all people with a learning disability, autism, or both can live happier, healthier, longer lives' (NHS Long Term Plan page 41, 2.31).

The long-term plan includes specific initiatives to improve outcomes for people with autism. One initiative was relevant to diagnosis and screening:

- Testing and implementing ways to reduce waiting times for specialist autism diagnostic services (NHS Long Term Plan page 52, 3.33).

Four initiatives were relevant to managing autism

- Reducing inappropriate use of psychotropic drugs (NHS Long Term Plan page 52, 3.31).
  - Topic expert comments relating to this issue are detailed in the section on pharmacological and biomedical interventions for children.
- Improved understanding of the needs of people with autism throughout the NHS and increased collaboration with the Department for Education and local authorities (NHS Long Term Plan page 52, 3.32).
- Supported internship opportunities targeted at people with autism, with at least half converting to paid employment by 2023-24 (NHS Long Term Plan page 117, 6).
  - We identified new evidence for improving employment outcomes for people with autism and this is discussed in the section on vocational and employment interventions for adults.

- Reducing suicides by investing in specialist community teams to help support children and young people with autism (NHS Long Term Plan page 72, 3.105).

Overall, the government reports and policies do not contradict any recommendations in NICE's autism guidelines. They do not suggest a need to update the guidelines.

Literature searches

We additionally identified 3 studies relevant to service capacity in literature searches:

Population-based studies (3,4) from Scotland indicated an overall prevalence of autism in children of 1.6%, and in adults this was 0.6%. The study reporting on autism in children was also highlighted by the topic experts.

The prevalence of autism of 1.6% reported in the surveillance evidence is higher than the 1% noted in the full version of the NICE guideline on diagnosing autism in children (section 2.11, prevalence of autism). Increasing prevalence of autism could have a negative effect on service capacity if services were planned for a smaller number of people than actually use the services. An update to the guideline is not necessary at this time because commissioners can determine local needs based on referrals in their population.

The prevalence in adults of 0.6% is lower than the 1.1% noted in the full version of the NICE guideline on autism in adults. However, this may indicate ongoing problems with getting a diagnosis in adulthood (section 2.2, incidence and prevalence). This does not suggest a need to update the guideline, but rather that services may need to catch up with currently recommended practice.

An online survey (5) of 12 UK-based autism diagnosis centres asked for retrospective recording of team members involved at each stage of a typical assessment and the time taken, including report writing and administration. Ten centres used two-stage assessment with an initial 'screening' clinic

determining whether the child needed to proceed to full multidisciplinary assessment. Median professional time involved was 13 hours (IQR 9.6 to 15.5 hours) and the cost of multidisciplinary diagnostic assessment was £809 (interquartile range £684 to £925). This study may be useful for planning services because it provides cost information for one model for conducting assessments. However, it does not impact on current recommendations because it does not compare alternative models (for example, 2-step model versus 1-step model) in terms of diagnostic accuracy or cost-effectiveness.

Inpatient mental health services and suicide

Several topic experts and patient organisations noted that people with autism are frequently admitted for inpatient psychiatric care. However, we did not identify any new studies reporting on this outcome.

Two initiatives from the NHS long-term plan were relevant to inpatient care:

- Reducing inpatient care through local provider control of budgets and availability of personal health budgets for people with autism, and increased investment in intensive, crisis and community support (NHS Long Term Plan page 53, 3.34 and 3.35).
- Increasing quality of inpatient care – 'restricting the use of seclusion, long-term segregation and restraint for all patients in inpatient settings, particularly for children and young people' (NHS Long Term Plan page 53, 3.36).

We noted the Parliamentary Joint Select Committee report on the detention of young people with learning disabilities and/or autism the detention of young people with learning disabilities and/or autism. This report highlights severe failings in mental health services, both in the lack of community-based care that could prevent mental health crises, and the poor quality of inpatient care received after admission to psychiatric facilities. We consider that the select committee's report describes care that is inconsistent with recommended practice described in a range of NICE guidelines, including service user experience in adult mental health (NICE guideline CG136), and the guidelines on autism.

The select committee made several recommendations including:

- the creation of legal duties on Clinical Commissioning Groups and local authorities to ensure the right services are available in the community narrowing of the Mental Health Act criteria to avoid inappropriate detention
- substantive reform of the Care Quality Commission's approach and processes.

Recommendations in the Joint Committee on Human Rights' report were aimed at organisations other than NICE, usually the Care Quality Commission. We consider that the government's focus on autism in the NHS long-term plan should create conditions to enable services to improve their adherence to existing NICE guidelines. Therefore an update to the guideline covering inpatient care for people with autism is not necessary.

Topic experts and patient groups additionally indicated that people with autism have higher rates of suicide. However, we did not identify any new studies reporting on this outcome. Preventing suicide in community and custodial settings (NICE guideline NG105) recognises that people with autism are a group at high risk of suicide. Therefore, an update to the autism guidelines is not necessary because NICE already has guidance on preventing suicide that includes people with autism.

Surveillance proposal

We propose not to update the NICE guidelines on autism to address service capacity issues.

This is because topic expert and patient group feedback, published evidence and policy reports do not indicate that the NICE recommendations no longer represent best practice, but rather that services have not been able to achieve recommended best practice. However, these issues are recognised by NHS England and government policy, including the NHS long-term plan, and work to improve services is planned. The review of the 2014 Autism Strategy is expected to inform the objectives in the long-term plan aimed at delivery of

autism services. We will monitor the progress of this review and asses its impact on recommendations when it is published.

Factors associated with an increased prevalence of autism

Background

NICE's guideline on diagnosing autism in children and young people covers factors associated with an increased prevalence of autism (see box 1: factors associated with an increased prevalence of autism). This section of the NICE guideline was last updated in 2017, based on the 2016 surveillance review findings.

The 2016 surveillance review identified 61 studies of risk factors. It concluded: 'a vast amount of evidence was identified evaluating different risk factors. Most of the studies reported an odds ratio of more than 1.25 for the risk factors, which was considered as clinically important by the NICE guideline committee during the development of NICE guideline CG128. Topic experts recommended that this review question should be updated and that any update should be limited to consider a small number of relevant risk factors.'

The update subsequently looked for evidence on the following risk factors:

- Small for gestational age
- Prenatal use of selective serotonin reuptake inhibitors (SSRIs)
- Fertility treatments
- Neurodevelopmental disorders such as attention deficit hyperactivity disorder (ADHD) and learning (intellectual) disability.

After reviewing the available evidence, only ADHD was added to the list of risk factors listed in the NICE guideline based on around 20-times higher increase in risk (risk approximated from reported odds ratio; see the guideline's evidence review, pages 17 and 78). For the other potential risk factors, the committee considered the evidence to be 'insufficient'. In the original NICE guideline, risk factors included in the list were mostly associated with at least

double the risk of autism, with reasonable precision (narrow confidence intervals). Therefore, in this surveillance review, we needed an odds ratio or relative risk and lower limit of the confidence interval of at least 2.0 to indicate a clinically meaningful result with possible impact of new evidence on current recommendations. Although odds ratios and risk ratios have different underlying calculations, we have set the limit at 2.0 for both statistics recognising that odds ratio values generally exaggerate the level of risk, and the divergence between the odds ratio and the risk ratio increases as outcomes become more common. With these caveats in mind, we have used the value of the odds ratio to approximate the value of the increased risk.

Evidence and intelligence review

Overview

In this surveillance review we identified 45 new studies on risk factors for autism. One notable requirement for inclusion in the review of evidence for the 2017 update of the NICE guideline was that studies had to report clinical diagnosis of autism by a healthcare professional. Surveillance looks only at abstract-level data, which did not always include details about clinical diagnosis. Therefore, the 2019 surveillance review was unable to determine whether this criterion was met by the identified studies.

Topic expert feedback in this area was minimal, with only one expert suggesting that new evidence on parental age as a risk factor could be considered. However, the supporting evidence cited by the topic expert was not eligible for inclusion in surveillance because it was an overview of systematic reviews that did not report any data in its abstract.

Cardiovascular and metabolic conditions in pregnancy and risk of autism

Seven systematic reviews and 2 observational studies reported on risk factors related to cardiovascular and metabolic conditions during pregnancy (see table: cardiovascular and metabolic conditions in pregnancy and risk of autism) for the outcomes considered in these studies were:

- Maternal diabetes or gestational diabetes (6–8)
- Maternal underweight, overweight, obesity or gestational weight gain (9–12)
- Maternal pre-eclampsia or hypertension (7,11,13,14).

These risk factors all had odd ratios of less than 2.0 (range 1.08 to 1.98), so did not reach the threshold value of 2.0 to indicate an impact on current recommendations. Therefore, an update to assess cardiovascular and metabolic risk factors during pregnancy is not being considered at this time.

Maternal mental health and neurological risk factors

Six systematic reviews addressed maternal mental health and neurological factors during pregnancy (see table: maternal mental health and neurological risk factors).

Maternal antidepressant use during or before pregnancy (11,15–17) and maternal stress during pregnancy (18) were assessed in a total of 5 studies. However, the results did not reach the threshold value of 2.0 to indicate an impact on current recommendations. Therefore, an update is not thought to be necessary at this time.

One study (19) indicated that antiepileptic drug use (lamotrigine, oxcarbazepine, and valproate) was associated with increased risk of autism. Of these, analyses including valproate had point estimates and a lower confidence interval limit greater than 2.0, but lamotrigine alone and oxcarbazepine did not have a lower confidence interval limit greater than 2.0. The NICE guideline already recognises valproate in pregnancy as a risk factor, and the MHRA has issued guidance that 'Valproate must not be used in any woman or girl able to have children unless there is a pregnancy prevention programme in place.' Although there is no similar advice for lamotrigine and oxcarbazepine, the BNF notes 'There is an increased risk of teratogenicity associated with the use of antiepileptic drugs… All pregnant women with epilepsy, whether taking medication or not, should be encouraged to notify the UK Epilepsy and Pregnancy Register'. NICE's guideline on epilepsy is currently being updated, and the update will cover use

of antiepileptic drugs during pregnancy. Therefore, we will pass the information on risk of autism to the developer of the update of NICE's epilepsy guideline for consideration. We will then consider whether the risk factors table in the guideline on diagnosing autism should be amended to reflect relevant recommendations in NICE's epilepsy guideline.

Risk of autism with dietary supplementation in pregnancy

One large observational study and 3 systematic reviews (20–23) showed reduced risk of autism with folic acid or multivitamin supplementation during pregnancy (see table: risk of autism with dietary supplementation in pregnancy). One observational study (24) indicated that maternal plasma folate or vitamin B12 in the highest decile increased the risk of autism compared with the middle 80th percentile. Although the odds ratio (2.5) met the threshold for considering as a potential impact on the guideline, the authors described the results as 'hypothesis-generating' and raising questions about 'extremely elevated' levels of plasma folate and vitamin B12 exposure on early brain development. Therefore, we do not propose updating the autism guideline in this area.

A further observational study was identified but not included in the table because it had more complex sampling that could not be easily captured in that format (25). It assessed prenatal vitamin supplementation in the first month of pregnancy in mothers (n=305) who had an older child with autism with a final sample of 241 younger siblings. The prevalence of autism in children whose mothers took prenatal vitamins in the first month of pregnancy was 14.1% compared with 32.7% (adjusted risk ratio 0.50, 95% CI 0.30 to 0.81). However, there was no difference in risk of non-typical development (adjusted RR 1.14, 95% CI 0.75 to 1.75). Children whose mothers took prenatal vitamins had significantly lower autism symptom severity (adjusted estimated difference -0.60, 95% CI -0.97 to -0.23) and higher cognitive scores (adjusted estimated difference 7.1, 95% CI 1.2 to 13.1). This study provides evidence that prenatal and early pregnancy vitamin supplementation may reduce recurrence of autism in children of women who already have a child with autism. However, this study did not define the type of vitamin

supplementation or establish whether the women had any nutrient deficiencies. Additionally, self-reported supplementation use might not accurately reflect plasma vitamin levels. Therefore, further research, ideally in randomised controlled trials, is necessary before considering an update to the NICE autism guidelines in this area.

Addressing vitamin supplementation during pregnancy is an area covered in NICE's guideline on maternal and child nutrition (NICE guideline PH11). This guideline recommends that women who may become pregnant and women in early pregnancy take daily folic acid supplementation (PH11-2). It also recommends offering the Healthy Start supplement (folic acid and vitamins C and D) to eligible pregnant women (PH11-4).

Neonatal risk factors for autism

We identified 5 observational studies of neonatal risk factors (see table: neonatal risk factors for autism)

Lower levels of neonatal vitamin D showed an increased risk of autism in one observational study (26), but the results did not meet the criteria of the lower limit of the confidence interval of at least 2.0 for considering as a potential impact on current recommendations. Vitamin D supplementation during pregnancy is covered in NICE's guideline on vitamin D supplementation in specific population groups. This guideline has had several recommendations about increasing uptake of vitamin D supplementation in pregnant and breastfeeding women.

We identified 4 other observational studies covering neonatal factors that may be associated with autism. Neonatal or early childhood infection (27) or raised interleukin 8 levels (28) were associated with increased risk of autism. Neonatal jaundice was associated with autism in preterm babies but not in those born at term (29). Finally, one study indicated that breastfeeding was associated with lower risk of autism, but top-up feeding was associated with increased risk of autism (30). However, none of these studies met the threshold of 2.0 for the lower limit of the confidence interval. Further studies

into these neonatal risk factors are thus needed before an update to the NICE guideline can be considered.

Other risk factors for autism related to pregnancy and birth

A further 7 observational studies and 3 systematic reviews looked at a range of other risk factors related to pregnancy and birth (see table: other risk factors for autism related to pregnancy and birth), which indicated increased risk of autism with:

- Caesarean delivery (31,32)
- Maternal age 35 years or over (11)
- Maternal anaemia during pregnancy (33)
- Maternal asthma in pregnancy (34)
- Maternal infections while admitted to hospital (35) or infections with fever in the second trimester (36)
- Maternal polycystic ovary syndrome (37)
- Higher use of paracetamol in pregnancy (38)
- Congenital cytomegalovirus infection (39)

Of these studies, only one (39) met the threshold of a lower limit of the confidence interval of 2.0. The authors of this systematic review of congenital cytomegalovirus infection noted that their findings had 'serious limitations' because of too few events in the included studies. Therefore, we do not consider that the evidence is robust enough to warrant an update to the NICE guideline at this time.

An observational study (40) was also identified but was not included in the table because it reported analyses that did not easily fit into the table format. It suggested that initiation of breastfeeding did not differ significantly between mothers whose children were later diagnosed with autism and mothers whose children did not have autism (adjusted OR 0.88, 95% CI 0.60 to 1.28). However, mothers of children with autism were less likely to report duration of breastfeeding for 12 months or longer than for less than 6 months (adjusted OR 0.61, 95% CI 0.45-0.84). Mothers of children with autism were also less likely to report duration of breastfeeding for 6 to 12 months than for less than

6 months (adjusted OR 0.72, 95% CI 0.54 to 0.98). The authors noted that they were 'unable to distinguish whether the difference in duration was due to difficulties breastfeeding children who later develop autism, other factors not adjusted in our study, or greater autism risk resulting from shorter breastfeeding duration.' Further research into the association between breastfeeding and risk of autism is therefore needed before considering an update to current guidance.

Topic expert feedback suggested that parental age was associated with autism. However, we identified only 1 study eligible for this surveillance review (11) that reported on this risk factor. It indicated an increase in odds of autism of about a third, but this did not meet the threshold of 2.0 for considering an update to the guideline. Therefore, we do not propose an update to consider the effects of parental age at this time.

Familial risk factors for autism

We identified 2 observational studies and 3 systematic reviews covering familial factors potentially associated with autism (see table: familial risk factors for autism).

Evidence from two systematic reviews indicates that parental depressive or affective disorders, including paternal exposure to antidepressants may be associated with an increased risk of autism (15,41). However, the results did not meet the threshold of 2.0 for considering an update to the guideline. The NICE guideline on diagnosing autism in children already recognises parental affective disorders as a risk factor, and the 2017 update looked at the effects of maternal antidepressant use on the risk of autism but found the evidence to be insufficient to add this to the NICE guideline. Evidence identified in this surveillance review (see maternal mental health and neurological risk factors) therefore suggests that evidence on the risk of autism associated with antidepressant use remains insufficient.

Paternal weight did not significantly affect the risk of autism in one systematic review (10), so an update to the guideline looking at the effect of fathers' weight is not necessary.

In an observational study, paternal asthma (34) showed a statistically significant association with autism, but did not meet the threshold value of 2.0 for considering an update to the guideline. Therefore, an update to investigate these potential risk factors is not needed at this time.

Finally, one observational study found a 30 times increased risk of autism in children who have a sibling with autism (42), which is consistent with the current table of risk factors in the NICE guideline, so no update is necessary.

Pollutants as risk factors for autism

We identified 2 systematic reviews and 5 observational studies that assessed the effects of pollutants on risk of autism (see Table: pollutants as risk factors for autism).

Particulate matter 2.5 showed clinically and statistically significant associations with increased risk of autism that appeared to be consistent across studies (43–46). One small study (43) in 297 children suggested that the odds of autism at the highest levels of particulate matter 2.5 exposure is up to 4 times greater when compared with those exposed to the lowest PM 2.5 exposure quartile. However, this study was conducted in China, so the levels of air pollution may not be applicable to the UK. This study also assessed whether exposure to high levels of air pollution (particulate matter 2.5 exposure of 89.5 ug/m^3) could predict diagnosis of autism. Particulate matter 2.5 exposure of 89.5 ug/m^3 had sensitivity of 65%, specificity of 63% and an area under the curve of 61%. These findings suggest that air pollution exposure is not a useful measure for diagnosing autism, so an update in this area is not needed. In the other studies, the increase in risk was less than double the original risk. Therefore, further research is needed to establish the effects of increasing exposure to particulate matter 2.5 on risk of autism, and whether such effects are causally related before considering an update in this area.

Ozone exposure (45,46) may have a small effect on increasing the risk of autism, but this was not clearly clinically significant (defined as more than 25%

increased risk) across the 2 identified studies; therefore, an update in this area is not necessary.

Nitrogen oxide (47) may be associated with a clinically and statistically significant increased risk of autism. However, this was reported in only one study, and the 40% increase in risk does not meet the threshold of 2.0 for considering this risk factor in the NICE guideline.

Neonicotinoid and organophosphate pesticides (48,49) do not appear to be associated with an increased risk of autism. Therefore, an update to investigate these risk factors is not necessary.

Other risk factors for autism

We identified 3 additional studies that addressed risk factors for autism that did not fit with the studies discussed in previous sections.

One observational study (50) (n= 1,104) in children aged 3–6 years indicated that a diagnosis of ADHD was associated with an increased risk of autism (odds ratio [OR] 9.5, p=0.001). This finding is broadly consistent with the NICE guideline, which added ADHD as a risk factor in the 2017 update, although the NICE guideline found a larger (20 times) increase in risk. Therefore, no update in this area is needed at this time.

One observational study (number of participants not reported in the abstract) (51) suggested that having insomnia was associated with an increased risk of autism (OR 1.739, 95% CI 1.217 to 2.486, p=0.002). However, the size of this increased risk did not meet the threshold of 2.0 for considering an update to the guideline. Therefore, an update to consider insomnia as a risk factor for autism is not necessary at this time.

Finally, one observational study (n=7,711) (52) suggested that having hypogonadotrophic hypogonadism is associated with increased risk of autism (OR 5.7, 95% CI 2.6 to 12.6). The authors noted that the association remained significant after adjusting for diagnosed malformation syndromes and chromosomal anomalies, but the data for the adjusted analyses was not reported in the abstract. The likely effect of this adjustment would be a

reduction in the point estimate and widening of the confidence intervals as the sample would effectively be reduced. The NICE guideline already recognises malformations and genetic and chromosomal disorders as risk factors. Therefore, this study supports existing recommendations.

Surveillance proposal

We propose not to update the section on risk factors for autism in the NICE guideline on diagnosing autism in children and young people.

Much of the evidence identified in this surveillance review was consistent with the lists of risk factors in current recommendations. Although we identified new evidence on possible risk factors not currently covered by the guideline, the size of the increase in risk was generally lower than the threshold of 2.0 for considering an update to the guideline. Congenital cytomegalovirus infection was the only potential risk factor that met the threshold for considering an update to the guideline, but this evidence was limited because of the small sample size of the study, so further evidence in this area is needed.

Data tables for factors associated with an increased prevalence of autism

Table: cardiovascular and metabolic conditions in pregnancy and risk of autism

Text citation	Study type	Number of participants	Number of studies	Age-group	Risk factor	Analysis	Point estimate	95% CI
Wan et al. (2018) (6)	Systematic review	NR	16	Children	Maternal diabetes	Risk ratio	1.48	NR
Cordero et al. (2019) (7)	Observational	2,564	–	Children	Maternal diabetes	Odds ratio	1.1	0.77 to 1.56
Yamamoto et al. (2019) (8)	Systematic review	2,875,369	19	Unspecified	Maternal diabetes in pregnancy (pre-existing)	Odds ratio	1.98	1.46 to 2.68
Windham et al. (2019) (9)	Observational	2,036	–	Children	Maternal obesity	Odds ratio	1.37	0.98 to 1.92
Lei et al. (2019) (10)	Systematic review	973,630	13	Unspecified	Maternal obesity	Odds ratio	1.41	1.19 to 1.67
Sanchez et al. (2018) (12)	Systematic review	NR	41	Children	Maternal obesity (before pregnancy)	Odds ratio	1.36	1.08 to 1.70
Lei et al. (2019) (10)	Systematic review	973,630	13	Unspecified	Maternal overweight	Odds ratio	1.16	1.05 to 1.27
Kim et al. (2019) (11)	Systematic review	82,284,046	46	Unspecified	Maternal overweight before or during pregnancy	Odds ratio	1.28	1.19 to 1.36
Lei et al. (2019) (10)	Systematic review	973,630	13	Unspecified	Maternal underweight	Odds ratio	1.08	0.98 to 1.20
Windham et al. (2019) (9)	Observational	2,036	–	Children	Maternal gestational weight gain (5th quintile versus 3rd quintile)	Odds ratio	1.58	1.08 to 2.31
Windham et al. (2019) (9)	Observational	2,036	–	Children	Maternal gestational weight gain in women with obesity	Odds ratio	1.9	0.98 to 3.68
Dachew et al. (2018) (13)	Systematic review	NR	10	Unspecified	Maternal pre-eclampsia	Relative risk	1.32	1.2 to 1.45

Text citation	Study type	Number of participants	Number of studies	Age-group	Risk factor	Analysis	Point estimate	95% CI
Kim et al. (2019) (11)	Systematic review	82,284,046	46	Unspecified	Maternal pre-eclampsia	Odds ratio	1.32	1.20 to 1.45
Kim et al. (2019) (11)	Systematic review	82,284,046	46	Unspecified	Maternal hypertension (chronic)	Odds ratio	1.48	1.29 to 1.70
Kim et al. (2019) (11)	Systematic review	82,284,046	46	Unspecified	Maternal gestational hypertension	Odds ratio	1.37	1.21 to 1.54
Cordero et al. (2019) (7)	Observational	2,564	–	Children	Maternal hypertension during pregnancy	Odds ratio	1.69	1.26 to 2.26
Maher et al. (2018) (14)	Systematic review	777,518	11	Children	Maternal hypertension during pregnancy	Odds ratio	1.35	1.11 to 1.64

Table: maternal mental health and neurological risk factors

Text citation	Study type	Number of participants	Number of studies	Age-group	Risk factor	Analysis	Point estimate	95% CI
Andalib et al. (2017) (17)	Systematic review	NR	–	Children	Maternal antidepressant (selective serotonin uptake inhibitor) use	Odds ratio	1.82	1.59 to 2.10
Kim et al. (2019) (11)	Systematic review	82,284,046	46	Unspecified	Maternal antidepressant (selective serotonin uptake inhibitor) use	Odds ratio	1.84	1.60 to 2.11
Kim et al. (2019) (11)	Systematic review	82,284,046	46	Unspecified	Maternal antidepressant use	Odds ratio	1.48	1.29 to 1.71
Morales et al. (2018) (15)	Systematic review	3,585,686	15	Children	Maternal antidepressant use (before pregnancy)	Risk ratio	1.48	1.29 to 1.71
Morales et al. (2018) (15)	Systematic review	3,585,686	15	Children	Maternal antidepressant use during pregnancy	Risk ratio	1.53	1.31 to 1.78

Text citation	Study type	Number of participants	Number of studies	Age-group	Risk factor	Analysis	Point estimate	95% CI
Zhou et al. (2018) (16)	Systematic review	2,957,717	14	Unspecified	Maternal antidepressant use during pregnancy (case-control studies)	Odds ratio	1.51	1.15 to 1.99
Zhou et al. (2018) (16)	Systematic review	2,839,980	14	Unspecified	Maternal antidepressant use during pregnancy (cohort studies)	Risk ratio	1.13	0.93 to 1.39
Morales et al. (2018) (15)	Systematic review	3,585,686	15	Children	Maternal antidepressant use during pregnancy (data from sibling studies only)	Risk ratio	0.96	0.65 to 1.42
Morales et al. (2018) (15)	Systematic review	3,585,686	15	Children	Maternal antidepressant use during pregnancy (women with affective disorder only)	Risk ratio	1.18	0.91 to 1.52
Veroniki et al. (2017) (19)	Systematic review	5,100	29	Children	Maternal lamotrigine during pregnancy or breastfeeding	Odds ratio	8.88	1.28 to 112.00
Veroniki et al. (2017) (19)	Systematic review	5,100	29	Children	Maternal lamotrigine plus valproate during pregnancy or breastfeeding	Odds ratio	132.7	7.41 to 3851
Veroniki et al. (2017) (19)	Systematic review	5,100	29	Children	Maternal oxcarbazepine during pregnancy or breastfeeding	Odds ratio	13.51	1.28 to 221.40
Veroniki et al. (2017) (19)	Systematic review	5,100	29	Children	Maternal valproate during pregnancy or breastfeeding	Odds ratio	17.29	2.40 to 217.60
Manzari et al. (2019) (18)	Systematic review	NR	15	Unspecified	Maternal stress during pregnancy	Odds ratio	1.64	1.15 to 2.34

Table: risk of autism with dietary supplementation in pregnancy

Text citation	Study type	Number of participants	Number of studies	Age-group	Risk factor	Analysis	Point estimate	95% CI
Levine et al. (2018) (21)	Observational	45,300	–	Children	Maternal folic acid or multivitamin before pregnancy	Risk ratio	0.39	0.3 to 0.5
Levine et al. (2018) (21)	Observational	45,300	–	Children	Maternal folic acid or multivitamin during pregnancy	Risk ratio	0.27	0.22 to 0.33
Li et al. (2019) (22)	Systematic review	NR	20	Children	Maternal folic acid or multivitamin supplementation	Odds ratio	0.64	0.46 to 0.90
Levine et al. (2018) (21)	Observational	45,300	–	Children	Maternal folic acid supplementation during pregnancy	Risk ratio	0.32	0.26 to 0.41
Guo et al. (2019) (22)	Systematic review	840,776	8	Children	Maternal folic acid supplementation during pregnancy	Odds ratio	0.91	0.73 to 1.13
Levine et al. (2018) (21)	Observational	45,300	–	Children	Maternal multivitamin before pregnancy	Risk ratio	0.36	0.24 to 0.52
Levine et al. (2018) (21)	Observational	45,300	–	Children	Maternal multivitamin during pregnancy	Risk ratio	0.35	0.28 to 0.44
Guo et al. (2019) (22)	Systematic review	231,163	5	Children	Maternal multivitamin supplementation	Risk ratio	0.62	0.45 to 0.86
Levine et al. (2018) (21)	Observational	45,300	–	Children	Maternal prenatal folic acid supplementation	Risk ratio	0.56	0.42 to 0.74
Raghavan et al. (2018) (24)	Observational	1,257	–	Children	Maternal plasma B12 in the highest decile (536.8 pmol/L or higher) compared with middle 80th percentile	Risk ratio	2.5	1.4 to 4.5
Raghavan et al. (2018) (24)	Observational	1,257	–	Children	Maternal plasma folate in the highest decile (60.3 nmol/L or higher) compared with middle 80th percentile	Risk ratio	2.5	1.3 to 4.6

Table: neonatal risk factors for autism

Text citation	Study type	Number of participants	Age-group	Risk factor	Analysis	Point estimate	95% CI
Wu et al. (2018) (26)	Observational	1,550	Children	Neonatal 25-hydroxyvitamin D3 levels, 2nd quartile compared with 4th quartile	Risk ratio	2.5	1.4 to 3.5
Wu et al. (2018) (26)	Observational	1,550	Children	Neonatal 25-hydroxyvitamin D3 levels, 3rd quartile compared with 4th quartile	Risk ratio	1.9	1.1 to 3.3
Wu et al. (2018) (26)	Observational	1,550	Children	Neonatal 25-hydroxyvitamin D3 levels, lowest quartile compared with 4th quartile	Risk ratio	3.6	1.8 to 7.2
Sabourin et al. (2019) (27)	Observational	NR	Children	Neonatal infection	Odds ratio	1.5	1.1 to 2.0
Sabourin et al. (2019) (27)	Observational	NR	Children	Neonatal infection	Odds ratio	1.8	1.1 to 2.9
Sabourin et al. (2019) (27)	Observational	NR	Children	Early childhood infection	Odds ratio	1.7	1.5 to 1.9
Heuer et al. (2019) (28)	Observational	888	Children	Neonatal raised interleukin 8 levels	Odds ratio	1.97	1.39 to 2.83
Cordero et al. (2019) (29)	Observational	2,339	Children	Neonatal jaundice at 35–37 weeks	Odds ratio	1.83	1.05 to 3.19
Cordero et al. (2019) (29)	Observational	2,339	Children	Neonatal jaundice at 38 weeks or older	Odds ratio	0.97	0.76 to 1.24
Manohar et al. (2018) (30)	Observational	60	Children	Breastfeeding	Odds ratio	0.166	0.025 to 0.65
Manohar et al. (2018) (30)	Observational	60	Children	Top-up feeding	Odds ratio	6	1.33 to 55.19

Table: other risk factors for autism related to pregnancy and birth

Text citation	Study type	Number of participants	Number of studies	Age-group	Risk factor	Analysis	Point estimate	95% CI
Zhang et al. (2019) (31)	Systematic review	20,607,935	61	Unspecified	Caesarean delivery	Odds ratio	1.33	1.25 to 1.41
Al-Zalabani et al. (2019) (32)	Observational	261	61	Children	Caesarean delivery	Odds ratio	2.9	1.57 to 5.35
Maeyama et al. (2018) (39)	Systematic review	NR	3	Children	Congenital cytomegalovirus infection	Odds ratio	11.31	3.07 to 44.66
Kim et al. (2019) (11)	Systematic review	82,284,046	46	Unspecified	Maternal age 35 years or over	Odds ratio	1.31	1.18 to 1.45
Wiegersma et al. (2019) (33)	Observational	532,232	–	Mixed	Maternal anaemia (diagnosed during the first 30 weeks of pregnancy matched sibling data)	Odds ratio	2.25	1.24 to 4.11
Wiegersma et al. (2019) (33)	Observational	532,232	–	Mixed	Maternal anaemia (diagnosed during the first 30 weeks of pregnancy)	Odds ratio	1.44	1.13 to 1.84
Gong et al. (2019) (34)	Observational	1,579,263	–	Children	Maternal asthma	Odds ratio	1.43	1.38 to 1.49
Al-Haddad et al. (2019) (35)	Observational	1,791,250	–	Children	Maternal infection (severe) while admitted to hospital during pregnancy	Hazard ratio	1.81	1.18 to 2.78
Al-Haddad et al. (2019) c	Observational	1,791,250	–	Children	Maternal infection while admitted to hospital during pregnancy	Hazard ratio	1.79	1.34 to 2.40
Croen et al. (2019) (36)	Observational	2,258	–	Children	Maternal infection with fever in the second trimester	Odds ratio	2.19	1.14 to 4.23
Ji et al. (2019) (38)	Observational	996	–	Children	Maternal paracetamol use in 2nd tertile, compared with 1st tertile	Odds ratio	2.14	0.93 to 5.13
Ji et al. (2019) (38)	Observational	996	–	Children	Maternal paracetamol use in 3rd tertile, compared with 1st tertile	Odds ratio	3.62	1.62 to 8.60

Text citation	Study type	Number of participants	Number of studies	Age-group	Risk factor	Analysis	Point estimate	95% CI
Katsigianni et al. (2019) (37)	Systematic review	355,548	10	Children	Maternal polycystic ovary syndrome	Risk ratio	1.66	1.51 to 1.83
Al-Haddad et al. (2019) (38)	Observational	1,791,250	–	Children	Maternal urinary tract infection while admitted to hospital during pregnancy	Hazard ratio	1.89	1.23 to 2.90

Table: familial risk factors for autism

Text citation	Study type	Number of participants	Number of studies	Age-group	Risk factor	Analysis	Point estimate	95% CI
Ayano et al. (2019) (41)	Systematic review	NR	9	Children	Parents with affective disorder	Odds ratio	1.65	1.45 to 1.88
Ayano et al. (2019) (41)	Systematic review	NR	9	Children	Parents with depression	Odds ratio	1.37	1.04 to 1.81
Ayano et al. (2019) (41)	Systematic review	NR	9	Children	Parents with bipolar disorder	Odds ratio	1.87	1.67 to 2.07
Ayano et al. (2019) (41)	Systematic review	NR	9	Children	Mother with affective disorder	Odds ratio	1.67	1.34 to 2.09
Ayano et al. (2019) (41)	Systematic review	NR	9	Children	Mother with depressive disorder	Odds ratio	1.62	1.32 to 1.99
Ayano et al. (2019) (41)	Systematic review	NR	9	Children	Father with affective and depressive disorders	Odds ratio	NR	NR
Gong et al. (2019) (34)	Observational	1,579,263	–	Children	Paternal asthma	Odds ratio	1.17	1.11 to 1.23
Lei et al. (2019) (10)	Systematic review	973,630	13	Unspecified	Paternal obesity	Odds ratio	1.28	0.94 to 1.74

Text citation	Study type	Number of participants	Number of studies	Age-group	Risk factor	Analysis	Point estimate	95% CI
Lei et al. (2019) (10)	Systematic review	973,630	13	Unspecified	Paternal overweight	Odds ratio	1.07	0.99 to 1.15
Lei et al. (2019) (10)	Systematic review	973,630	13	Unspecified	Paternal underweight	Odds ratio	1.12	0.87 to 1.44
Morales et al. (2018) (15)	Systematic review	3,626,271	15	Children	Paternal antidepressant exposure during pregnancy	Risk ratio	1.29	1.08 to 1.53
Miller et al. (2019) (42)	Observational	15,175	–	Children	Sibling with autism	Odds ratio	30.38	17.73 to 52.06

Table: pollutants as risk factors for autism

Text citation	Study type	Number of participants	Number of studies	Age-group	Risk factor	Analysis	Point estimate	95% CI
Geng et al. (2019) (43)	Observational	297	–	Children	Particulate matter 2.5 exposure in the 3rd quartile	Odds ratio	2.03	1.13 to 5.54
Geng et al. (2019) (43)	Observational	297	–	Children	Particulate matter 2.5 exposure in the 4th quartile	Odds ratio	4.15	2.04 to 9.45
Fu et al. (2019) (44)	Systematic review	NR	80	Mixed	Particulate matter 2.5 exposure	Odds ratio	1.68	1.20 to 2.34
Kaufman et al. (2019) (45)	Observational	6,848	–	Unspecified	Particulate matter 2.5 exposure during 2nd trimester	Odds ratio	1.41-144	NR
Kaufman et al. (2019) (45)	Observational	6,848	–	Unspecified	Particulate matter 2.5 exposure during 1st year of life	Odds ratio	1.54-1.84	NR
Kaufman et al. (2019) (45)	Observational	6,848	–	Unspecified	Particulate matter 2.5 exposure cumulative through pregnancy to 2nd year	Odds ratio	1.41-152	NR

Text citation	Study type	Number of participants	Number of studies	Age-group	Risk factor	Analysis	Point estimate	95% CI
McGuinn et al. (2019) (46)	Observational	1,529	–	Children	Particulate matter 2.5 exposure during 1st year (per 1.6 microgram increase)	Odds ratio	1.3	1.0 to 1.6
Kaufman et al. (2019) (45)	Observational	6,848	–	Unspecified	Ozone exposure in 2nd year	Odds ratio	1.29 to 1.42	NR
McGuinn et al. (2019) (46)	Observational	1,529	–	Children	Ozone exposure during 3rd trimester, (per 6.6 parts per billion increase in ozone)	Odds ratio	1.2	1.1 to 1.4
Oudin et al. (2019) (47)	Observational	48,571	–	Unspecified	Nitrogen oxide exposure (4th versus 1st quartile)	Odds ratio	1.4	1.02 to 1.93
Cimino et al. (2017) (48)	Systematic review	NR	8	Unspecified	Neonicotinoid exposure (chronic)	Odds ratio	1.3	0.78 to 2.2
Philippat et al. (2018) (49)	Observational	203	–	Children	Organophosphate metabolite concentrates	Odds ratio	NR	NR
Philippat et al. (2018) (49)	Observational	203	–	Children	Dimethylthiophosphate (doubling of concentration – boys only)	Odds ratio	0.84	0.63 to 1.11
Philippat et al. (2018) (49)	Observational	203	–	Children	Dimethylthiophosphate (doubling of concentration – girls only)	Odds ratio	1.64	0.95 to 2.82

Assessing coexisting conditions in the autism diagnostic assessment

Background

The guideline on diagnosing autism in children and young people recommends considering whether the child or young person may have any of the following as a coexisting condition, and if suspected, to carry out appropriate assessments and referrals:

- mental and behaviour problems and disorders
- neurodevelopmental problems and disorders:
- medical or genetic problems and disorders:
- functional problems and disorders (CG128-1.5.15).

The guideline on diagnosis and management of autism in adults similarly recommends that during a comprehensive assessment, healthcare professionals should take into account and assess for possible differential diagnoses and coexisting disorders or conditions, such as:

- other neurodevelopmental conditions
- mental disorders
- neurological disorders
- physical disorders
- communication difficulties
- hyper- and/or hypo-sensory sensitivities (CG142-1.2.10).

Only 2 studies of coexisting conditions were identified in previous surveillance. Both were consistent with the current guidelines, finding:

- a high prevalence of autism in children with neurofibromatosis type 1 (see evidence summaries for 2016 surveillance of NICE guideline CG128).
- a high prevalence of psychiatric comorbidity in adults with autism (see evidence summaries for 2016 surveillance of NICE guideline CG142).

To be included in this section of the surveillance review, abstracts needed to report analysis indicating the difference in prevalence in people with autism and in the general population the groups, such as odds ratios or risk ratios.

Evidence and intelligence review

Overview

We found 14 studies covering conditions commonly found in people with autism. 7 included children, 1 study included infants, 1 study included toddlers, 3 studies included adults, and 2 studies did not specify the age-group in the abstract. The data on coexisting conditions did not appear to differ substantially by age, so the summaries below focus on the type of condition.

Topic experts and patient organisations provided detailed feedback on concerns around recognition of coexisting conditions. This included observations that diagnosis of autism was sometimes delayed when a coexisting condition was diagnosed first, which applies to both other behavioural conditions such as ADHD and physical disabilities such as cerebral palsy.

The topic experts raised concerns about whether existing tools for diagnosing the coexisting conditions were suitable for use in people with autism. Similarly, patient organisations indicated that people with autism need appropriately modified treatments for mental health disorders. However, we did not identify any new studies reporting diagnostic accuracy of adaptations to either established tools or treatments for mental health disorders for people with autism that could enable us to explore this issue further at this time.

Further topic expert and patient organisation feedback related to specific conditions is described in the subsections below.

Functional, medical and genetic disorders

Disorders already recognised in the guideline

We identified 2 systematic reviews and 6 observational studies reporting on functional, medical, and genetic disorders that are more common in people with autism (see Table: functional, medical and genetic disorders).

Of the coexisting conditions identified in the new evidence, the following are already included in the list of coexisting conditions in the guideline on autism in children and young people.

- epilepsy (53)
- hearing impairment (3,4,54)
- visual impairment (3,4,54)

Current recommendations list these possible coexisting conditions so an update to the NICE guideline on diagnosing autism in children and young people is not necessary.

One topic expert observed that autism diagnosis can be delayed in children with cerebral palsy because their social communication weaknesses are thought to be explained by their movement disorder. The NICE guideline on diagnosis of autism in children (CG128-1.5.6) recommends performing a general physical examination and looking specifically for congenital anomalies (which would include cerebral palsy). Additionally, the guideline noted cerebral palsy as a risk factor for autism (CG128-1.3.3) and that the autism team should either have or have access to the skills needed to carry out an autism diagnostic assessment, for children and young people with special circumstances including cerebral palsy (CG128-1.1.9). NICE's guidelines on assessment and management of cerebral palsy in under 25s and in adults also recommend following guidance on identifying and managing specific mental health problems, and psychological and neurodevelopmental disorders. These recommendations include cross-references to NICE's autism guidelines. Therefore, guidance on identifying autism in people with cerebral palsy is sufficient and no update is necessary.

We also identified 2 studies (3,4) suggesting that autism may frequently coexist with long-term health conditions and physical disabilities (there was no further definition of this term in the full-text reports). Some of the long-term health conditions seen in people with autism may already be covered in the conditions listed in the NICE guideline on diagnosing autism in children and young people. Since the reports did not define what conditions were covered by the term physical disabilities, the evidence is insufficient to trigger an update.

Conditions not currently covered in the guideline

Overall, we identified 5 studies that measured the rates of functional, medical or genetic disorders that are not currently covered in NICE's autism guidelines.

We identified 2 studies (55,56) that suggested that children with autism were at increased risk of overweight or obesity. First, a systematic review (55) reported that 22% of children with autism had obesity, and that this figure represented a 41% increase in risk of obesity in children with autism (p=0.018). This study was not included in the data table because the reported data did not fit with the format of the table.

Second, an observational study (56) reported an increased risk of obesity of 85% (approximated from the odds ratio). The authors of this study noted that in children with autism, mood stabilisers, antipsychotics, antiepileptic drugs, and SSRIs were associated with obesity. They concluded that obesity in children with autism may be partially related to treatment. Since the findings in the other study could also be influenced by the effects of drug treatments commonly used in children with autism, the evidence does not sufficiently establish a link between autism and obesity, so an update to NICE's autism guidelines is not proposed.

One large systematic review (57), indicated that although the prevalence of asthma appeared to be higher in people with autism (20% compared with 15% in people without autism, p<0.001), the risk of asthma in people with autism

was not significantly higher than in people without autism. Therefore, an update to NICE's autism guidelines is not necessary.

We identified one small observational study (58) (n=200) indicating that infants with autism had higher rates of persistent crying as infants (32% in infants with autism compared with 9% in infants without autism; RR=4.4, p<0.001) despite slightly lower occurrence of infant colic (16% in infants with autism compared with 17% in infants without autism, p=0.05). We also identified one small observational study (59) (n=158) indicating that people with autism had a higher risk of hypocholesterolaemia (at the 25th centile).

Because persistent crying as infants and hypocholesterolaemia were each linked to autism in only one study we would encourage replication of these findings in larger datasets before considering an update to the NICE autism guidelines.

Mental health, behavioural and neurodevelopmental disorders

We identified 6 studies (see table: mental health, behavioural and neurodevelopmental disorders) assessing the association between autism and neurodevelopmental disorders. Evidence also suggested that people with autism may frequently have the following coexisting mental health and neurodevelopmental conditions:

- Mental health disorders (3,4)
- Hyperkinetic disorders (classed as attention deficit and hyperactivity disorder in ICD-11) (60)
- Depressive disorders (60)
- Obsessive-compulsive disorder (60)
- Schizophrenia (61) and other psychotic disorders (60)
- Tic disorders (60)
- Learning disabilities (3,4,62)

These studies generally measured the frequency of learning disabilities in people with autism. However, one study (62) measured the frequency of autism in adults with 'moderate to profound' learning disabilities (OR 63.5,

95% CI 27.4 to 147.2, data not included in the table because autism was the coexisting condition rather than the primary condition in the analysis).

These conditions are consistent with those listed in the NICE guidelines' recommendations. Therefore, there is no need to update the NICE autism guidelines in this area.

Conditions highlighted by topic experts and patient groups

Anorexia

Topic experts and patient organisations noted that anorexia should be recognised as a coexisting condition. In developing the NICE guideline on diagnosing autism in children (see the full guideline, page 157), the committee suggested anorexia as a possible coexisting condition, but no evidence was identified, and anorexia was not included in the list. In this surveillance review, we did not identify any new evidence meeting the inclusion criteria (that is, the abstract reported statistical data on the difference in rates of the condition in people with autism and those without autism).

Pathological demand avoidance

Topic experts, patient groups, and other correspondence received since the NICE guideline was published has suggested that the guideline should consider pathological demand avoidance as a specific profile for people with autism. The term is used to describe complex behavioural problems that mainly manifest as extreme avoidance of everyday requests and expected behaviours. Disagreement remains about whether pathological demand avoidance should be recognised as a distinct diagnosis. Some topic experts considered that appropriate recognition of coexisting conditions and individualised management strategies are sufficient. Because we did not identify any new evidence in this area, pathological demand avoidance is not being proposed as an area for update.

Surveillance proposal

We propose not to update the sections of the NICE autism guidelines covering coexisting conditions.

Most of the evidence identified in this surveillance review was consistent with the lists of coexisting conditions in current recommendations. Evidence for conditions not currently on the list (obesity, asthma, persistent crying as infants, and hypocholesterolaemia) tended to be from studies with methodological limitations and did not sufficiently establish links between autism and other coexisting conditions. We did not identify suitable evidence on possible links with anorexia or pathological demand avoidance that supported external feedback we received about these disorders.

Data tables for assessing coexisting conditions in the autism diagnostic assessment

Table: functional, medical and genetic disorders

Text citation	Study type	Number of participants	Number of included studies	Age-group	Coexisting condition	Analysis	Point estimate	95% CI
Zheng et al. (2016) (57)	Systematic review	184,215	10	Unspecified	Asthma	Odds ratio	1.26	0.98 to 1.61
Zheng et al. (2016) (57)	Systematic review	184,215	10	Unspecified	Asthma	Odds ratio	0.98	0.68 to 1.43
Barger et al. (2017) (53)	Observational	NR	–	Unspecified	Epilepsy	Odds ratio	1.59	1.31 to 1.95
Rydzewska et al. (2018) (3)	Observational	3,746,584	–	Adults	Hearing impairment	Odds ratio	3.3	3.1 to 3.6
Do et al. (2017) (54)	Systematic review	NR	16	Children	Hearing impairment	Relative risk	14.1	3.41 to 58.62
Rydzewska et al. (2019) (4)	Observational	1,548,819	–	Children	Hearing impairment	Odds ratio	5.4	5.1 to 5.6
Benachenhou et al. (2019) (59)	Observational	158	–	Unspecified	Hypocholesterolaemia at 25th centile	Odds ratio	3.04	1.57 to 6.65
Shedlock et al. (2016) (56)	Observational	292,572	–	Children	Obesity	Odds ratio	1.85	1.78 to 1.921
Rydzewska et al. (2019) (4)	Observational	1,548,819	–	Children	Physical disabilities	Odds ratio	15.8	14.1 to 17.8
Rydzewska et al. (2018) (3)	Observational	3,746,584	–	Adults	Physical disability	Odds ratio	6.2	5.8 to 6.6
Rydzewska et al. (2018) (3)	Observational	3,746,584	–	Adults	Vision impairment	Odds ratio	8.5	7.9 to 9.2
Do et al. (2017) (54)	Systematic review	NR	15	Children	Visual impairment	Relative risk	31	18.62 to 51.56

Rydzewska et al. (2019) (4)	Observational	1,548,819	–	Children	Visual impairment	Odds ratio	8.9	8.1 to 9.7

Table: mental health, behavioural and neurodevelopmental disorders

Text citation	Study type	Number of participants	Number of included studies	Age-group	Coexisting condition	Analysis	Point estimate	95% CI
Downs et al. (2016) (60)	Observational	3,482	–	Children	Depressive disorders	Odds ratio	2.36	1.37 to 4.09
Downs et al. (2016) (60)	Observational	3,482	–	Children	Hyperkinetic disorders (attention deficit and hyperactivity disorder in ICD-11)	Odds ratio	1.44	1.01 to 2.06
Rydzewska et al. (2018) (3)	Observational	3,746,584	–	Adults	Learning disability	Odds ratio	94.6	89.4 to 100.0
Rydzewska et al. (2019) (4)	Observational	1,548,819	–	Children	Learning disability	Odds ratio	15.7	13.4 to 18.5
Rydzewska et al. (2018) (3)	Observational	3,746,584	–	Adults	Mental health disorders	Odds ratio	8.6	8.2 to 9.0
Rydzewska et al. (2019) (4)	Observational	1,548,819	–	Children	Mental health disorders	Odds ratio	49.7	38.1 to 64.9
Downs et al. (2016) (60)	Observational	3,482	–	Children	Obsessive-compulsive disorder	Odds ratio	2.31	1.16 to 4.61
Downs et al. (2016) (60)	Observational	3,482	–	Children	Psychotic disorders	Odds ratio	5.71	3.3 to 10.6
Zheng et al. (2018) (61)	Systematic review	1,965,058	–	Unspecified	Schizophrenia spectrum disorders	Odds ratio	3.55	2.08 to 6.05
Downs et al. (2016) (60)	Observational	3,482	–	Children	Tic disorders	Odds ratio	2.76	1.09 to 6.95

Identifying possible autism

Background

The NICE guideline on autism in children and young people investigated the predictive accuracy of screening tools for autism. The review protocol for this section of the NICE guideline (see the full version of NICE guideline CG128, page 43) specified that the sensitivity and specificity of a tool should be at least 80% and the lower limit of the 95% confidence interval should be at least 70%. None of the instruments assessed during NICE's guideline development met the predefined level of accuracy specified by NICE's guideline committee for identifying children and young people with autism (see the full version of NICE guideline CG128, page 75). The guideline thus recommended:

'Be aware that tools to identify children and young people with an increased likelihood of autism may be useful in gathering information about signs and symptoms of autism in a structured way but are not essential and should not be used to make or rule out a diagnosis of autism. Also be aware that:

- a positive score on tools to identify an increased likelihood of autism may support a decision to refer but can also be for reasons other than autism
- a negative score does not rule out autism' (CG128-1.3.5).

The 2016 surveillance review of diagnosis of autism in children and young people identified 36 studies of a wide range of screening tools for autism. However, the evidence did not fully meet the threshold for predictive accuracy from the NICE guideline, so the surveillance review concluded that no update was needed.

The NICE guideline on diagnosing and managing autism in adults did not specify limits for predictive accuracy. The NICE guideline committee judged the clinical utility of the AQ-10 to be good, given that it is quick to administer and is free and available online (see the full version of NICE guideline CG142, p106). The guideline recommended considering using the AQ-10 tool for adults with possible autism who do not have a moderate or severe learning disability. If a person scores above six on the AQ-10, or autism is suspected

based on clinical judgement (taking into account any past history provided by an informant), offer a comprehensive assessment for autism (NG142-1.2.3). No suitable tools were identified for identifying autism in adults with a learning disability, and so the NICE guideline committee formulated a list of indicators of autism in this population from existing diagnostic manuals and tools identified in the NICE guideline's evidence review.

The 2016 surveillance review of autism in adults identified no new evidence on screening tools.

Evidence and intelligence review

Screening tools for autism in under 19s

We identified 16 studies of screening tools for autism in children and young people (see table: screening tools for autism in children) that reported a variety of measures of diagnostic performance including sensitivity, specificity, predictive value, area under the curve, and classification accuracy):

- Autism Detection in Early Childhood (brief version) (63)
- Autism Spectrum Screening Questionnaire (ASSQ) adapted for preschool children (64)
- Autistic Behavioural Indicators Instrument - parent questionnaire (ABII-PQ) (65)
- Baby and Infant Screen for Children with aUtIsm Traits (BISCUIT) – abbreviated (66)
- CHAT at 24 months (67)
- Developmental Check-in (68)
- Global Developmental Screening (GDS) (69)
- Machine learning using children's autism screening evaluations (70)
- Modified Checklist for Autism in Toddlers (M-CHAT) (71–75)
- Modified Checklist for Autism in Toddlers revised with follow-up (M-CHAT-/F) (69,72)
- Parent's Observations of Social Interactions (POSI) (74)
- Preaut grid at 4 months (67)

- Preaut grid plus CHAT (67)
- Social Communication Questionnaire (SCQ) (75,76)
- Three-item Direct Observation Screen (TIDOS) (72)

Because none of the tools met or reported on all criteria for predictive accuracy specified in the guideline on diagnosing autism in children and young people, there is no indication that the NICE guideline should be updated in relation to screening tools for autism in children and young people.

Screening tools for autism in adults

We identified 3 studies of screening tools for autism in adults (see Table: screening tools for autism in adults).

One UK-based study (77) highlighted by topic experts assessed the AQ-10 in 476 adults attending at a national autism diagnostic referral service. It found very low specificity and poor negative predictive value of this tool. In this sample, 64% of people not meeting the threshold had false negative results and did have autism. Topic experts suggested that this finding meant that the recommendation to consider using the AQ-10 was now out of date.

In developing the guideline on autism in adults, evidence on the AQ-10 indicated it had sensitivity of 88% (95% CI 85% to 90%) and specificity of 91% (95% CI 88% to 93%) for detecting autism in the general population. The sample used in the study was people with autism and control participants without autism. The new evidence addressed a different population – people with suspected autism, and the presence of characteristics leading a clinician to suspect autism means that even those people without autism in this sample may not be directly comparable with healthy controls.

The recommendation intended for the AQ-10 to be considered for use in primary care, social care and other non-specialist settings to support the decision to refer for a specialist assessment (see the full version of NICE guideline CG142, page 110). The guideline committee noted that the AQ-10 was quick to use and could be used without needing expertise in its administration and scoring for people in whom there was already a clinical

suspicion of autism. The recommendation to offer comprehensive assessment for autism depends on AQ-10 score or clinical suspicion of autism (CG142-1.2.3) therefore clinicians should not rely only on AQ-10 scores alone for referral for assessment. The new evidence suggests that people referred for specialist assessment did not all meet the AQ-10 threshold, which suggests that referring clinicians did take other factors into account when deciding to refer, which is consistent with current guidance. However, the study also highlighted a high false negative rate strongly suggesting the AQ-10 misses a high number of cases of autism.

We also identified 2 studies that assessed adaptations of screening tools for adults with learning disabilities. An adapted AQ-10 for adults with borderline or mild learning disability (78) showed that the adapted AQ-10 had good sensitivity and moderate specificity. However, the abstract did not report the sample size or 95% CI and described this study as a 'pilot'. The Social Communication Questionnaire for adults with intellectual disability (SCQ-AID) (79) had acceptable sensitivity but only moderate specificity. Therefore, the evidence does not suggest sufficient utility of these tools to trigger an update of the NICE guideline.

Surveillance proposal

We propose not to update the sections of the NICE guidelines covering identifying people with possible autism because the new evidence does not clearly show good predictive accuracy of any screening tool in children, young people, or adults. We identified a study indicating that the AQ-10 has low specificity in people with suspected autism referred for specialist assessment. The guideline on autism in adults contains recommendation 1.2.3 to consider using the AQ-10 alongside clinical judgement to inform decisions about referral for a comprehensive autism assessment.in people with possible autism. We plan to consult with stakeholders about how widely used the AQ-10 is in practice.

Data tables for identifying possible autism

Table: screening tools for autism in children

Text citation	Study type	Number of participants	Number of included studies	Age-group	Test	Gold standard	Comparator population	Outcome	Result	95% CI
Nah et al. (2019) (63)	Observational	270	–	Toddlers	Autism Detection in Early Childhood (brief version)	DSM5	Non-typical' development or typical development	Negative predictive value	78%	NR
Nah et al. (2019) (63)	Observational	270	–	Toddlers	Autism Detection in Early Childhood (brief version)	DSM5	Non-typical' development or typical development	Positive predictive value	81%	NR
Nah et al. (2019) (63)	Observational	270	–	Toddlers	Autism Detection in Early Childhood (brief version)	DSM5	Non-typical' development or typical development	Sensitivity	81%	NR
Nah et al. (2019) (63)	Observational	270	–	Toddlers	Autism Detection in Early Childhood (brief version)	DSM5	Non-typical' development or typical development	Specificity	78%	NR
Adachi et al. (2018) (64)	Observational	1390	–	Toddlers	Autism Spectrum Screening Questionnaire (ASSQ) adapted for preschool children – used in the community	Unclear in abstract	Unclear in abstract	Sensitivity	93%	NR
Adachi et al. (2018) (64)	Observational	1390	–	Toddlers	Autism Spectrum Screening Questionnaire (ASSQ) adapted for preschool children – used in the community	Unclear in abstract	Unclear in abstract	Specificity	84%	NR
Ward et al. (2017) (65)	Observational	102	–	Children	Autistic Behavioural Indicators Instrument - parent questionnaire (ABII-PQ) at optimum threshold	Unclear in abstract	Healthy controls	Classification accuracy for Asperger syndrome	93%	NR

Text citation	Study type	Number of participants	Number of included studies	Age-group	Test	Gold standard	Comparator population	Outcome	Result	95% CI
Ward et al. (2017) (65)	Observational	102	–	Children	Autistic Behavioural Indicators Instrument - parent questionnaire (ABII-PQ) at optimum threshold	Unclear in abstract	Healthy controls	Classification accuracy for autism	100%	NR
Ward et al. (2017) (65)	Observational	102	–	Children	Autistic Behavioural Indicators Instrument - parent questionnaire (ABII-PQ) at optimum threshold	Unclear in abstract	Healthy controls	Classification accuracy for pervasive development disorder not otherwise specified	93%	NR
Ward et al. (2017) (65)	Observational	102	–	Children	Autistic Behavioural Indicators Instrument - parent questionnaire (ABII-PQ) at optimum threshold	Unclear in abstract	Healthy controls	Sensitivity	97%	NR
Ward et al. (2017) (65)	Observational	102	–	Children	Autistic Behavioural Indicators Instrument - parent questionnaire (ABII-PQ) at optimum threshold	Unclear in abstract	Healthy controls	Specificity	95%	NR
Cervantes et al. (2017) (66)	Observational	6003	–	Infants	Baby and Infant Screen for Children with aUtIsm Traits (BISCUIT) – abbreviated; 6 items with threshold of 3	Unclear in abstract	Toddlers with 'atypical development'	Sensitivity	96%	NR
Cervantes et al. (2017) (66)	Observational	6003	–	Infants	Baby and Infant Screen for Children with aUtIsm Traits (BISCUIT) – abbreviated; 6 items with threshold of 3	Unclear in abstract	Toddlers with 'atypical development'	Specificity	86%	NR
Olliac et al. (2017) (67)	Observational	12,179	–	Toddlers	CHAT at 24 months	Clinical diagnosis based on ICD-10	Mixed populations (mostly healthy control)	Positive predictive value	27% to 26%	NR

Text citation	Study type	Number of participants	Number of included studies	Age-group	Test	Gold standard	Comparator population	Outcome	Result	95% CI
Olliac et al. (2017) (67)	Observational	12,179	–	Toddlers	CHAT at 24 months	Clinical diagnosis based on ICD-10	Mixed populations (mostly healthy control)	Sensitivity	34% to 42%	NR
Janvier et al. (2019) (68)	Observational	376	–	Toddlers	Developmental Check-in	Unclear in abstract	Unclear in abstract	Area under the curve	75%	NR
Kerub et al. (2018) (69)	Observational	1591	–	Toddlers	Global Developmental Screening (GDS)	Unclear in abstract	Unclear in abstract	Sensitivity	50%	NR
Kerub et al. (2018) (69)	Observational	1591	–	Toddlers	Global Developmental Screening (GDS)	Unclear in abstract	Unclear in abstract	Specificity	97%	NR
Maenner et al. (2016) (70)	Observational	1450	–	Children	Machine learning using children's autism screening evaluations	Clinical diagnosis	Unclear in abstract	Area under the curve	93%	NR
Maenner et al. (2016) (70)	Observational	1450	–	Children	Machine learning using children's autism screening evaluations	Clinical diagnosis	Unclear in abstract	Concordance with clinical diagnosis	87%	NR
Maenner et al. (2016) (70)	Observational	1450	–	Children	Machine learning using children's autism screening evaluations	Clinical diagnosis	Unclear in abstract	Positive predictive value	89%	NR
Maenner et al. (2016) (70)	Observational	1450	–	Children	Machine learning using children's autism screening evaluations	Clinical diagnosis	Unclear in abstract	Sensitivity	84%	NR
Kim et al. (2016) (71)	Observational	827	–	Toddlers	Modified Checklist for Autism in Toddlers (M-CHAT)	Clinical diagnosis at age 10	Children born very preterm without autism	Negative predictive value	96%	NR
Topcu et al. (2018) (72)	Observational	511	–	Toddlers	Modified Checklist for Autism in Toddlers (M-CHAT)	Clinical diagnosis	Healthy controls	Negative predictive value	99%	NR

Text citation	Study type	Number of participants	Number of included studies	Age-group	Test	Gold standard	Comparator population	Outcome	Result	95% CI
Kim et al. (2016) (71)	Systematic review	NR	13	Toddlers	Modified Checklist for Autism in Toddlers (M-CHAT)	Unclear in abstract	Low-risk children	Positive predictive value	6%	1% to 14%
Topcu et al. (2018) (72)	Observational	511	–	Toddlers	Modified Checklist for Autism in Toddlers (M-CHAT)	Clinical diagnosis	Healthy controls	Positive predictive value	14%	NR
Yuen et al. (2018) (73)	Observational	827	–	Toddlers	Modified Checklist for Autism in Toddlers (M-CHAT)	Clinical diagnosis at age 10	Children born very preterm without autism	Positive predictive value	20%	NR
Yuen et al. (2018) (73)	Systematic review	NR	13	Toddlers	Modified Checklist for Autism in Toddlers (M-CHAT)	Unclear in abstract	High-risk children	Positive predictive value	53%	43% to 63%
Charman et al. (2016) (75)	Observational	827	–	Toddlers	Modified Checklist for Autism in Toddlers (M-CHAT)	Clinical diagnosis at age 10	Children born very preterm without autism	Sensitivity	52%	NR
Kim et al. (2016) (71)	Observational	511	–	Toddlers	Modified Checklist for Autism in Toddlers (M-CHAT)	Clinical diagnosis	Healthy controls	Sensitivity	60%	NR
Salisbury et al. (2018) (74)	Observational	120	–	Toddlers	Modified Checklist for Autism in Toddlers (M-CHAT)	Clinical diagnosis	Children referred to community paediatric and speech and language therapy services	Sensitivity	82%	72% to 92%
Topcu et al. (2018) (72)	Systematic review	NR	13	Toddlers	Modified Checklist for Autism in Toddlers (M-CHAT)	Unclear in abstract	Unclear in abstract	Sensitivity	83%	75% to 90%
Yuen et al. (2018) (73)	Observational	NR	–	Toddlers	Modified Checklist for Autism in Toddlers (M-CHAT)	Unclear in abstract	Children referred to a developmental clinic	Sensitivity	75% or greater	NR

Text citation	Study type	Number of participants	Number of included studies	Age-group	Test	Gold standard	Comparator population	Outcome	Result	95% CI
Charman et al. (2016) (75)	Observational	120	–	Toddlers	Modified Checklist for Autism in Toddlers (M-CHAT)	Clinical diagnosis	Children referred to community paediatric and speech and language therapy services	Specificity	50%	33% to 64%
Kim et al. (2016) (71)	Systematic review	NR	13	Toddlers	Modified Checklist for Autism in Toddlers (M-CHAT)	Unclear in abstract	Unclear in abstract	Specificity	51%	41% to 61%
Topcu et al. (2018) (72)	Observational	827	–	Toddlers	Modified Checklist for Autism in Toddlers (M-CHAT)	Clinical diagnosis at age 10	Children born very preterm without autism	Specificity	84%	NR
Yuen et al. (2018) (73)	Observational	511	–	Toddlers	Modified Checklist for Autism in Toddlers (M-CHAT)	Clinical diagnosis	Healthy controls	Specificity	96%	NR
Topcu et al. (2018) (72)	Observational	511	–	Toddlers	Modified Checklist for Autism in Toddlers revised with follow-up (M-CHAT-/F)	Clinical diagnosis	Healthy controls	Negative predictive value	99%	NR
Topcu et al. (2018) (72)	Observational	511	–	Toddlers	Modified Checklist for Autism in Toddlers revised with follow-up (M-CHAT-/F)	Clinical diagnosis	Healthy controls	Positive predictive value	18%	NR
Kerub et al. (2018) (69)	Observational	511	–	Toddlers	Modified Checklist for Autism in Toddlers revised with follow-up (M-CHAT-/F)	Clinical diagnosis	Healthy controls	Sensitivity	60%	NR
Topcu et al. (2018) (72)	Observational	1591	–	Toddlers	Modified Checklist for Autism in Toddlers revised with follow-up (M-CHAT-/F)	Unclear in abstract	Unclear in abstract	Sensitivity	70%	NR
Kerub et al. (2018) (69)	Observational	511	–	Toddlers	Modified Checklist for Autism in Toddlers revised with follow-up (M-CHAT-/F)	Clinical diagnosis	Healthy controls	Specificity	97%	NR

Text citation	Study type	Number of participants	Number of included studies	Age-group	Test	Gold standard	Comparator population	Outcome	Result	95% CI
Topcu et al. (2018) (72)	Observational	1591	–	Toddlers	Modified Checklist for Autism in Toddlers revised with follow-up (M-CHAT-/F)	Unclear in abstract	Unclear in abstract	Specificity	98%	NR
Salisbury et al. (2018) (74)	Observational	NR	–	Toddlers	Parent's Observations of Social Interactions (POSI)	Unclear in abstract	Children referred to a developmental clinic	Sensitivity	75% or greater	NR
Olliac et al. (2017) (67)	Observational	12,179	–	Toddlers	Preaut grid at 4 months	Clinical diagnosis based on ICD-10	Mixed populations (mostly healthy control)	Positive predictive value	20% to 36%	NR
Olliac et al. (2017) (67)	Observational	12,179	–	Toddlers	Preaut grid at 4 months	Clinical diagnosis based on ICD-10	Mixed populations (mostly healthy control)	Positive predictive value	25% to 26%	NR
Olliac et al. (2017) (67)	Observational	12,179	–	Toddlers	Preaut grid at 4 months	Clinical diagnosis based on ICD-10	Mixed populations (mostly healthy control)	Sensitivity	16% to 21%	NR
Olliac et al. (2017) (67)	Observational	12,179	–	Toddlers	Preaut grid at 4 months	Clinical diagnosis based on ICD-10	Mixed populations (mostly healthy control)	Sensitivity	31% to 41%	NR
Olliac et al. (2017) (67)	Observational	12,179	–	Toddlers	Preaut grid plus CHAT	Clinical diagnosis based on ICD-10	Mixed populations (mostly healthy control)	Positive predictive value	19% to 28%	NR
Olliac et al. (2017) (67)	Observational	12,179	–	Toddlers	Preaut grid plus CHAT	Clinical diagnosis based on ICD-10	Mixed populations (mostly healthy control)	Sensitivity	68% to 78%	NR

Text citation	Study type	Number of participants	Number of included studies	Age-group	Test	Gold standard	Comparator population	Outcome	Result	95% CI
Suren et al. (2019) c	Observational	58,520	–	Toddlers	Social Communication Questionnaire (SCQ)	Unclear in abstract	Healthy controls	Sensitivity (threshold of 11 in children without phrase speech at 36 months)	69%	58% to 79%
Charman et al. (2016) c	Observational	120	–	Toddlers	Social Communication Questionnaire (SCQ)	Clinical diagnosis	Children referred to community paediatric and speech and language therapy services	Sensitivity	64%	51% to 80%
Suren et al. (2019) (67)	Observational	58,520	–	Toddlers	Social Communication Questionnaire (SCQ)	Unclear in abstract	Healthy controls	Sensitivity (threshold of 11 in children with phrase speech at 36 months)	34%	29% to 40%
Suren et al. (2019) (67)	Observational	58,520	–	Toddlers	Social Communication Questionnaire (SCQ)	Unclear in abstract	Healthy controls	Sensitivity (threshold of 11)	42%	37% to 47%
Suren et al. (2019) (67)	Observational	58,520	–	Toddlers	Social Communication Questionnaire (SCQ)	Unclear in abstract	Healthy controls	Sensitivity (threshold of 15 in children with phrase speech at 36 months)	13%	9% to 17%
Suren et al. (2019) (67)	Observational	58,520	–	Toddlers	Social Communication Questionnaire (SCQ)	Unclear in abstract	Healthy controls	Sensitivity (threshold of 15 in children without phrase speech at 36 months)	46%	35% to 57%
Suren et al. (2019) (67)	Observational	58,520	–	Toddlers	Social Communication Questionnaire (SCQ)	Unclear in abstract	Healthy controls	Sensitivity (threshold of 15)	20%	16% to 24%

Text citation	Study type	Number of participants	Number of included studies	Age-group	Test	Gold standard	Comparator population	Outcome	Result	95% CI
Charman et al. (2016) (67)	Observational	120	–	Toddlers	Social Communication Questionnaire (SCQ)	Clinical diagnosis	Children referred to community paediatric and speech and language therapy services	Specificity	75%	63% to 85%
Suren et al. (2019) (67)	Observational	58,520	–	Toddlers	Social Communication Questionnaire (SCQ)	Unclear in abstract	Healthy controls	Specificity (threshold of 11)	89%	89% to 90%
Suren et al. (2019) (67)	Observational	58,520	–	Toddlers	Social Communication Questionnaire (SCQ)	Unclear in abstract	Healthy controls	Specificity (threshold of 15)	99%	99% to 99%
Topcu et al. (2018) (72)	Observational	511	–	Toddlers	Three-item Direct Observation Screen (TIDOS)	Clinical diagnosis	Healthy controls	Negative predictive value	99%	NR
Topcu et al. (2018) (72)	Observational	511	–	Toddlers	Three-item Direct Observation Screen (TIDOS)	Clinical diagnosis	Healthy controls	Positive predictive value	80%	NR
Topcu et al. (2018) (72)	Observational	511	–	Toddlers	Three-item Direct Observation Screen (TIDOS)	Clinical diagnosis	Healthy controls	Sensitivity	80%	NR
Topcu et al. (2018) (72)	Observational	511	–	Toddlers	Three-item Direct Observation Screen (TIDOS)	Clinical diagnosis	Healthy controls	Specificity	99%	NR

Table: screening tools for autism in adults

Text citation	Study type	Number of participants	Age-group	Test	Gold standard	Comparator population	Measurement	Result	95% CI
Ashwood et al. (2016) (77)	Observational	476	Adults	Autism-Spectrum Quotient (AQ)	Clinical diagnosis	Adults referred for suspected autism	Sensitivity	77%	72% to 82%

Ashwood et al. (2016) (77)	Observational	476	Adults	Autism-Spectrum Quotient (AQ)	Clinical diagnosis	Adults referred for suspected autism	Positive predictive value	76%	70% to 80%
Ashwood et al. (2016) (77)	Observational	476	Adults	Autism-Spectrum Quotient (AQ)	Clinical diagnosis	Adults referred for suspected autism	Specificity	29%	20% to 38%
Ashwood et al. (2016) (77)	Observational	476	Adults	Autism-Spectrum Quotient (AQ)	Clinical diagnosis	Adults referred for suspected autism	Negative predictive value	36%	22% to 40%
Derks et al. (2017) (79)	Observational	451	Adults	Social Communication Questionnaire for adults with intellectual disability (SCQ-AID)	Unclear in abstract	Unclear in abstract	Sensitivity	81% to 89%	NR
Derks et al. (2017) (79)	Observational	451	Adults	Social Communication Questionnaire for adults with intellectual disability (SCQ-AID)	Unclear in abstract	Unclear in abstract	Specificity	62% to 72%	NR
Kent et al. (2018) (78)	Observational	NR	Adults	Autism Questionnaire 10 adapted for learning disability (AQ-10-ID)	Unclear in abstract	Unclear in abstract	Sensitivity	85%	NR
Kent et al. (2018) (78)	Observational	NR	Adults	Autism Questionnaire 10 adapted for learning disability (AQ-10-ID)	Unclear in abstract	Unclear in abstract	Specificity	77%	NR

Autism diagnostic assessment

Background

The NICE guideline on diagnosing autism in children and young people assessed the diagnostic accuracy of autism assessment tools. The guideline specified sensitivity and specificity of at least 80% and the lower limit of the 95% CI of at least 70%. The NICE guideline evidence review found the combination of ADI/ADI-R plus autism diagnostic observation schedule (ADOS) was accurate in diagnosing autism in preschool children and in children with a learning disability (full version of NICE guideline CG128, page 110). The 3di tool was accurate for diagnosing autism. However, the NICE guideline committee thought that the benefits of using these tools remained uncertain and believed that reliance on the scores could result in harm from either incorrect diagnosis of autism or false reassurance. The committee recognised that tools could help with systematic information gathering but did not recommend any specific tool. In December 2017 we updated references to DSM-IV to refer to the new DSM-5.

Recommendations therefore include:

- Consider using an autism-specific tool to gather information on developmental and behavioural features, and social and communication skills (CG128-1.5.5).
- Use information from all sources, together with clinical judgement, to diagnose autism based on ICD-10 or DSM-5 criteria (CG128-1.5.10).
  - Also see the section on ICD-11 and DSM-5 in this surveillance review.
- Do not rely on any autism-specific diagnostic tool alone to diagnose autism (CG128-1.5.11).

In 2016 surveillance of the NICE guideline on diagnosing autism in children and young people identified 21 studies of diagnostic tools. However, none of the studies fully met the diagnostic accuracy criteria so an update of the NICE guideline was not recommended.

The NICE guideline on diagnosing and managing autism in adults also looked at evidence for autism assessment tools. A range of tools had sufficient diagnostic accuracy, but no data on reliability and validity and so these were not included in recommendations (full version of NICE guideline CG142, page 131). The tools that had sufficient diagnostic accuracy and adequate data on reliability and validity were recommended. The NICE guideline recommended considering using these tools to aid more complex diagnosis and assessment for adults (CG142-1.2.8):

- the following tools for people who do not have a learning disability:
  - the Adult Asperger Assessment (AAA; includes the Autism Spectrum Quotient [AQ] and the Empathy Quotient [EQ])
  - the Autism Diagnostic Interview – Revised (ADI-R)
  - the Autism Diagnostic Observation Schedule – Generic (ADOS-G)
  - the Asperger Syndrome (and high-functioning autism) Diagnostic Interview (ASDI)
  - the Ritvo Autism Asperger Diagnostic Scale – Revised (RAADS-R)
- the following tools in particular for people with a learning disability:
  - the ADOS-G
  - the ADI-R.

The NICE guideline committee additionally thought that the DISCO tool was useful for 'structuring a more complex assessment of adults with possible autism and in particular identifying their needs for care, even if the absence of good-quality psychometric data precluded their use as a diagnostic tool' (full version of NICE guideline CG142 pages 118, 130 and 135) The ADOS-G, ADI-R and DISCO tools were thus recommended for organising and structuring the process of a more complex assessment (CG142-1.2.9).

In 2016 surveillance of the NICE guideline on diagnosing and managing autism in adults, 3 studies of diagnostic tools for autism were identified, all of which included people with learning disabilities; however, the findings were considered to have no impact on current recommendations.

Evidence and intelligence review

Diagnosing autism in children and young people

We identified 15 studies (see table: diagnosing autism in children and young people) of the following autism diagnostic tools:

- Autism Diagnostic Interview - Revised (ADI-R) (80)
- Autism Diagnostic Observation Schedule - Generic (ADOS) (80)
- Autism mental status exam (AMSE) (81,82)
- Childhood Autism Rating Scale (CARS) (80,83)
- Development and Well-Being Assessment (DAWBA) with and without clinician review of responses (84)
- DSM-5 criteria (85)
- DSM-IV criteria (83)
- Infant-Toddler Social Emotional Assessment (ITSEA) (86)
- International Epidemiology Network Diagnostic Tool for Autism Spectrum Disorder (INDT-ASD) (87)
- Telehealth diagnosis based on Naturalistic Observation Diagnostic Assessment (NODA) (88)

Although some tools (AMSE, DAWBA, and NODA) (80–82,84,88) met the threshold of 80% sensitivity and specificity specified in the NICE guideline, 95% CI data were rarely reported in the abstracts of identified studies, so none of the tools could be judged to have met the criterion of a lower 95% CI limit of at least 70%.

The studies showing the highest diagnostic accuracy tended to have small sample sizes so replication of results is needed for tools such as telehealth diagnosis based on NODA, the AMSE and the DAWBA. Additionally, there was no indication from topic experts that new evidence for diagnostic tools in children and young people was sufficient to overturn the NICE guideline committee's concerns about using a single diagnostic tool as the basis for assessment. Therefore, an update to the guideline on diagnosing autism in children and young people is not currently being proposed.

Many topic experts and patient organisations highlighted that autism may be underdiagnosed in girls and women. The guideline notes that clinicians should be aware that autism may be underdiagnosed in girls (CG128-1.2.5). However, no evidence was identified that looked at the diagnostic accuracy of tools in girls, either compared with boys' scores or of tools adapted for girls. It is unclear how assessment of girls with possible autism would differ from assessment of boys, therefore an update to the guideline is not necessary at this time. Also see the section on autism in girls in this surveillance review.

Diagnosing autism in adults

We identified 2 studies of autism diagnostic tools in adults (see table: tools for diagnosing autism in adults), both of which focused on people with a learning disability. Neither the Music-based Scale for Autism Diagnostics (MUSAD) (89) nor the Diagnostic Behavioral Assessment for autism Spectrum disorders-revised (DiBAS-R) (90) met the threshold of 80% for both sensitivity and extraplolated from the guideline on diagnosing autism in children and young people. Additionally, 95% CI data were not reported in the abstracts of identified studies, so none of the tools could be judged to have met the criterion of a lower 95% CI limit of at least 70%. The NICE guideline on autism in adults only recommends tools as an aid to more complex diagnosis in addition to other sources of information. The new evidence did not clearly show an improvement over the tools already recommended in the guideline (ADOS-G and ADI-R), Therefore, an update to the guideline is not proposed at this time.

Machine learning using diagnostic tool data

Finally, we identified 3 studies of machine learning used in the diagnosis of autism (see table: machine learning using information from tools for diagnosing autism). The diagnostic accuracy of machine learning based on personal characteristics (91) or electronic health records (92) did not meet the diagnostic accuracy criteria specified in the guideline, so an update in this area is not needed. A further study (93) suggested that machine learning could correctly classify whether toddlers had autism based on data from the Modified Checklist for Autism in Toddlers, Revised (M-CHAT-R). However,

this study did not measure the diagnostic accuracy of the M-CHAT-R so cannot inform whether this tool is clinically useful, therefore we do not propose an update in this area.

ICD-11

No new evidence relevant to the ICD-11 was identified; however, topic experts and patient organisations highlighted the need to update the NICE guideline when the ICD-11 comes into effect in January 2022. Topic experts suggested that the terminology in the NICE guideline should also be updated to align with ICD-11. We will track ICD-11 and assess its impact post-adoption.

Surveillance proposal

We propose not to update the sections of the autism guidelines covering the autism diagnostic assessment.

New evidence did not clearly show that any autism diagnostic tool had sufficient diagnostic accuracy to change current recommendations for diagnosis of autism in children, young people, or adults. The NICE guidelines suggest that tools can be useful for structuring assessments, but other information should also be taken into consideration when making a diagnosis of autism.

However, we will consider how to update the references to ICD-11 and consider the effects on the wording of recommendations in line with its planned adoption in January 2022.

Data tables for diagnosing autism

Table: tools for diagnosing autism in children and young people

Text citation	Study type	Number of participants	Number of included studies	Age-group	Test	Gold standard	Comparator population	Measurement	Result	95% CI
Randall et al. (2018) (80)	Cochrane review	634	5	Toddlers	Autism Diagnostic Interview - Revised (ADI-R)	Multidisciplinary assessment	Children with suspected autism	Sensitivity	52%	32% to 71%
Randall et al. (2018) (80)	Cochrane review	634	5	Toddlers	Autism Diagnostic Interview - Revised (ADI-R)	Multidisciplinary assessment	Children with suspected autism	Specificity	84%	61% to 95%
Randall et al. (2018) (80)	Cochrane review	1,625	12	Toddlers	Autism Diagnostic Observation Schedule - Generic (ADOS)	Multidisciplinary assessment	Children with suspected autism	Sensitivity	94%	89% to 97%
Randall et al. (2018) (80)	Cochrane review	1,625	12	Toddlers	Autism Diagnostic Observation Schedule - Generic (ADOS)	Multidisciplinary assessment	Children with suspected autism	Specificity	80%	68% to 88%
Betz et al. (2019) (81)	Observational	108	–	Toddlers	Autism Mental Status Exam (AMSE)	Unclear in abstract	Healthy controls	Sensitivity	81%	NR
Grodberg et al. (2016) (82)	Observational	45	–	Toddlers	Autism mental status exam (AMSE)	Autism Diagnostic Observation Schedule and the Autism Diagnostic Interview-Revised	Unclear in abstract	Sensitivity	94%	NR
Betz et al. (2019) (81)	Observational	108	–	Toddlers	Autism Mental Status Exam (AMSE)	Unclear in abstract	Healthy controls	Specificity	91%	NR

Text citation	Study type	Number of participants	Number of included studies	Age-group	Test	Gold standard	Comparator population	Measurement	Result	95% CI
Grodberg et al. (2016) (82)	Observational	45	–	Toddlers	Autism mental status exam (AMSE)	Autism Diagnostic Observation Schedule and the Autism Diagnostic Interview-Revised	Unclear in abstract	Specificity	100%	NR
Randall et al. (2018) (80)	Cochrane review	641	4	Toddlers	Childhood Autism Rating Scale (CARS)	Multidisciplinary assessment	Children with suspected autism	Sensitivity	80%	61% to 95%
Randall et al. (2018) (80)	Cochrane review	641	4	Toddlers	Childhood Autism Rating Scale (CARS)	Multidisciplinary assessment	Children with suspected autism	Specificity	88%	64% to 96%
Moon et al. (2019) (83)	Systematic review	4433	24	Children	Childhood Autism Rating Scale (CARS)	Unclear in abstract	Unclear in abstract	Sensitivity (threshold of 30)	86%	NR
Moon et al. (2019) (83)	Systematic review	4433	24	Children	Childhood Autism Rating Scale (CARS)	Unclear in abstract	Unclear in abstract	Sensitivity (threshold of 30)	79%	NR
McEwen et al. (2016) (84)	Observational	276	–	Teenagers	Development and Well-Being Assessment (DAWBA)	Clinical diagnosis using ADI-R and autism diagnostic observation schedule (ADOS)	Unclear in abstract	Sensitivity	88%	NR
McEwen et al. (2016) (84)	Observational	276	–	Teenagers	Development and Well-Being Assessment (DAWBA)	Clinical diagnosis using ADI-R and autism diagnostic observation schedule (ADOS)	Unclear in abstract	Specificity	85%	NR

Text citation	Study type	Number of participants	Number of included studies	Age-group	Test	Gold standard	Comparator population	Measurement	Result	95% CI
McEwen et al. (2016) (84)	Observational	276	–	Teenagers	Development and Well-Being Assessment (DAWBA) plus clinician review of responses	Clinical diagnosis using ADI-R and autism diagnostic observation schedule (ADOS)	Unclear in abstract	Correct classification	86%	NR
McEwen et al. (2016) (84)	Observational	276	–	Teenagers	Development and Well-Being Assessment (DAWBA) plus clinician review of responses	Clinical diagnosis using ADI-R and autism diagnostic observation schedule (ADOS)	Unclear in abstract	Sensitivity	86%	NR
McEwen et al. (2016) (84)	Observational	276	–	Teenagers	Development and Well-Being Assessment (DAWBA) plus clinician review of responses	Clinical diagnosis using ADI-R and autism diagnostic observation schedule (ADOS)	Unclear in abstract	Specificity	87%	NR
Wiggins et al. (2019) (85)	Observational	1061	–	Toddlers	DSM-5 criteria	DSM-IV	Other developmental disorder	Sensitivity	90%	NR
Wiggins et al. (2019) (85)	Observational	1061	–	Toddlers	DSM-5 criteria	DSM-IV	Other developmental disorder	Specificity	78%	NR
Moon et al. (2019) (83)	Systematic review	4433	24	Children	DSM-IV criteria	Unclear in abstract	Unclear in abstract	Sensitivity	71%	NR
Moon et al. (2019) (83)	Systematic review	4433	24	Children	DSM-IV criteria	Unclear in abstract	Unclear in abstract	Specificity	75%	NR

Text citation	Study type	Number of participants	Number of included studies	Age-group	Test	Gold standard	Comparator population	Measurement	Result	95% CI
Raza et al. (2019) (86)	Observational	NR	–	Toddlers	Infant-Toddler Social Emotional Assessment (ITSEA)	Clinical diagnosis	Unclear in abstract	Sensitivity	23% to 44%	NR
Raza et al. (2019) (86)	Observational	NR	–	Toddlers	Infant-Toddler Social Emotional Assessment (ITSEA)	Clinical diagnosis	Unclear in abstract	Sensitivity	74% to 89%	NR
Vats et al. (2018) (87)	Observational	118	–	Children	International Epidemiology Network Diagnostic Tool for Autism Spectrum Disorder (INDT-ASD)	Clinical diagnosis based on DSM5	Children with suspected autism	Sensitivity	100%	NR
Vats et al. (2018) (87)	Observational	118	–	Children	International Epidemiology Network Diagnostic Tool for Autism Spectrum Disorder (INDT-ASD)	Clinical diagnosis based on DSM5	Children with suspected autism	Specificity	75%	NR
Smith et al. (2017) (88)	Observational	51	–	Children	Telehealth diagnosis based on Naturalistic Observation Diagnostic Assessment (NODA)	Clinical diagnosis	Children with suspected autism or healthy controls	Sensitivity	85%	NR
Smith et al. (2017) (88)	Observational	51	–	Children	Telehealth diagnosis based on Naturalistic Observation Diagnostic Assessment (NODA)	Clinical diagnosis	Children with suspected autism	Sensitivity	85%	NR

Text citation	Study type	Number of participants	Number of included studies	Age-group	Test	Gold standard	Comparator population	Measurement	Result	95% CI
Smith et al. (2017) (88)	Observational	51	–	Children	Telehealth diagnosis based on Naturalistic Observation Diagnostic Assessment (NODA)	Clinical diagnosis	Children with suspected autism	Specificity	86%	NR
Smith et al. (2017) (88)	Observational	51	–	Children	Telehealth diagnosis based on Naturalistic Observation Diagnostic Assessment (NODA)	Clinical diagnosis	Children with suspected autism or healthy controls	Specificity	94%	NR

Table: tools for diagnosing autism in adults

Text citation	Study type	Number of participants	Number of included studies	Age-group	Test	Gold standard	Comparator population	Measurement	Result	95% CI
Bergmann et al. (2019) (89)	Observational	124	–	Adults	Music-based Scale for Autism Diagnostics (MUSAD)	Clinical diagnosis	Adults with learning disability without autism	Sensitivity	79%	NR
Bergmann et al. (2019) (89)	Observational	124	–	Adults	Music-based Scale for Autism Diagnostics (MUSAD)	Clinical diagnosis	Adults with learning disability without autism	Specificity	74%	NR
Bergmann et al. (2019) (89)	Observational	124	–	Adults	Music-based Scale for Autism Diagnostics (MUSAD)	Clinical diagnosis	Adults with learning disability without autism	Area under the curve	81%	NR

Text citation	Study type	Number of participants	Number of included studies	Age-group	Test	Gold standard	Comparator population	Measurement	Result	95% CI
Heinrich et al. (2018) (90)	Observational	381	–	Adults	Diagnostic behavioral assessment for autism spectrum disorders-revised (DiBAS-R)	Unclear in abstract	Unclear in abstract	Sensitivity (overall sample)	82%	NR
Heinrich et al. (2018) (90)	Observational	381	–	Adults	Diagnostic behavioral assessment for autism spectrum disorders-revised (DiBAS-R) in adults with learning disability	Unclear in abstract	Unclear in abstract	Specificity (overall sample)	67%	NR
Heinrich et al. (2018) (90)	Observational	381	–	Adults	Diagnostic behavioral assessment for autism spectrum disorders-revised (DiBAS-R) in adults with learning disability	Unclear in abstract	Unclear in abstract	Sensitivity (mild-to-moderate learning disability)	79%	NR
Heinrich et al. (2018) (90)	Observational	381	–	Adults	Diagnostic behavioral assessment for autism spectrum disorders-revised (DiBAS-R) in adults with learning disability	Unclear in abstract	Unclear in abstract	Specificity (mild-to-moderate learning disability)	84%	NR
Heinrich et al. (2018) (90)	Observational	381	–	Adults	Diagnostic behavioral assessment for autism spectrum disorders-revised (DiBAS-R) in adults with learning disability	Unclear in abstract	Unclear in abstract	Sensitivity (profound learning disability)	83%	NR
Heinrich et al. (2018) (90)	Observational	381	–	Adults	Diagnostic behavioral assessment for autism spectrum disorders-revised (DiBAS-R) in adults with learning disability	Unclear in abstract	Unclear in abstract	Specificity (profound learning disability)	34%	NR

Table: machine learning using information from tools for diagnosing autism

Text citation	Study type	Number of participants	Number of included studies	Age-group	Test	Gold standard	Comparator population	Measurement	Result	95% CI
Parikh et al. (2019) (91)	Observational	851	–	Unspecified	Machine learning using personal characteristics (age, sex, handedness, IQ – best performing model)	Unclear in abstract	Healthy controls	AUC	65%	NR
Achenie et al. (2019) (93)	Observational	14,995	–	Toddlers	Machine learning based on The Modified Checklist for Autism in Toddlers, Revised (M-CHAT-R) data	Clinical diagnosis	Unclear in abstract	Correct classification using 16 items	99.75%	NR
Achenie et al. (2019) (93)	Observational	14,995	–	Toddlers	Machine learning based on The Modified Checklist for Autism in Toddlers, Revised (M-CHAT-R) data	Clinical diagnosis	Unclear in abstract	Correct classification using 18 items in boys	99.64%	NR
Achenie et al. (2019) (93)	Observational	14,995	–	Toddlers	Machine learning based on The Modified Checklist for Autism in Toddlers, Revised (M-CHAT-R) data	Clinical diagnosis	Unclear in abstract	Correct classification using 18 items	99.72%	NR
Achenie et al. (2019) (93)	Observational	14,995	–	Toddlers	Machine learning based on The Modified Checklist for Autism in Toddlers, Revised (M-CHAT-R) data	Clinical diagnosis	Unclear in abstract	Correct classification using 18 items in girls	99.95%	NR
Leroy et al. (2018) (92)	Observational	50	–	Children	Machine learning using electronic health records (baseline)	Unclear in abstract	Unclear in abstract	Sensitivity	30%	NR
Leroy et al. (2018) (92)	Observational	50	–	Children	Machine learning using electronic health records (baseline)	Unclear in abstract	Unclear in abstract	Specificity	NR	NR
Leroy et al. (2018) (92)	Observational	50	–	Children	Machine learning using electronic health records (rule based)	Unclear in abstract	Unclear in abstract	Sensitivity	43%	NR

Text citation	Study type	Number of participants	Number of included studies	Age-group	Test	Gold standard	Comparator population	Measurement	Result	95% CI
Leroy et al. (2018) (92)	Observational	50	–	Children	Machine learning using electronic health records (rule based)	Unclear in abstract	Unclear in abstract	Specificity	99%	NR

Autism in girls

Background

The NICE guideline on diagnosing autism in children and young people recognises that autism may be underdiagnosed in girls. This was based on the committee's clinical experience, and no evidence specifically on diagnosis in girls was reviewed (see the full version of NICE guideline CG128, page 113). Recommendations do not differ by sex; clinicians should use information from all sources, together with clinical judgement, to diagnose autism based on ICD-10 or DSM- criteria (CG128-1.2.5).

In NICE's 2016 surveillance of the guideline on diagnosing autism in children and young people we identified 3 studies that reported on observed differences in symptoms between girls and boys with autism. The evidence was considered to be broadly consistent with current recommendations so an update to the NICE guideline was not needed.

The NICE guideline on diagnosing and managing autism in adults sought evidence for identifying women with autism. No tools that specifically addressed the needs of women were identified (see the full version of NICE guideline CG142, page 107). The guideline recommends that the 'autism strategy group should develop local care pathways that promote access to services for all adults with autism, including…women' (CG142-1.8.3).

No new evidence for diagnosing autism in women was identified in the 2016 surveillance review of this NICE guideline.

Evidence and intelligence review

Many topic experts and patient organisations highlighted that autism was thought to be under-recognised in girls and women.

We identified a systematic review (94) (n= 13,784,284) that was also highlighted by topic experts. This study indicated that 4.2 boys are diagnosed with autism for each girl diagnosed (95% CI 3.84 to 4.60). In subgroup analysis, 4.56 boys were diagnosed for each girl (95% CI 4.10 to 5.07) in

studies in which participants had a pre-existing diagnosis of autism. However, in studies rated by the authors as high quality, 3.32 boys were diagnosed for each girl (95% CI 2.88 to 3.84) and in population screening studies, 3.25 boys were diagnosed for each girl (95% CI 2.93 to 3.62). These findings support the topic experts' views that girls may be underdiagnosed, however, this study also suggests that high quality diagnostic assessment may reduce the disparity.

We also found an observational study (95) suggesting that compared with boys (n=106), girls with autism (n=24) are less likely to have repetitive and restricted behaviour (OR 0.41, 95% CI 0.18 to 0.92, p=0.03), and are more likely to have emotional and behavioural problems (OR 2.44, 95% CI 1.13 to 5.29, p=0.02). The NICE guideline on diagnosing autism in children and young people recognises that autism may be underdiagnosed in girls (CG128-1.2.5). Additionally, the NICE guideline recommends using information from all sources, together with clinical judgement, to diagnose autism based on ICD-10 or DSM-5 criteria. Therefore, an update is not proposed because the NICE guideline recognises the importance of considering each person's individual signs and symptoms of autism.

Surveillance proposal

We propose not to update the autism guidelines to address autism in girls. Although new evidence suggests that autism is underdiagnosed in girls and women, the new evidence identified did not indicate that different diagnostic criteria are needed, but that high quality diagnostic assessment may reduce the disparity in diagnoses between boys and girls. CG128 research recommendation 1 Training professionals to recognise signs and symptoms of autism acknowledges this issue and we will highlight this to the National Institute for Health Research (NIHR) as an area of potential inequality where research is needed.

Diagnostic stability in toddlers

Background

The NICE guideline on diagnosing autism in children and young people looked for evidence on the stability of autism diagnoses in toddlers. Overall, diagnostic stability was high, with little likelihood of a change from autism to no autism, but a substantial proportion of children under 24 months who did not have a diagnosis of autism at an initial assessment were diagnosed as having autism at a subsequent assessment (see the full version of NICE CG128, page 133).

The NICE guideline recommended that clinicians should 'be aware that in some children and young people there may be uncertainty about the diagnosis of autism, particularly in…children younger than 24 months' (CG128-1.5.12).

In NICE's 2016 surveillance of the guideline on diagnosing autism in children and young people we identified 1 systematic review that assessed the stability of autism diagnosis. This study suggested variability across studies in the proportion of children whose diagnosis changed over time. The findings were thought to be consistent with the recommendation to consider keeping the child or young person under review if there is uncertainty about the diagnosis (CG128-1.6.1).

Evidence and intelligence review

We identified 2 observational studies that assessed the stability of diagnosis of autism in toddlers.

One study (96) found that in toddlers aged 24 to 48 months (n=77), the stability of the autism diagnosis was 88.3%. Behavioural markers at 24 months were associated with a change in diagnosis from autism to no autism: better eye contact, more directed vocalisations, the integration of gaze and directed vocalisations or gestures and higher non-verbal developmental quotient.

The other study (97) found that in toddlers aged 12 to 36 months, the stability of autism diagnosis was 84% (95% CI 80% to 87%). However, only 1.8% of toddlers had a change in diagnosis from autism to typical development. Younger toddlers aged 12 to 13 months had 50% diagnostic stability (95% CI 32% to 69%), which rose to 79% by 14 months and 83% by 16 months. Overall, 23.8% of toddlers assessed did not receive a diagnosis of autism at their first visit but did receive a diagnosis of autism at a later visit.

These studies indicate that diagnoses are fairly stable after 24 months, but in younger children about half of diagnoses of autism may be incorrect, although those children are not likely to be classed as having typical development. These findings are consistent with the guideline's recommendation for clinicians to be aware that the diagnosis of autism can be uncertain, particularly in children younger than 24 months.

Surveillance proposal

We propose not to update the guideline on diagnosing autism in children to address the stability of autism diagnoses in toddlers because the identified evidence is consistent with current recommendations.

Medical investigations in people with autism

Background

The NICE guideline on diagnosis of autism in children and young people assessed evidence for the use of medical investigations including electroencephalogram (EEG), brain imaging, genetic testing, and biochemical tests such as metabolic tests, blood tests and urine tests. Outcomes covered by the NICE guideline were the proportion of abnormal results and the yield of diagnoses of alternative or coexisting conditions.

The NICE guideline recommended:

'Do not routinely perform any medical investigations as part of an autism diagnostic assessment, but consider the following in individual circumstances

and based on physical examination, clinical judgement and the child or young person's profile:

- genetic tests, as recommended by your regional genetics centre, if there are specific dysmorphic features, congenital anomalies and/or evidence of intellectual disability
- electroencephalography if there is suspicion of epilepsy' (CG128-1.7.1).

In 2016, surveillance of the NICE guideline on diagnosing autism in children and young people identified 33 studies of medical investigations. Overall, most of the studies reported on abnormalities related to autism rather than on the yield of diagnoses of coexisting conditions. The 2016 surveillance review concluded that the evidence did not show that any specific medical investigation was useful for diagnosing autism, which was consistent with the current recommendation not to routinely use medical investigations in the autism diagnostic assessment; and an update was therefore not proposed.

The NICE guideline on diagnosis and management of autism in adults did not identify any evidence on biological measures (see the full version of NICE guideline CG142, page 133). Therefore, the NICE guideline recommended: 'Do not use biological tests, genetic tests or neuroimaging for diagnostic purposes routinely as part of a comprehensive assessment' (CG142-1.2.11). No new evidence for biological measures was identified in the 2016 surveillance review of this guideline.

Topic experts generally did not indicate that evidence for medical investigations had moved on substantially since the NICE guidelines were published.

Evidence and intelligence review

Genetic tests

One study (98) assessed a commercial 'medical exome' genetic testing kit. The medical exome is the protein-coding sections of DNA known to be related to disease. It found a diagnostic yield for autism of 4% in a population with autism or other neurodevelopmental disorders in which 54 of 216 people

(25%) in the sample had autism. This finding suggests that this genetic test may not be useful for diagnosing the autism, and an update to the NICE guideline in this area is not needed.

Biomedical tests

We identified 15 studies assessing the usefulness of biochemical tests for diagnosing autism (see table: biochemical tests), including:

- blood tests (99–103)
- cerebrospinal fluid volume (104)
- gut microbiome (measured by faecal microbial metabolites) (105)
- urine tests (106,107)
- micronutrient metabolism (108).

Since none of the studies identified in the NICE guideline reported diagnostic accuracy data for the use of medical tests in diagnosing autism, we applied the thresholds used for screening and assessment tools (80% for both sensitivity and specificity, and a lower 95% CI limit of 70%).

The evidence for biomedical tests met thresholds for sensitivity and specificity in 4 studies (99,103,106,108) but 95% CI were not reported in the abstracts for these studies. Additionally, most biomarkers were investigated in only a single small study, so replication of results in other populations to establish whether these biomarkers are truly common in people with autism and rare in people without autism is necessary before considering an update to the NICE guideline.

Computerised vision analysis

We identified 3 studies (109–111) that assessed computerised measurement of eye movement for diagnosing autism (see table: machine learning in medical investigations). One topic expert suggested that surveillance should consider evidence on eye tracking. In all 3 studies, sensitivity was greater than the threshold of 80%, and specificity was greater than the threshold in 2 of the 3 studies. However, none of the studies reported 95% CI in the abstracts. Therefore, the evidence does not clearly meet all the diagnostic

criteria specified in the NICE guideline on diagnosing autism in children and young people. Taken alongside the small sample size of the 3 studies combined, and the fact that eye movement is only one of many signs and symptoms of autism, an update in this area is not being proposed at this time. We will add computerised vision analysis to the autism issues log in order to flag it as a promising diagnostic tool and to look for studies in this area at the next surveillance timepoint.

Machine learning in medical investigations

We identified 13 studies that used machine learning based on data from medical investigations including:

- DNA methylation assay (112)
- EEG (113)
- folate metabolism (114)
- urinary metabolites (115)
- MRI (116–120)
- genotype (121)
- functional near-infrared spectroscopy (122)

Diagnostic accuracy results met the threshold of 80% sensitivity and specificity in 4 studies, (112–114,122) although 95% CI were rarely reported in the abstracts. Additionally, apart from MRI, only 1 small study was identified for each medical investigation that was coupled with machine learning.

Results for MRI were variable across studies, but one systematic review (119) met the threshold for sensitivity and specificity and may have met the 95% CI threshold for analysis of structural MRI findings. In order to get a more detailed understanding of the study results for structural MRI, we looked at the full text. This systematic review included 3 studies (123–125) of machine learning based on MRI identified in surveillance. The individual results from these studies are not reported in the table on machine learning to avoid double counting.

The systematic review included 11 studies of structural MRI features, 9 studies of fMRI features, 9 studies of behaviour traits, 5 studies of biochemical features, 4 studies of electroencephalogram (EEG) features, and 2 studies of text or voice features.

Studies were included in the meta-analysis if they reported diagnostic data or if the authors of the systematic review could calculate these values. The meta-analysis included 40 studies (n=12,128) which included 53 independent samples from which true positive, false positive, true negative and false negative values were extracted.

The meta-analysis identified substantial heterogeneity, with 12 of the 53 samples having results outside of the 95% predictive region of the summary receiver operating characteristics curve (SROC). Total specificity and sensitivity confidence intervals were very wide (0.55 to 1.00 and 0.56 to 0.99, respectively).

In an attempt to resolve this heterogeneity subgroup analyses were carried out. This found that 12 samples using only structural MRI data as predictors were within the predictive area of the SROC indicating low heterogeneity. The pooled sensitivity of the structural MRI meta-analysis was 83% (95% CI 76% to 89%), specificity was 84% (95% CI 74% to 91%), and the area under the curve (AUC) was 90%. Selecting only samples using structural MRI as a predictor and support vector machine as a classifier (n=6) resolved the heterogeneity further and resulted in pooled sensitivity of 87% (95% CI 78% to 93%), specificity of 87% (95% CI 71% to 95%) and AUC of 92%.

Despite the resolved heterogeneity for samples using structural MRI data as a predictor, the authors of this study reported concerns with the results and quality of the included studies. Firstly, they regarded the confidence intervals for summary sensitivity and specificity as very wide, noting that as a result their ‘clinical usefulness…can be difficult to determine’. Secondly, they reported that in 11 of the 12 samples the populations from which the structural MRI data used to train the machine learning tools was taken were very similar to those used to test them. This may have resulted in those samples having a

high risk of overfitting, compromising their generalisability to different populations and overestimating the results of the meta-analysis.

Machine learning based on structural MRI data appears to be promising, but current evidence has limitations as noted above. Further studies using datasets with independent training and validation samples are needed.

Topic experts did not highlight machine learning as an area of interest and the evidence did not suggest machine learning algorithms had progressed from the research environment to be widely used in clinical practice. Therefore, we propose not to update the NICE guideline in this area at this time.

Surveillance proposal

We propose not to update the sections of the autism guidelines on medical investigations in people with autism. New evidence did not clearly show that any medical investigation or machine learning based on medical investigations had sufficient diagnostic accuracy to overturn current recommendations not to routinely use medical investigations in the autism diagnostic assessment in children, young people, or adults.

Data tables for medical investigations

Table: biochemical tests

Text citation	Study type	Number of participants	Number of included studies	Age-group	Test	Gold standard	Comparator population	Measurement	Result	95% CI
Kelly et al. (2019) (99)	Observational	403	–	Toddlers	Blood (plasma metabolites) plus Ages and Stages Questionnaire	Unclear in abstract	Communication skills 'on schedule'	Sensitivity	89%	NR
Kelly et al. (2019) (99)	Observational	403	–	Toddlers	Blood (plasma metabolites) plus Ages and Stages Questionnaire	Unclear in abstract	Communication skills 'on schedule'	Specificity	85%	NR
Cai et al. (2016) (100)	Observational	153	–	Children	Blood (plasma) C-reactive protein	Childhood Autism Rating Scale Score	Children with learning disability or healthy controls	Area under the curve	64%	55% to 75%
Cai et al. (2016) (100)	Observational	153	–	Children	Blood (plasma) glutamate	Childhood Autism Rating Scale Score	Children with learning disability or healthy controls	Area under the curve	92%	87% to 96%
Cai et al. (2016) (100)	Observational	153	–	Children	Blood (plasma) homocysteine	Childhood Autism Rating Scale Score	Children with learning disability or healthy controls	Area under the curve	72%	64% to 81%
Cirnigliaro et al. (2017) (101)	Observational	104	–	Unspecified	Blood (serum) miR-140-3p	Unclear in abstract	Healthy controls	Area under the curve	70%	NR

Text citation	Study type	Number of participants	Number of included studies	Age-group	Test	Gold standard	Comparator population	Measurement	Result	95% CI
Cirnigliaro et al. (2017) (101)	Observational	104	–	Unspecified	Blood (serum) miR-140-3p	Unclear in abstract	Tourette syndrome	Area under the curve	72%	NR
Cirnigliaro et al. (2017) (101)	Observational	104	–	Unspecified	Blood (serum) miR-140-3p	Unclear in abstract	Tourette syndrome and autism	Area under the curve	78%	NR
Cirnigliaro et al. (2017) (101)	Observational	104	–	Unspecified	Blood (serum) miR-140-3p	Unclear in abstract	Healthy controls	Sensitivity	63%	NR
Cirnigliaro et al. (2017) (101)	Observational	104	–	Unspecified	Blood (serum) miR-140-3p	Unclear in abstract	Tourette syndrome	Sensitivity	67%	NR
Cirnigliaro et al. (2017) (101)	Observational	104	–	Unspecified	Blood (serum) miR-140-3p	Unclear in abstract	Tourette syndrome and autism	Sensitivity	73%	NR
Cirnigliaro et al. (2017) (101)	Observational	104	–	Unspecified	Blood (serum) miR-140-3p	Unclear in abstract	Healthy controls	Specificity	68%	NR
Cirnigliaro et al. (2017) (101)	Observational	104	–	Unspecified	Blood (serum) miR-140-3p	Unclear in abstract	Tourette syndrome	Specificity	71%	NR

Text citation	Study type	Number of participants	Number of included studies	Age-group	Test	Gold standard	Comparator population	Measurement	Result	95% CI
Cirnigliaro et al. (2017) (101)	Observational	104	–	Unspecified	Blood (serum) miR-140-3p	Unclear in abstract	Tourette syndrome and autism	Specificity	76%	NR
Barone et al. (2018) (102)	Observational	162	–	Children	Blood acylcarnitine metabolites	Unclear in abstract	Healthy controls	Sensitivity	72%	71% to 74%
Barone et al. (2018) (102)	Observational	162	–	Children	Blood acylcarnitine metabolites	Unclear in abstract	Healthy controls	Specificity	72%	71% to 73%
Altun et al. (2018) (103)	Observational	100	–	Children	Blood catalase	Unclear in abstract	Healthy controls	Area under the curve	100%	NR
Altun et al. (2018) (103)	Observational	100	–	Children	Blood malondialdehyde	Unclear in abstract	Healthy controls	Area under the curve	94%	NR
Altun et al. (2018) (103)	Observational	100	–	Children	Blood superoxide dismutase	Unclear in abstract	Healthy controls	Area under the curve	100%	NR
Shen et al. (2017) (104)	Observational	343	–	Toddlers	Cerebrospinal fluid volume (extra-axial)	Unclear in abstract	High-risk and low-risk children	Accuracy	69%	NR
Shen et al. (2017) (104)	Observational	343	–	Toddlers	Cerebrospinal fluid volume (extra-axial)	Unclear in abstract	High-risk and low-risk children	Sensitivity	66%	NR
Shen et al. (2017) (104)	Observational	343	–	Toddlers	Cerebrospinal fluid volume (extra-axial)	Unclear in abstract	High-risk and low-risk children	Specificity	68%	NR

Text citation	Study type	Number of participants	Number of included studies	Age-group	Test	Gold standard	Comparator population	Measurement	Result	95% CI
Kang et al. (2018) (105)	Observational	44	–	Children	Faecal microbial metabolites (caprate, nicotinate, glutamine, thymine, aspartate)	Unclear in abstract	Healthy controls	Sensitivity	78%	NR
Kang et al. (2018) (105)	Observational	44	–	Children	Faecal microbial metabolites (caprate, nicotinate, glutamine, thymine, aspartate)	Unclear in abstract	Healthy controls	Specificity	81%	NR
Li et al. (2018) (106)	Observational	NR	–	Children	Urinary free amino acids (valine plus tryptophan)	Unclear in abstract	Healthy controls	Sensitivity	93%	NR
Li et al. (2018) (105)	Observational	NR	–	Children	Urinary free amino acids (valine plus tryptophan)	Unclear in abstract	Healthy controls	Specificity	89%	NR
Xiong et al. (2019) (107)	Observational	102	–	Children	Urinary metabolites (creatinine:creatine ratio)	Unclear in abstract	Healthy controls	Area under the curve	91%	NR
Curtin et al. (2018) (108)	Observational	NR	–	Infants	Zinc-copper cycle measured by tooth-matrix biomarkers	Unclear in abstract	Unclear in abstract	Diagnostic accuracy (at optimum threshold)	90%	NR
Curtin et al. (2018) (108)	Observational	NR	–	Infants	Zinc-copper cycle measured by tooth-matrix biomarkers	Unclear in abstract	Unclear in abstract	Sensitivity (across varied thresholds)	85% to 100%	NR
Curtin et al. (2018) (108)	Observational	NR	–	Infants	Zinc-copper cycle measured by tooth-matrix biomarkers	Unclear in abstract	Unclear in abstract	Specificity (across varied thresholds)	90% to 100%	NR

Table: computerised vision analysis

Text citation	Study type	Number of participants	Number of included studies	Age-group	Test	Gold standard	Comparator population	Measurement	Result	95% CI
Campbell et al. (2019) (109)	Observational	104	–	Toddlers	Computerised vision analysis	Unclear in abstract	Children with learning disability or healthy controls	Sensitivity	96%	NR
Campbell et al. (2019) (109)	Observational	104	–	Toddlers	Computerised vision analysis	Unclear in abstract	Children with learning disability or healthy controls	Specificity	38%	NR
Fujioka et al. (2016) (111)	Observational	61	–	Mixed	Computerised vision analysis	Unclear in abstract	Healthy controls	Sensitivity	81%	NR
Fujioka et al. (2016) (111)	Observational	61	–	Mixed	Computerised vision analysis	Unclear in abstract	Healthy controls	Specificity	80%	NR
Wan et al. (2019) (110)	Observational	74	–	Children	Eye tracking while watching video of woman speaking	Unclear in abstract	Healthy controls	Sensitivity	87%	NR
Wan et al. (2019) (110)	Observational	74	–	Children	Eye tracking while watching video of woman speaking	Unclear in abstract	Healthy controls	Specificity	84%	NR
Wan et al. (2019) (110)	Observational	74	–	Children	Eye tracking while watching video of woman speaking	Unclear in abstract	Healthy controls	Classification accuracy	85%	NR

Table: machine learning in medical investigations

Text citation	Study type	Number of participants	Number of included studies	Age-group	Test	Gold standard	Comparator population	Measurement	Result	95% CI
Bahado-Singh et al. (2019) (112)	Observational	24	–	Infants	Machine learning based on assay of DNA methylation	Unclear in abstract	Healthy controls	Area under the curve	100%	80% to 100%
Bahado-Singh et al. (2019) (112)	Observational	24	–	Infants	Machine learning based on assay of DNA methylation	Unclear in abstract	Healthy controls	Sensitivity	98%	NR
Bahado-Singh et al. (2019) (112)	Observational	24	–	Infants	Machine learning based on assay of DNA methylation	Unclear in abstract	Healthy controls	Specificity	100%	NR
Ghafouri-Fard (2019) (121)	Observational	942	–	Unspecified	Machine learning based on genotype	Unclear in abstract	Healthy controls	Area under the curve	81%	NR
Ghafouri-Fard (2019) (121)	Observational	942	–	Unspecified	Machine learning based on genotype	Unclear in abstract	Healthy controls	Accuracy	74%	NR
Ghafouri-Fard (2019) (121)	Observational	942	–	Unspecified	Machine learning based on genotype	Unclear in abstract	Healthy controls	Sensitivity	83%	NR
Ghafouri-Fard (2019) (121)	Observational	942	–	Unspecified	Machine learning based on genotype	Unclear in abstract	Healthy controls	Specificity	64%	NR
Heunis et al. (2018) (113)	Observational	62	–	Children	Machine learning based on EEG data	Unclear in abstract	Healthy controls	Accuracy	93%	NR
Heunis et al. (2018) (113)	Observational	62	–	Children	Machine learning based on EEG data	Unclear in abstract	Healthy controls	Sensitivity	100%	NR
Heunis et al. (2018) (113)	Observational	62	–	Children	Machine learning based on EEG data	Unclear in abstract	Healthy controls	Specificity	86%	NR

Zou et al. (2019) (114)	Observational	178	–	Unspecified	Machine learning based on folate metabolism measured by serological metabolites and 2 genetic variants	Unclear in abstract	Healthy controls	Area under the curve	91%	NR
Zou et al. (2019) (114)	Observational	178	–	Unspecified	Machine learning based on folate metabolism measured by serological metabolites and 2 genetic variants	Unclear in abstract	Healthy controls	Sensitivity	87%	NR
Zou et al. (2019) (114)	Observational	178	–	Unspecified	Machine learning based on folate metabolism measured by serological metabolites and 2 genetic variants	Unclear in abstract	Healthy controls	Specificity	85%	NR
Chen et al. (2019) (115)	Observational	220	–	Toddlers	Machine learning based on measurements of 20 (best performing) organic acids in urine	Unclear in abstract	Healthy controls	Area under the curve	94%	NR
Chen et al. (2019) (115)	Observational	220	–	Toddlers	Machine learning based on measurements of 76 organic acids in urine	Unclear in abstract	Healthy controls	Area under the curve	93%	NR
Xiao et al. (2019) (116)	Observational	198	–	Children	Machine learning based on MRI data	Unclear in abstract	Unclear in abstract	Accuracy	96%	NR
Wang et al. (2019) (117)	Observational	531	–	Unspecified	Machine learning based on MRI data	Unclear in abstract	Healthy controls	Classification accuracy	91%	NR
Wang et al. (2019) (117)	Observational	531	–	Unspecified	Machine learning based on MRI data	Unclear in abstract	Healthy controls	Sensitivity	91%	NR
Xiao et al. (2019) (116)	Observational	198	–	Children	Machine learning based on MRI data	Unclear in abstract	Unclear in abstract	Sensitivity	98%	NR
Wang et al. (2019) (117)	Observational	531	–	Unspecified	Machine learning based on MRI data	Unclear in abstract	Healthy controls	Specificity	91%	NR
Xiao et al. (2019) (116)	Observational	198	–	Children	Machine learning based on MRI data	Unclear in abstract	Unclear in abstract	Specificity	94%	NR
Katuwal et al. (2016) (118)	Observational	734	–	Unspecified	Machine learning based on MRI data (ABIDE dataset)	Unclear in abstract	Healthy controls	Area under the curve	68%	NR

Katuwal et al. (2016) (118)	Observational	734	–	Unspecified	Machine learning based on MRI data (ABIDE dataset) plus verbal IQ plus age	Unclear in abstract	Healthy controls	Area under the curve	92%	NR
Moon et al. (2019) (119)	Systematic review	1,345	43	Unspecified	Machine learning based on MRI data (functional)	Unclear in abstract	Unclear in abstract	Area under the curve	71%	NR
Moon et al. (2019) (119)	Systematic review	1,345	43	Unspecified	Machine learning based on MRI data (functional)	Unclear in abstract	Unclear in abstract	Sensitivity	69%	62% to 75%
Moon et al. (2019) (119)	Systematic review	1,345	43	Unspecified	Machine learning based on MRI data (functional)	Unclear in abstract	Unclear in abstract	Specificity	66%	61% to 70%
Moon et al. (2019) (119)	Systematic review	1,776	43	Unspecified	Machine learning based on MRI data (structural)	Unclear in abstract	Unclear in abstract	Area under the curve	90%	NR
Moon et al. (2019) (119)	Systematic review	1,776	43	Unspecified	Machine learning based on MRI data (structural)	Unclear in abstract	Unclear in abstract	Sensitivity	83%	76% to 89%
Moon et al. (2019) (119)	Systematic review	1,776	43	Unspecified	Machine learning based on MRI data (structural)	Unclear in abstract	Unclear in abstract	Specificity	84%	74% to 91%
Aghdam et al. (2019) (120)	Observational	NR	–	Children	Machine learning based on MRI data from Autism Brain Imaging Data Exchange I and II (ABIDE I and ABIDE II) datasets	Unclear in abstract	Unclear in abstract	Sensitivity	68%	NR
Aghdam et al. (2019) (120)	Observational	NR	–	Children	Machine learning based on MRI data from Autism Brain Imaging Data Exchange I and II (ABIDE I and ABIDE II) datasets	Unclear in abstract	Unclear in abstract	Specificity	74%	NR
Li et al. (2016) (122)	Observational	47	–	Children	Machine learning using functional near-infrared spectroscopy	Unclear in abstract	Healthy controls	Sensitivity	82%	NR
Li et al. (2016) (122)	Observational	47	–	Children	Machine learning using functional near-infrared spectroscopy	Unclear in abstract	Healthy controls	Specificity	95%	NR

Excess mortality in people with autism

Background

Neither the NICE guideline on diagnosing autism in children and young people (NICE guideline CG128) nor the NICE guideline on diagnosing and managing autism in adults (NICE guideline CG142) covered excess mortality associated with autism. Therefore, consideration of excess mortality would be a new area for the guideline to consider.

In NICE's 2016 surveillance of the guideline on diagnosing autism in children and young people we did not identify any new evidence in this area.

In the NICE's 2016 surveillance review of the guideline on diagnosing and managing autism in adults we identified 2 studies that reported higher death rates in people with autism, including those with learning disabilities or epilepsy. The evidence was thought to support current the recommendation for staff to understand the course of autism and its impact on, and interaction with, other conditions (CG142-1.1.3) and emphasised the need for appropriate monitoring and management of coexisting conditions in adults with autism.

Evidence and intelligence review

We identified one study (126) (n=2,699,307), indicating that people with autism have higher mortality than the general population (OR 2.56, 95% CI 2.38 to 2.76). Topic experts and patient organisations also indicated that excess mortality in people with autism remains a concern. However, improving adherence to NICE guidelines in terms of managing autism and any coexisting conditions is a mechanism to improve mortality outcomes. Therefore, improvements to services driven by the NHS long term plan are expected to deliver these changes.

Surveillance proposal

We propose not to update the autism guidelines to cover excess mortality in people with autism. New evidence on excess mortality in people with autism is

consistent with recommendations that highlight the need for appropriate monitoring and management of autism and any coexisting conditions in people with autism.

Exercise interventions for autism

Background

The guideline on managing autism in under 19s (NICE guideline CG170) does not currently make recommendations about exercise as a specific intervention for the core features such as rigid and repetitive behaviours of autism or behaviour that challenges. During guideline development, a single small trial assessing the effects of kata training exercise on rigid and repetitive behaviours was identified. The guideline committee considered the evidence to be too low quality to base recommendations on. Based on guideline committee consensus, the guideline acknowledged that exercise is important, particularly for managing sleep problems (CG170-1.7.4).

No evidence on exercise interventions was identified in 2016 surveillance of the guideline on managing autism in under 19s.

The guideline on diagnosing and managing autism in adults has no recommendations on exercise interventions, but recommended that health and social care professionals 'offer advice about the beneficial effects of …exercise' (CG142-1.1.9). No studies looking specifically at exercise interventions were identified during guideline development.

No evidence on exercise interventions was identified in 2016 surveillance of the guideline on diagnosing and managing autism in adults.

Evidence and intelligence review

One RCT (127) (n=18) reported that tai chi (18 sessions of 60 minutes), compared with no intervention, improved balance but had no effect on manual agility in children with autism aged 6 to 12 years at 6 months' follow-up. It is uncertain how improvements in balance in children with autism affects the

core features of autism or associated behaviours. Therefore, this small study is unlikely to impact on the guideline on managing autism in under 19s.

A topic expert highlighted a study investigating the effectiveness of an exercise intervention to reduce stress in adults with autism, but the study's abstract did not include enough analytic data and thus could not be included in this review. No other studies of exercise interventions in adults with autism were identified so an update to the guideline on diagnosing and managing autism in adults is not proposed.

We identified an ongoing trial relevant to exercise interventions:

- Can exercises involving movement and the senses improve behaviour and life skills in non-speaking children with severe autism? (ISRCTN67447997).

This study will be monitored and its impact on recommendations assessed when results are published.

Surveillance proposal

We propose to not update recommendations on exercise in the autism guidelines because of a lack of substantial new evidence in this area.

Psychosocial interventions for children with autism

Background

NICE's guideline on managing autism in under 19s (NICE guideline CG170) recommends considering a specific social-communication intervention for the core features of autism in children and young people (CG170-1.3.1). This was based on evidence indicating positive effects of social communications mediated by caregivers, preschool teachers or peers. Some evidence was found for the educational interventions Early Start Denver Model (ESDM), collaborative model for promoting competence and success (COMPASS) and learning experiences an alternative program for preschoolers and parents (LEAP), but the guideline committee were unable to make specific recommendations to use these tools.

During guideline development, a qualitative review of parents and carers highlighted a desire for improved access to music therapy because it had a calming effect on some children. No evidence was found for a treatment effect on social, verbal or non-verbal communication as measured by CARS. However, one study (moderate quality evidence) showed an effect of music therapy on expressive language.

During guideline development, evidence suggested horseback riding improved social reciprocity, communication and behaviour that challenges. The guideline committee concluded it was not possible to draw conclusions about the relative benefit of animal-based interventions as the evidence was noted as being low to very low quality. The guideline thus does not contain any recommendations about animal therapy.

In the 2016 surveillance review of the guideline on managing autism in under 19s:

- evidence on psychosocial interventions was considered to support current recommendations because the interventions targeted and improved core features of autism (joint attention, engagement and reciprocal communication).
- several stakeholders noted controversy around applied behaviour analysis (ABA), because many psychosocial interventions, such as ESDM, use this approach; however, an update to the guideline was not proposed.

Evidence and intelligence review

Applied behavioural analysis

A Health Technology Assessment (128) assessed early intensive (more than 15 hours) applied behaviour analysis-based therapy compared with any other therapy in a systematic review (20 studies) with individual participant data analysis (n=654) and economic evaluation. Outcomes on the Vineland Adaptive Behaviour Scale showed no clear evidence of benefit, although the intervention appeared to improve cognitive function at 1 year and at 2 years. The authors noted that: ‘Autism symptom severity was not measured in most

studies and the results were too limited to be conclusive, with no clear evidence that early intensive applied behaviour analysis-based interventions had any effect.' Data on language, behaviour that challenges, and adverse events were also lacking. The economic analysis suggested that the incremental cost-effectiveness ratio of intensive applied behavioural analysis was £189,122 per quality-adjusted life-year, which would not be considered to be cost effective. The guideline on managing autism in children and young does not include recommendations on applied behavioural analysis and the new evidence suggested that an update in this area is not necessary.

Educational interventions

Two RCTs (129,130) investigated the impact of educational interventions on children's autism-related self-awareness, language skills and behaviour that challenges (see table educational interventions for children and young people).

One small study (130) (n=40) suggested that the ESDM is effective in managing core features of autism and problem behaviours at 3 months' follow-up. However, the small sample size of this study means that it is unlikely to represent a substantial advance in the evidence base, which was considered to be insufficient to make recommendations during guideline development.

One small study (129) (n=48) that was also highlighted by topic experts reported that weekly group sessions over 6 weeks of a psychoeducational group intervention (PEGASUS) improved autism knowledge and self-awareness in high performing children with autism compared with care as usual. However, there was no effect on self-esteem. These results appear promising but may be of limited generalisability because the study included only high performing children with autism. Additionally, the outcomes reported in the abstract are not directly relevant to the core features of autism. Therefore, we do not propose an update in this area.

Social skills group training for children

Five studies (131–135) evaluated interventions to improve social skills (see Table: social skills training for children and young people. These studies had relatively large participant sample sizes compared with other studies of psychosocial interventions identified in this surveillance review. They indicated improvements in:

- socialisation and social responsiveness (131,132,134)
- reciprocal social interaction and parental synchrony (133)
- language development (135)
- improved scores on various subscales of the Aberrant Behaviour Checklist (134).

These findings are consistent with the current recommendation to consider a specific social communication intervention for the core features of autism in children and young people.

Other psychosocial interventions

Overall 3 reports from 2 RCTs (136–138) assessing the effects of music and theatre therapy on children 4 to 12 years with autism (see table other psychosocial interventions for children and young people) showed no effect or inconsistent results:

- Music therapy did not improve ADOS scores or parent-reported social responsiveness (136,138). The report by Bieleninik et al. (2017) (136) has also been covered in an NIHR alert – Specialist-led improvised music therapy did not improve children's symptoms of autism. Therefore, because of a lack of effectiveness an update to the guideline on managing autism in under 19s is not proposed.
- A theatre-based intervention improved trait anxiety but not state anxiety or cortisol levels (137). These inconsistent results mean that an update in this area is not warranted.

One RCT (139) indicated that therapeutic horseback riding reduced irritability but not hyperactivity at 6 months after the intervention. This report was long-

term follow-up of a study identified in 2016 surveillance, which suggested that therapeutic horseback riding improved irritability, hyperactivity, social cognition and social communication (140).

An RCT (141) investigated the use of 'feedback-informed treatment' which systematically incorporates feedback from patients on treatment progress and treatment satisfaction into their treatment. Feedback-informed treatment improved quality of life but not symptom severity. These findings appear to be conflicting, because without an improvement in symptoms, it is unclear how the improvement in quality of life was achieved. Therefore, an update covering this intervention is not proposed.

An RCT (142) (n=71) assessed a wearable digital technology intervention plus applied behavioural analysis therapy compared with applied behavioural analysis therapy alone in children with autism. The digital intervention used Google Glass worn by the child with autism, which linked to a smartphone app. The intervention aimed to promote facial engagement and emotion recognition by detecting facial expressions and providing reinforcing social cues. Families were asked to conduct 20-minute sessions at home 4 times per week for 6 weeks. The digital technology intervention improved socialisation (Vineland Adaptive Behaviors Scale socialization subscale) but the authors noted that 3 other primary measures (not defined in the abstract) were not significantly improved. Therefore, because of inconsistent results, this study does not suggest that an update to the guideline is needed.

Surveillance proposal

We propose not to update recommendations on psychosocial interventions for children for the core features of autism because the evidence was either consistent with current recommendations or did not add sufficiently to the evidence base to warrant an update.

Data tables for psychosocial interventions in children and young people

Table: educational interventions for children and young people

Reference	Study type	Number of participants	Number of included studies	Age	Intervention	Comparator	Outcome	Result
Hong-Hua et al. (2018) (130)	RCT	40	–	2-5 years	Early start Denver model	Usual care	Aberrant Behaviour Checklist social withdrawal subscale	Improvement with intervention
Hong-Hua et al. (2018) (130)	RCT	40	–	2-5 years	Early start Denver model	Usual care	Aberrant Behaviour Checklist hyperactivity subscale	Improvement with intervention
Hong-Hua et al. (2018) (130)	RCT	40	–	2-5 years	Early start Denver model	Usual care	Aberrant Behaviour Checklist mood swings subscale	Improvement with intervention
Hong-Hua et al. (2018) (130)	RCT	40	–	2-5 years	Early start Denver model	Usual care	Childhood Autism Rating Scale (CARS)	Improvement with intervention
Hong-Hua et al. (2018) (130)	RCT	40	–	2-5 years	Early start Denver model	Usual care	Clinician Global Impression severity subscale (CGI-S)	Improvement with intervention
Gordon et al. (2015) (129)	RCT	48	–	9-14 years	Psychoeducation group for autism spectrum understanding and support (PEGASUS)	Usual care	Autism knowledge	Improvement with intervention
Gordon et al. (2015) (129)	RCT	48	–	9-14 years	Psychoeducation group for autism spectrum understanding and support (PEGASUS)	Usual care	Autism self-awareness	Improvement with intervention
Gordon et al. (2015) (129)	RCT	48	–	9-14 years	Psychoeducation group for autism spectrum understanding and support (PEGASUS)	Usual care	Self-reported self-esteem	No effect of intervention
Gordon et al. (2015) (129)	RCT	48	–	9-14 years	Psychoeducation group for autism spectrum understanding and support (PEGASUS)	Usual care	Parental reported self-esteem	No effect of intervention

Table: social skills training for children and young people

Reference	Study type	Number of participants	Number of included studies	Age	Intervention	Comparator	Outcome	Result
Choque et al. (2017) (131)	RCT	296	N/A	8-17 years	Social skills group training (KONTAKT)	Usual care	Parent-reported Social Responsiveness Scale	Improvement with intervention
Freitag et al. (2016) (132)	RCT	228	N/A	8-19 years	Group-based psychotherapy intervention (SOSTA-FRA)	Usual care	Parent-reported social responsiveness	Improvement with intervention
Tachibana et al. (2018) (133)	SR	594	14	<6 years	Individual and group interventions	Control interventions	Parent synchrony	Improvement with intervention
Tachibana et al. (2018) (133)	SR	594	14	<6 years	Individual and group interventions	Control interventions	Reciprocity of social interactions towards others	Improvement with intervention
Wang et al. (2019) (134)	Other	80	N/A	4-6 years	Group sandplay	Individual sandplay	Aberrant Behaviour Checklist social withdrawal subscale	Improvement with intervention
Wang et al. (2019) (134)	Other	80	N/A	4-6 years	Group sandplay	Individual sandplay	Aberrant Behaviour Checklist total score	Improvement with intervention
Wang et al. (2019) (134)	Other	80	N/A	4-6 years	Group sandplay	Individual sandplay	Autism Treatment Evaluation Checklist (ATEC) speech subscale	Improvement with intervention
Wang et al. (2019) (134)	Other	80	N/A	4-6 years	Group sandplay	Individual sandplay	Autism Treatment Evaluation Checklist (ATEC) sociability subscale	Improvement with intervention
Wang et al. (2019) (134)	Other	80	N/A	4-6 years	Group sandplay	Individual sandplay	Autism Treatment Evaluation Checklist (ATEC) sensory and cognitive awareness subscale	Improvement with intervention

Reference	Study type	Number of participants	Number of included studies	Age	Intervention	Comparator	Outcome	Result
Wang et al. (2019) (134)	Other	80	N/A	4-6 years	Group sandplay	Individual sandplay	Autism Treatment Evaluation Checklist (ATEC) total score	Improvement with intervention
Wang et al. (2019) (134)	Other	80	N/A	4-6 years	Group sandplay	Individual sandplay	Eye contact	Improvement with intervention
Wang et al. (2019) (134)	Other	80	N/A	4-6 years	Group sandplay	Individual sandplay	Sand stereotyped arrangement	Improvement with intervention
Parsons et al. (2019) (135)	RCT	71	Children	NR	Play-based pragmatic language intervention	Waitlist group	Pragmatic observational measure (POM-2)	Improvement with intervention

Table: other psychosocial interventions for children and young people

Reference	Study type	Number of participants	Number of included studies	Age	Intervention	Comparator	Outcome	Result
Bieleninik et al. (2017) (136)	RCT	364	N/A	4-7 years	Music therapy plus parent counselling plus other therapy sessions	Parent counselling plus other therapy sessions	Autism diagnostic observation schedule (ADOS)	No effect of intervention
Crawford et al. (2017) (138)	RCT	364	N/A	4-7 years	Music therapy plus enhanced standard care	Enhanced standard care	Parent-rated social responsiveness	No effect of intervention
Corbett et al. (2017) (137)	RCT	30	N/A	8-14 years	Theatre-based intervention	Waitlist for intervention	Trait anxiety	Improvement with intervention
Corbett et al. (2017) (137)	RCT	30	N/A	8-14 years	Theatre-based intervention	Waitlist for intervention	State anxiety	No effect of intervention
Corbett et al. (2017) (137)	RCT	30	N/A	8-14 years	Theatre-based intervention	Waitlist for intervention	Cortisol levels	No effect of intervention

Reference	Study type	Number of participants	Number of included studies	Age	Intervention	Comparator	Outcome	Result
Gabriels et al. (2018) (139)	Other	64	N/A	6-16 years	Therapeutic horseback riding	Non-horse contact active control	Irritability	Improvement with intervention
Gabriels et al. (2018) (139)	Other	64	N/A	6-16 years	Therapeutic horseback riding	Non-horse contact active control	Hyperactivity	No effect of intervention
De Jong et al. (2019) (141)	RCT	166	N/A	6-18 years	Feedback-informed treatment plus usual care	Usual care	Quality of life	Improvement with intervention
De Jong et al. (2019) (141)	RCT	166	N/A	6-18 years	Feedback-informed treatment plus usual care	Usual care	Symptom severity	No effect of intervention

Psychosocial and employment interventions for adults with autism

Background

The guideline on autism in adults (NICE guideline CG142) recommends psychosocial interventions including social learning programmes for the core features of autism (CG142-1.4.1; CG142-1.4.2), training programmes, leisure programmes, anger management interventions, anti-victimisation interventions and individual supported employment programmes for improving life skills (CG142-1.4.4 to CG142-1.4.12). These recommendations were largely based on guideline committee consensus because little evidence was identified for the effectiveness of psychosocial interventions for managing autism in adults.

The 2016 surveillance review of the guideline on autism in adults found 7 pieces of evidence covering psychosocial interventions including cognitive behavioural therapy (CBT), mindfulness-based therapy, behavioural interventions, social robotics, group social skills and recreational activity. The 2016 surveillance review concluded that further research was needed because studies had small samples sizes or because the abstracts did not clearly report that adults had a confirmed diagnosis of autism.

Evidence and intelligence review

We identified 5 studies of psychosocial interventions (see Table: psychosocial interventions for adults with autism).

An RCT (143) found some benefits of cognitive enhancement therapy, compared with active enrichment supportive therapy, on social cognitive improvements at 9 months but these were not sustained at 18 months. However, more people having cognitive enhancement therapy gained successful employment. A cost-effectiveness analysis (144) found that modified CBT was not cost effective compared with usual care. The new evidence does not indicate that CBT is consistently clinically effective or cost effective as such, the section on psychosocial interventions for the core features of autism will not be updated at this time.

An RCT (145) of the PEERS social skills intervention found improvements in knowledge, empathy and social anxiety, but there was no improvement in direct interactions. One study (146) of Treatment & Education of Autistic and Communication Related Handicapped Children (TEACCH) found improvements in functional skills and goal attainment in young adults, but no difference in the TEACH transitional assessment profile. The comparator in this study was not defined in the abstract. The new surveillance evidence shows some benefits of social learning interventions and generally supports the current recommendations to consider a social learning

programme for the core features of autism. Therefore, an update in this area is not necessary at this time.

An RCT (147) evaluated the role of an integrated employment success tool compared with usual care for employers of autistic adults. The trial found an improvement in self-efficacy post intervention, but this was no better than support as usual and there was no effect on attitudes to disability in the workplace compared with support as usual. The new evidence identified through surveillance does not cover all features of a supported employment programme, only support for the employer, which it did not find to be generally effective. The guideline on autism in adults recommends employer support as part of a package of interventions making up an individual supported employment programme. The NHS long term plan (page 117) also notes a planned increase in supported internship opportunities for people with autism. Therefore, an update to NICE guidance in this area is not proposed.

Surveillance proposal

We propose to not update recommendations on drug treatments for children and young people with autism because overall, the evidence base remains consistent with evidence identified during guideline development.

Data tables for psychosocial interventions in adults

Table: psychosocial interventions for adults with autism

Reference	Study type	Number of participants	Number of included studies	Intervention	Comparator	Outcome	Impact of intervention
Doble et al. (2017) (144)	Economic analysis plus RCT	NR	N/A	Modified group CBT	Treatment as usual	Cost-effectiveness	Intervention unlikely to be cost effective
Eack et al. (2018) (143)	RCT	54	N/A	Cognitive enhancement therapy	Active enrichment supportive therapy	Neurocognitive function	Improvement with intervention
Eack et al. (2018) (143)	RCT	54	N/A	Cognitive enhancement therapy	Active enrichment supportive therapy	Social cognitive improvements at 9 months	Improvement with intervention
Eack et al. (2018) (143)	RCT	54	N/A	Cognitive enhancement therapy	Active enrichment supportive therapy	Social cognitive improvements 18 months	No effect of intervention
Eack et al. (2018) (143)	RCT	54	N/A	Cognitive enhancement therapy	Active enrichment supportive therapy	Gain competitive employment	Improvement with intervention
Siu et al. (2019) (146)	Experimental design	63	N/A	Treatment & Education of Autistic and Communication Related Handicapped Children (TEACCH)	Not defined	Improvements in functional skills	Improvement with intervention
Siu et al. (2019) (146)	Experimental design	63	N/A	Treatment & Education of Autistic and Communication Related Handicapped Children (TEACCH)	Not defined	Goal attainment scaling scores	Improvement with intervention
Siu et al. (2019) (146)	Experimental design	63	N/A	Treatment & Education of Autistic and Communication Related Handicapped Children (TEACCH)	Not defined	TEACCH Transitional Assessment Profile	No effect of intervention
McVey et al. (2016) (145)	RCT	56	N/A	PEERS for Young Adults Social Skills Intervention	Not reported	Social responsiveness	Improvement with intervention
McVey et al. (2016) (145)	RCT	56	N/A	PEERS for Young Adults Social Skills Intervention	Not reported	PEERS knowledge	Improvement with intervention

Reference	Study type	Number of participants	Number of included studies	Intervention	Comparator	Outcome	Impact of intervention
McVey et al. (2016) (145)	RCT	56	N/A	PEERS for Young Adults Social Skills Intervention	Not reported	Empathy	Improvement with intervention
McVey et al. (2016) (145)	RCT	56	N/A	PEERS for Young Adults Social Skills Intervention	Not reported	Social anxiety	Improvement with intervention
McVey et al. (2016) (145)	RCT	56	N/A	PEERS for Young Adults Social Skills Intervention	Not reported	Direct interactions	No effect of intervention
Scott et al. (2018) (147)	RCT	84	N/A	Integrated Employment Success Tool	Support as usual	Self-efficacy, intervention versus control	No effect of intervention
Scott et al. (2018) (147)	RCT	84	N/A	Integrated Employment Success Tool	Support as usual	Attitude towards disability in the workplace	No effect of intervention

Drug treatments for children and young people with autism

Background

The guideline on managing autism in under 19s (NICE guideline CG170) states 'do not use antipsychotics, antidepressants or anticonvulsants for the management of core features of autism in children and young people' (CG170-1.3.2). This was in response to evidence of side effects for the SSRI citalopram and antipsychotics, and limited evidence of effects of these drugs on the core features of autism identified during guideline development.

For behaviour that challenges, antipsychotic medication may be considered when other interventions are insufficient or not deliverable because of behaviour severity (CG170-1.4.10). The guideline also advises about approaches to dosage, monitoring, side effects and transfer of prescribing from specialist to primary care services (CG170-1.4.11 to CG170-1.4.13).

During guideline development, low-to-moderate quality evidence for positive effects on behaviour that challenges was found for risperidone and aripiprazole from 6 trials. The guideline committee considered that, for behaviour that challenges, the benefits outweighed the adverse effects. The guideline committee also considered recommendations on the use of these drugs in other NICE guidelines such as psychosis and schizophrenia in children and young people (NICE guideline CG155) and schizophrenia in adults (NICE guideline CG178). The guideline committee concluded that recommending any specific antipsychotic was not appropriate, noting that the choice of antipsychotic medication should be influenced by considering the side-effect profile, patient's preference, history of taking the drug and cost.

In 2016 surveillance of managing autism in children and young people, new evidence on drug treatments including antidepressants and antipsychotics was identified. Studies were generally small, and often reported on combined interventions so the effects of a particular drug were not always clear. Overall, the evidence was considered to have no impact on the recommendations.

Evidence and intelligence review

Anxiolytics

We identified one study (148) of the anxiolytic drug buspirone (see table: antidepressants and anxiolytics in children and young people with autism).

Buspirone showed no overall effect on the Autism Diagnostic Observation Schedule (ADOS) score in children aged 2 to 6 years. However, inconsistent results were seen for the restricted and repetitive behaviour component of ADOS, with buspirone 2.5 mg showing an improvement but a 5 mg dose showing no effect.

Buspirone is licensed for the treatment of anxiety in children and its use is off-label in the evidence described. The BNF for children and the electronic medicine compendium notes that the efficacy and safety of buspirone has not been determined in children. Current guidance on treating autism in children and young people (NICE guideline CG170), has no recommendations on buspirone for treating autism. Because of the inconsistent effects seen in the new evidence there is no impact on current guidance.

Antidepressants

We identified one study (149) of the antidepressant fluoxetine (see table: antidepressants and anxiolytics in children and young people with autism).

Fluoxetine improved obsessive-compulsive behaviour measured with Children's Yale Brown obsessive-compulsive scale (CYBOCS) in children with autism aged 7.5 to 18 years. However, participants may not have met diagnostic criteria for obsessive-compulsive disorder because the inclusion criterion was a score of at least 6 on a 40-point scale.

Fluoxetine is licensed in the UK for treating obsessive-compulsive disorder but not for treating autism. NICE's guideline on obsessive-compulsive disorder and body dysmorphic disorder (NICE guideline CG31) recommends that SSRIs (such as fluoxetine) should be used with caution in children and young people (section 1.5.5: poor response to initial treatment in children and young

people). The guideline on treating autism in children and young people cross-refers to the guideline on obsessive-compulsive disorder (CG170-1.7.1). This guideline recommends that antidepressants should not be used for managing the core features of autism because during guideline development no evidence for effectiveness was identified, but evidence did indicate harmful effects of citalopram.

The new evidence has no impact on current guidance because its population may not have had clinically important obsessive or compulsive behaviour, and the abstract did not report on core features of autism.

Stimulants

We identified 3 studies of stimulants; 2 of these studies (150–152) are in the table antidepressants and anxiolytics in children and young people with autism. The third study (151) had a different analytical approach, and so did not fit with the other studies in the table and is described narratively.

One systematic review (150) of the stimulant atomoxetine indicated improvements in hyperactivity and inattention, but adverse effects on appetite, sleep and nausea and vomiting. The abstract did not report whether participants had autism plus diagnosed ADHD or whether atomoxetine was studied for treating the core features of autism.

We also identified a follow-up study of atomoxetine (151). The original study (153) was included in 2016 surveillance. This study assessed atomoxetine with or without parent training in children with autism plus ADHD (n=128). Improvements in parent-rated ADHD and non-compliance observed after the original 34-week trial reduced somewhat over the 10-month follow-up study but remained significantly higher than at baseline. The effects seem to have been driven by atomoxetine because the parental training did not have a significant effect on outcomes at the end of follow-up.

A Cochrane review (152) (4 RCTs) of the effects of high doses (0.43 to 0.60 mg/kg) of the stimulant methylphenidate in children aged 5 to 13 years reported improvement for teacher-rated and parent-rated hyperactivity and

teacher-rated inattention on the Aberrant Behaviour Checklist but no effect on core features of autism or stereotypy compared with placebo. The study also reported reduced appetite with methylphenidate.

Atomoxetine and methylphenidate are licensed for the treatment of ADHD in children aged 6 years and older but are not licensed for treating autism. The NICE guideline on attention deficit hyperactivity disorder recommends methylphenidate as the first-line option for treating ADHD in children older than 5 years (NG87-1.7.7) and atomoxetine is an option if children have not responded to or cannot tolerate initial treatment options (NG87-1.7.10). The guideline on treating autism in children and young people (NICE guideline CG170) cross-refers to the guideline on ADHD. The new evidence appears to be consistent with current guidance recommending methylphenidate and atomoxetine as options for treating ADHD, including in children with autism, but does not clearly show whether atomoxetine affects core features of autism, therefore an update to current guidance is not necessary.

Antipsychotics

Seven studies reported on the effects of antipsychotic drugs in children with autism.

A systematic review and network meta-analysis (154) (8 studies; n=878) indicated that risperidone and aripiprazole each significantly reduced Aberrant Behaviour Checklist irritability scores compared with placebo in children with autism, whereas lurasidone showed no effect.

A systematic review (155) pooling RCT data (n=408) found that aripiprazole increased mean change in Aberrant Behaviour Checklist score for irritability, hyperactivity or non-compliance, inappropriate speech and stereotypic behaviour compared with placebo. Scores for lethargy or social withdrawal did not differ from placebo.

An RCT(156) compared risperidone with aripiprazole in children aged 6 to 17 years (n=61). Aberrant Behaviour Checklist irritability score reduction at 22 weeks' follow-up was greater with risperidone. Mean weight gain in the

aripiprazole group was significantly less than that in the risperidone group at week 4 but at 22 weeks both groups showed similar weight gain.

Four studies investigated the effect of risperidone on the rate of adverse events.

- One study (157) reported increased weight gain, waist circumference and BMI in 97 children with autism and serious behavioural problems (mean age 6.9 years) exposed to risperidone for about 24 weeks.
- One study (158) reported increased levels of hyperuricaemia in children (n=127; age not specified in abstract) using risperidone compared with risperidone-naïve controls. This was particularly pronounced in adolescents and with longer risperidone exposure.
- One study (159) reported no difference in QT interval between risperidone and placebo in children (age not specified abstract).
- A systematic review (160) (40 RCTs, 14 observational studies) indicated that adverse events were higher with antipsychotics compared with placebo. The most commonly reported adverse events were increased appetite and weight gain.

We additionally identified several small studies reporting on treatments used in combination with antipsychotics in children with autism.

- One RCT (161) (n=64) reported a larger reduction in hyperactivity measured by the Antecedent, Behaviour, Consequence scale with risperidone plus baclofen compared with risperidone plus placebo at 10 weeks' follow-up in children aged 3 to 12 years.
- Risperidone plus simvastatin improved irritability and hyperactivity/non-compliance on the Aberrant Behaviour Checklist scale more than risperidone plus placebo at 10 weeks' follow-up in children aged 4 to 12 years in one RCT (n=70) (162).
- In children on risperidone, minocycline improved the Aberrant Behaviour Checklist irritability and hyperactivity subscales (n=46) compared with placebo at 10 weeks' follow-up. No effects were seen on lethargy/social

withdrawal, stereotypy or inappropriate speech. No adverse effects were observed (163).

- Palmitoylethanolamide plus risperidone improved the hyperactivity/non-compliance and irritability subscales of the Aberrant Behaviour Checklist in children aged 4 to 12 years (n=70) compared with placebo plus risperidone at 10 weeks' follow-up (164). Palmitoylethanolamide is not licensed in the UK.
- In an RCT (165) (n=70), in children taking risperidone, carnosine improved hyperactivity or non-complicance measured by the Aberrant Behaviour Checklist but had no effect on lethargy or social withdrawal, stereotypy, or inappropriate speech.

No antipsychotic drug is licensed in the UK for managing behaviour that challenges in children and young people with autism. Risperidone is licensed for the short-term symptomatic treatment (up to 6 weeks) of persistent aggression in conduct disorder in children from the age of 5 years and adolescents with subaverage intellectual functioning or mental retardation. Risperidone is therefore potentially licensed for use with some groups of children with autism.

The guideline on managing autism in children and young people (NICE guideline CG170) recommends that antipsychotics should not be used for treating core features of autism because of limited evidence of effectiveness and robust data on potential harms identified during guideline development (CG170-1.3.2).

An antipsychotic may be considered for managing behaviour that challenges in children and young people with autism when psychosocial or other interventions are insufficient or could not be delivered because of the severity of the behaviour (CG170-1.4.10). This is supported by further recommendations on monitoring effectiveness and side-effects (CG170-1.4.10 to CG170-1.4.13).

New evidence identified through surveillance suggests positive effects for antipsychotics on potentially challenging behaviours, particularly irritability and

therefore supports current guideline recommendations. However, studies looking at antipsychotics in combination with other treatments showed inconsistent results and had small sample sizes. The new evidence was consistent with previous findings of adverse effects associated with antipsychotics.

It was not clear from the abstracts of included studies whether the children in these studies met the criteria for considering antipsychotics as described in NICE guidance. Therefore, further evidence in this area will be needed before an update to the guideline can be considered.

Memantine

An RCT (166) reported that memantine 5 mg per day plus ABA improved the symptoms of autism on the Gilliam autism scale of children <14 years old (n=60) compared with ABA only at 3 months' follow-up. See table: other drug treatments in children and young people with autism. The guideline on managing autism in children and young people (NICE guideline CG170) does not contain recommendations about memantine, a drug currently licensed in the UK for treating Alzheimer's disease but not for managing autism. No evidence for the effectiveness of memantine in children was identified during guideline development or during 2016 surveillance. Memantine is also associated with side effects and further evidence of its benefit and potential harms is required before an assessment of impact on recommendations can be made.

Cycloserine

In one study (167), weekly social skills group training plus cycloserine (50 mg weekly, administered 30 mins prior to session) with children was no more effective than weekly social skills training alone in children with autism. See table: other drug treatments in children and young people with autism. Cycloserine is not licensed in the UK for treating autism and is not mentioned in current recommendations in the guideline on managing autism in children and young people (NICE guideline CG170). The new evidence did not

suggest that it would be an effective treatment. New evidence is currently unlikely to impact recommendations.

Guanfacine

In one RCT (168) (n=62), guanfacine improved oppositional behaviour and repetitive behaviour compared with placebo in children aged 5 to 14 years at 8 weeks' follow-up but had no effect on anxiety or sleep. See table: other drug treatments in children and young people with autism. This report was of secondary outcomes from a trial identified in the 2016 surveillance review (169) that included children with autism and 'hyperactivity, impulsiveness, and distractibility'.

Currently the guideline on managing autism in children and young people (NICE guideline CG170) does not provide advice on guanfacine, a non-stimulant treatment licensed in the UK for treating ADHD in children. Guanfacine is not licensed for the treatment of autism in the UK, but is recommended as a treatment option in the guideline on attention deficit hyperactivity disorder (NICE guideline NG87), which is cross-referred to by the guideline on managing autism in children and young people (NICE guideline CG170).

The inclusion of children with autism and symptoms of ADHD rather than a diagnosis of coexisting ADHD means that determining an impact on current recommendations is difficult. It is possible that the participants may have met criteria for diagnosis of ADHD, which would mean that the results are consistent with current guidance. Further evidence is necessary to determine whether guanfacine would be effective in children with autism without a diagnosis of coexisting ADHD, meaning there is no impact on current guidance at this time.

Gastrin-releasing peptide

In one small study (170), gastrin-releasing peptide 160 pmol per kg administered over 4 consecutive days to boys aged 4-9 years (n=10) has no effect on hyperactivity/non-compliance (Aberrant Behaviour Checklist

subscale) compared with placebo. See table: other drug treatments in children and young people with autism.

The guideline on managing autism in children and young people (NICE guideline CG170) does not make any recommendations about gastrin-releasing peptide because no evidence for its effectiveness was identified during development or previous surveillance. Gastrin-releasing peptide is not licensed in the UK and this new evidence suggests it is not effective in autism. Therefore no update in this area is needed.

Specialist psychiatric pharmacist intervention

One RCT (171) (n=25) investigated the impact of a psychiatry pharmacist on identifying and resolving drug-related problems in children with autism and disruptive behaviour (aged 2.5 to 12 years). The intervention increased the number of patients who resolved at least one drug-related problem and irritability at 8 weeks' follow-up compared with a hospital pharmacist. Inappropriate drug selection, medication non-adherence and subtherapeutic dosage were the most common problems identified in the study.

The guideline on managing autism spectrum disorder in under 19s recommends that antipsychotic drug prescriptions for behaviour that challenges should initially be prescribed by a paediatrician or psychiatrist and the benefits and any adverse events monitored (CG170-1.4.10). The activities performed by the psychiatry pharmacist included selecting the antipsychotic drug, adjusting dosage based on response and providing individualised drug counselling, which represent good practice and are broadly consistent with the recommendations on drug treatment for behaviour that challenges (CG170-1.4.10 to CG170-1.4.13).

Although the guideline does not make specific recommendations about management by pharmacists it does not rule this out. New evidence suggests a positive impact for a specialist pharmacist in a hospital setting, but the certainty of the study result is limited by its sample size. Further larger scale research in this setting, and how this approach would translate to a

community setting, is required before an assessment of impact can be made. New evidence is unlikely to impact on recommendations.

Other intelligence on drug treatments for children and young people with autism

Topic experts and patients' groups expressed concern that drug treatments continue to be inappropriately used in children and young people with autism despite current guidance, which sets criteria for appropriate use. NHS England has established the Supporting Treatment and Appropriate Medication in Paediatrics (STAMP) initiative.

The issue of over medication is acknowledged in the NHS's Long-term plan. Paragraph 3.31 of the plan states: "We will expand the Stopping over medication of people with a learning disability, autism or both and Supporting Treatment and Appropriate Medication in Paediatrics (STOMP-STAMP) programmes to stop the overmedication of people with a learning disability, autism or both."

We consider the STAMP initiative to support current recommendations on drug treatments for autism and has potential to increase the implementation of the guideline on managing autism in children and young people, therefore an update to the guideline is not necessary.

Surveillance proposal

We propose to not update recommendations on drug treatments for children and young people with autism because overall, the evidence base remains consistent with evidence identified during guideline development.

Data tables for drug treatments for children and young people with autism

Table: antidepressants, anxiolytics or stimulants in children and young people with autism

Reference	Study type	Number of participants	Number of included studies	Age	Intervention	Comparator	Outcome	Impact of intervention
Chugani et al. (2016) (148)	RCT	166	NA	2-6 years	2.5 mg Buspirone twice daily	Placebo twice daily	ADOS composite total score	No effect of intervention
Chugani et al. (2016) (148)	RCT	166	NA	2-6 years	5 mg Buspirone twice daily	Placebo twice daily	ADOS composite total score	No effect of intervention
Chugani et al. (2016) (148)	RCT	166	NA	2-6 years	2.5 mg Buspirone twice daily	Placebo twice daily	ADOS restricted and repetitive behaviour score	Improvement with intervention
Chugani et al. (2016) (148)	RCT	166	NA	2-6 years	5 mg Buspirone twice daily	Placebo twice daily	ADOS restricted and repetitive behaviour score	No effect of intervention
Reddihough et al. (2019) (149)	RCT	146	NA	7.5-18 years	Fluoxetine	Placebo	Children's Yale Brown Obsessive-Compulsive Scale (CYBOCS)	Improvement with intervention
Patra et al. (2019) (150)	SR	241	3	NR	Atomoxetine	Placebo	Parent-rated hyperactivity	Improvement with intervention
Patra et al. (2019) (150)	SR	241	3	NR	Atomoxetine	Placebo	Parent-rated inattention	Improvement with intervention
Patra et al. (2019) (150)	SR	241	3	NR	Atomoxetine	Placebo	Adverse effect - nausea and vomiting	Worse with intervention
Patra et al. (2019) (150)	SR	241	3	NR	Atomoxetine	Placebo	Adverse effect - decreased sleep	Worse with intervention
Patra et al. (2019) (150)	SR	241	3	NR	Atomoxetine	Placebo	Adverse effect - appetite	Worse with intervention

Reference	Study type	Number of participants	Number of included studies	Age	Intervention	Comparator	Outcome	Impact of intervention
Sturman et al. (2017) (152)	SR	113	4	5-13 years	Methylphenidate	Placebo	Aberrant Behaviour Checklist hyperactivity subscale rated by teachers and parents	Improvement with intervention
Sturman et al. (2017) (152)	SR	113	4	5-13 years	Methylphenidate	Placebo	Teacher-rated inattention	Improvement with intervention
Sturman et al. (2017) (152)	SR	113	4	5-13 years	Methylphenidate	Placebo	Core features of autism	No effect of intervention
Sturman et al. (2017) (152)	SR	113	4	5-13 years	Methylphenidate	Placebo	Stereotypy	No effect of intervention
Sturman et al. (2017) (152)	SR	113	4	5-13 years	Methylphenidate	Placebo	Adverse effect- reduced appetite (parent-rated)	Worse with intervention

Table: antipsychotics in children and young people with autism

Reference	Study type	Number of participants	Number of included studies	Age	Intervention	Comparator	Outcome	Impact of intervention
Alfageh et al. (2019) (160)	SR	NR	54	NR	Antipsychotics	Various	Adverse events (relative risk)	Worse with intervention
Alfageh et al. (2019) (160)	SR	NR	54	NR	Antipsychotics	Various	Adverse events (prevalence)	Worse with intervention
De Vane et al. (2019) (156)	RCT	61	NA	6-17 years	Risperidone	Aripriprazole	Aberrant Behaviour Checklist irritability subscale	Improvement with intervention
De Vane et al. (2019) (156)	RCT	61	NA	6-17 years	Risperidone	Aripriprazole	Mean weight gain (week 4)	Worse with intervention

De Vane et al. (2019) (156)	RCT	61	NA	6-17 years	Risperidone	Aripriprazole	Mean weight gain (week 22 week)	No effect of intervention
Fallah et al. (2019) (154)	SR	878	8	NR	Risperidone	Placebo	Aberrant Behaviour Checklist irritability subscale	Improvement with intervention
Scahill et al. (2016) (157)	RCT	124	NA	NR	Risperidone	Risperidone plus parent training	Weight gain	Worse with intervention
Scahill et al. (2016) (157)	RCT	124	NA	NR	Risperidone	Risperidone plus parent training	Waist circumference increase	Worse with intervention
Scahill et al. (2016) (157)	RCT	124	NA	NR	Risperidone	Risperidone plus parent training	Increase in BMI	Worse with intervention
Scahill et al. (2016) (157)	RCT	124	NA	NR	Risperidone	Risperidone plus parent training	Increase in biochemical indices	Worse with intervention
Vanwong et al. (2017) (158)	RCT	127	NA	NR	Risperidone	Age matched controls with no risperidone use	Hyperuricemia	Worse with intervention
Vo et al. (2016) (159)	RCT	101	NA	5-17 years	Risperidone	Placebo	Mean change in QTc interval	No effect of intervention
Fallah et al. (2019) (154)	SR	878	8	NR	Aripriprazole	Placebo	Aberrant Behaviour Checklist irritability subscale	Improvement with intervention
Maneeton et al. (2018) (155)	SR	408	NR	NR	Aripriprazole	Placebo	Aberrant Behaviour checklist irritability subscale	Improvement with intervention
Maneeton et al. (2018) (155)	SR	408	NR	NR	Aripriprazole	Placebo	Aberrant Behaviour Checklist hyperactivity/non-compliance irritability subscale	Improvement with intervention
Maneeton et al. (2018) (155)	SR	408	NR	NR	Aripriprazole	Placebo	Aberrant Behaviour Checklist inappropriate speech subscale	Improvement with intervention

Maneeton et al. (2018) (155)	SR	408	NR	NR	Aripriprazole	Placebo	Aberrant Behaviour Checklist stereotypical behaviour subscale	Improvement with intervention
Maneeton et al. (2018) (155)	SR	408	NR	NR	Aripriprazole	Placebo	Aberrant Behaviour Checklist lethargy/social withdrawal subscale	No effect of intervention
Fallah et al. (2019) (154)	SR	878	8	NR	Lurasidone	Placebo	Aberrant Behaviour Checklist irritability subscale	No effect of intervention
Mahdavinasab et al. (2019) (161)	RCT	64	NA	3-12 years	Baclofen plus risperidone	Placebo plus risperidone	Antecedent, behaviour, consequence hyperactivity subscale (week 10)	Improvement with intervention
Mahdavinasab et al. (2019) (161)	RCT	64	NA	3-12 years	Baclofen plus risperidone	Placebo plus risperidone	Antecedent, behaviour, consequence hyperactivity subscale (week 5)	No effect of intervention
Ghaleiha et al. (2016) (163)	RCT	46	NA	NR	Minocycline twice daily plus risperidone	Placebo plus risperidone titrated to body weight	Aberrant Behaviour Checklist irritability subscale	Improvement with intervention
Ghaleiha et al. (2016) (163)	RCT	46	NA	NR	Minocycline twice daily plus risperidone	Placebo plus risperidone titrated to body weight	Aberrant Behaviour Checklist hyperactivity/non-compliance subscale	Improvement with intervention
Ghaleiha et al. (2016) (163)	RCT	46	NA	NR	Minocycline twice daily plus risperidone	Placebo plus risperidone titrated to body weight	Aberrant Behaviour Checklist lethargy/social withdrawal subscale	No effect of intervention
Ghaleiha et al. (2016) (163)	RCT	46	NA	NR	Minocycline twice daily plus risperidone	Placebo plus risperidone titrated to body weight	Aberrant Behaviour Checklist stereotypy subscale	No effect of intervention
Ghaleiha et al. (2016) (163)	RCT	46	NA	NR	Minocycline twice daily plus risperidone	Placebo plus risperidone titrated to body weight	Aberrant Behaviour Checklist inappropriate speech subscale	No effect of intervention

Ghaleiha et al. (2016) (163)	RCT	46	NA	NR	Minocycline twice daily plus risperidone	Placebo plus risperidone titrated to body weight	Adverse events	No effect of intervention
Moazen-Zadeh et al. (2018) (162)	RCT	70	NA	4-12 years	Simvastatin plus risperidone	Placebo plus risperidone	Aberrant Behaviour Checklist community scale irritability subscale	Improvement with intervention
Moazen-Zadeh et al. (2018) (162)	RCT	70	NA	4-12 years	Simvastatin plus risperidone	Placebo plus risperidone	Hyperactivity/non-compliance	Improvement with intervention
Khalaj et al. (2018) (164)	RCT	70	NA	4-12 years	Palmitoylethanolamide plus risperidone	Placebo plus risperidone	Aberrant Behaviour Checklist irritability	Improvement with intervention
Khalaj et al. (2018) (164)	RCT	70	NA	4-12 years	Palmitoylethanolamide plus risperidone	Placebo plus risperidone	Aberrant Behaviour Checklist hyperactivity/non-compliance	Improvement with intervention

Table: other drug treatments in children and young people with autism

Reference	Study type	Number of participants	Number of included studies	Age	Intervention	Comparator	Outcome	Impact of intervention
Karahmadi et al. (2018) (166)	RCT	60	NA	<14 years	Memantine plus applied behaviour analysis	Placebo plus applied behavioural analysis	Gilliam autism rating scale	Improvement with intervention
Minshawi et al. (2016) (166)	RCT	NR	NA	NR	Cycloserine plus weekly group social training	Placebo plus weekly group social training	Social responsiveness scale (SRS)	No effect of intervention
Politte et al. (2018) (168)	RCT	62	NA	5-14 years	Guanfacine	Placebo	Parent rating of oppositional behaviour on HSQ	Improvement with intervention

Politte et al. (2018) (168)	RCT	62	NA	5-14 years	Guanfacine	Placebo	Repetitive behaviour in the CYBOCS-ASD scale	Improvement with intervention
Politte et al. (2018) (168)	RCT	62	NA	5-14 years	Guanfacine	Placebo	CASI anxiety	No effect of intervention
Politte et al. (2018) (168)	RCT	62	NA	5-14 years	Guanfacine	Placebo	CSHQ	No effect of intervention
Wang et al. (2019) (172)	SR	520	16	NR	Oxytocin	Placebo	Social function	No effect of intervention
Wang et al. (2019) (172)	SR	520	16	NR	Oxytocin	Placebo	Repetitive behaviours	No effect of intervention
Marchezan et al. (2017) (170)	RCT	10	NA	4-9 years	Gastrin-releasing peptide	Placebo	Aberrant Behaviour Checklist - Hyperactivity/non-compliance	No effect of intervention

Drug treatments for adults with autism

Background

The guideline on autism in adults (NICE guideline CG142) recommends antipsychotic medications for challenging behaviour, but not routinely for treating core features of autism (CG142-1.5.8; CG142-1.5.9). This was based on the results of 3 RCTs in people with autism and results extrapolated from 9 RCTs in people with learning disabilities. Positive effects for antipsychotics were seen for behaviour that challenges rather than the core features of autism. The guideline committee assessed the evidence as limited and did not think it appropriate to recommend a specific antipsychotic. They concluded that antipsychotics should be used in conjunction with other treatments and that treatment should not be continued past 6 weeks.

No evidence for drug treatments relating to the treatment of challenging behaviour in adults was identified in 2016 surveillance of the guideline on autism in adults.

CG142 makes several 'do not do' recommendations (CG142-1.4.13 to CG142-1.4.22) for several drug treatments for the core features of autism including: anticonvulsants, drugs to improve cognitive functioning, oxytocin, secretin, antipsychotics and antidepressants. This was based on a lack of evidence for their effectiveness balanced with their known side effects.

Evidence for SSRIs, D-cycloserine, opioid antagonists, acetylcholinesterase inhibitors, oxytocin and mavoglurant for treating core features of autism in adults was identified in 2016 surveillance of the guideline on autism in adults. The surveillance review assessed the new evidence as inconclusive, due to the small sample sizes and mixed adult and child age groups. It concluded there was insufficient new evidence on drug treatments and further research would be needed before a full assessment could be made.

Evidence and intelligence review

Oxytocin

A systematic review (172) (16 RCTs, n=520) (age range not described in abstract) found no effect of oxytocin on social function and repetitive behaviours compared with placebo. A further 2 RCTs published after this systematic review (173,174) found that compared with placebo, oxytocin improved enhanced social learning and increased facial expressions. However, these outcomes are related to core features of autism, rather than direct measures of core features.

The guideline on autism in adults states do not use oxytocin for the management of core features of autism in adults (CG142-1.4.17). The new evidence does not show a clear effect of oxytocin on core features of autism and as such an update to the guideline is not warranted.

Other intelligence on drug treatments for adults with autism

Topic experts and patients' groups expressed concern that drug treatments continue to be inappropriately used in people with autism despite current guidance, which sets criteria for appropriate use. NHS England has established the Stopping over medication of people with a learning disability, autism or both (STOMP) initiative which aims to address this issue.

The issue of over medication is also acknowledged in the NHS long-term plan. Paragraph 3.31 of the plan states: "We will expand the Stopping over medication of people with a learning disability, autism or both and STOMP-STAMP programmes to stop the overmedication of people with a learning disability, autism or both." Public Health England published an early evaluation of the STOMP programme in 2019.

We consider the STOMP initiative to support current recommendations on drug treatments for autism as it has the potential to increase the implementation of the guideline, therefore an update to the guideline on managing autism in adults is not necessary.

Surveillance proposal

We propose to not update recommendations on drug treatments for adults with autism because new evidence supports current recommendations and national policy aims to improve services, which will support further implementation of existing recommendation.

Data table for drug treatments for adults with autism

Table 5 Drug treatments for adults with autism

Reference	Study type	Number of participants	Number of studies	Intervention	Comparator	Outcome	Impact of intervention
Kruppa et al. (2019) (173)	RCT	39	N/A	Oxytocin	Placebo	Enhanced learning – social versus non-social target	Improvement with intervention
Owada et al. (2019) (174)	RCT	124	N/A	Oxytocin	Placebo	Facial expressions	Improvement with intervention
Wang et al. (2019) (172)	SR	520	16	Oxytocin	Placebo	Social function	No effect of intervention
Wang et al. (2019) (172)	SR	520	16	Oxytocin	Placebo	Repetitive behaviours	No effect of intervention

Interventions for sleep disorders in children with autism

Background

The guideline on managing autism in children and young people (NICE guideline CG170) recommends designing a sleep plan (often a specific sleep behavioural intervention) and modifications to the physical environment to encourage sleep. Drug treatments for sleep problems are not recommended unless symptoms persist after implementation of a sleep plan or they are having a negative effect. The guideline further advises that drug treatments for sleep should only be prescribed after expert consultation and should be used in combination with non-drug treatments (CG170-1.7.4 to CG170-1.7.8). These recommendations were based on guideline committee consensus.

During guideline development, two small RCTs investigating melatonin were identified which reported large and statistically significant effects for melatonin for several sleep outcomes. However, in one of the studies, improvement in sleep time was not statistically significant. The guideline committee agreed that the evidence for melatonin was promising but results would need replication in further RCTs before they could consider recommending this treatment.

A research recommendation suggested a 3-stage RCT to address this gap, beginning with assessing the sleep issue, then treatment with a sleep hygiene intervention, followed by melatonin if sleep problems persist. The recommended primary outcome was total sleep time.

Melatonin was not licensed for use in children when the guideline on managing autism in children and young people was being developed. Prolonged release melatonin is now licensed for treating insomnia in children and adolescents aged 2 to 18 years with autism when sleep hygiene measures have been insufficient. This use is consistent with current recommendations, which note that a drug treatment to aid sleep can be used if problems persist after following a sleep plan (CG170-1.7.7).

No new evidence assessing interventions to improve sleep was identified in 2016 surveillance of the guideline on managing autism in children and young people.

NICE's 2015 guideline on challenging behaviour and learning disabilities (NICE guideline NG11) states 'Do not offer medication to aid sleep unless the sleep problem persists after a behavioural intervention… If medication is needed to aid sleep, consider melatonin.' (NG11-1.11). One of 4 studies of melatonin considered in developing this recommendation children with autism (n=160) (see the full version of NG11, page 284).

NICE's 2017 guideline on cerebral palsy in under 25s (NICE guideline NG62) recommends: 'If no treatable cause is found, consider a trial of melatonin to manage sleep disturbances for children and young people with cerebral palsy, particularly for problems with falling asleep.' Of 4 studies of melatonin considered in developing the guideline (see full version of NG62, page 315); in one 63 of the 146 participating children had 'developmental delay' and autism. Another study (n=50) included children with 'neurodevelopmental disabilities' including autism; it was not clear from the abstract how many of the participants had autism.

Evidence and intelligence review

Non-drug interventions for sleep

A systematic review and meta-analysis (175) of 3 RCTs (number of participants not reported in the abstract) assessed behavioural interventions for sleep disturbance in children with autism. Behavioural interventions improved sleep duration by about 25 minutes, reduced time to sleep by around 20 minutes and increased sleep efficiency. The authors judged the risk of bias to be low in included studies. This evidence is consistent with current recommendations to develop a sleep plan, which is usually a specific sleep behavioural intervention.

We identified an ongoing trial: Sleeping Sound with Autism Spectrum Disorder (ASD) (ISRCTN14077107). This trial will investigate the effectiveness of a

brief behavioural sleep intervention in children with autism aged 5 to 13 years old. We will check regularly for published results from this trial and assess the impact on recommendations.

Melatonin

A systematic review (176) (13 studies) reported a statistically significant increase in diary reported total sleep time for melatonin compared with placebo (mean difference of 29.2 mins) in children with neurodisabilities and sleep disturbances. The same systematic review reports that a meta-analysis of 2 studies in populations of people with autism found total sleep time for melatonin compared with placebo was greater than 64 minutes, but that heterogeneity was very high. As a consequence of this the authors concluded that this 'finding should be interpreted with caution'. The authors reported that all included trials except one were at high or unclear risk of bias. and the pooled estimates were from studies assessed as having considerable methodological differences.

We identified 2 reports from an RCT (177,178) (n=125) assessing a prolonged release formulation of melatonin designed for children and young people compared with placebo in children and adolescents aged 2-17 years with autism or autism plus ADHD. Melatonin 2–5 mg nightly increased sleep time by around an hour compared with placebo at 13 weeks' follow-up. Time to sleep was around half an hour shorter with melatonin than with placebo (177).In a year-long follow-up study (178) (n=95) all participants took melatonin 2–10 mg nightly. Sleep duration, time to sleep and nightly awakenings improved compared with baseline. All participants increased sleep time by 1 hour irrespective of whether they were originally in the active group or placebo group.

New evidence suggests melatonin decreases sleep latency and increases overall sleep time. This new evidence partly addresses the research recommendation in autism in under 19s (NICE guideline CG170).

Melatonin is now licensed for use in children with autism and is recommended by Challenging behaviour and learning disabilities (NICE guidance NG11) for

children and young people with conditions that commonly occur alongside autism, based on evidence that included children with autism. Additionally, we identified new evidence for melatonin's effectiveness in children with autism. Recommendation 1.7.7 in autism in under 19s accommodates the use of drug interventions for sleep disorder. We propose to consult on a of refresh to recommendation CG170-1.7.7 to include consideration of melatonin as the first-line option if drug treatment is needed for sleep disorders in children with autism

Carnosine

An RCT (179) (n=43) of carnosine supplementation (500 mg per day) in children aged 4 to 16 years reported improvement in sleep duration, parasomnias and total sleep disorders compared with placebo. However there was no effect on autism severity at 2 months. In developing the guideline on managing autism in children and young people, evidence indicated that carnosine had no effect on core features of autism (full guideline, page 312), but no evidence on sleep outcomes was identified. The new evidence shows promise for carnosine in managing sleep disorders, but we have identified only 1 small study; therefore this finding should be replicated in larger studies before an impact on current recommendations may be considered.

Surveillance proposal

We propose to refresh recommendations on sleep disorder management for children with autism to include consideration of melatonin if behavioural interventions are unsuccessful.

Increasing dietary variety in children with autism

Background

The guideline on managing autism in children and young people advises discussing help available locally with carers and offering information, advice, training and support, especially if carers need help with the personal, social or emotional care of the child or young person (CG170-1.2.3). This was based on a qualitative review of experiences of care that reported a need for

interventions supporting diet and healthy living. Repetitive and restrictive behaviours can extend to food resulting in limited diet. No studies investigating interventions for restricted diet were identified during guideline development or in previous surveillance.

Evidence and intelligence review

An RCT (180) (n= 38) compared an intervention to increase the variety of food eaten – 'Managing Eating Aversions and Limited variety' (MEAL) Plan compared with parental education. MEAL Plan provided parents with nutrition, education and meal strategies to expand a child's diet. The comparator, parent education, provided information about autism without guidance on nutrition, meal structure, or diet. MEAL Plan improved Clinican's Global Impression - Improvement score, the Brief Autism Mealtime Behaviors Inventory, and for grams of food consumed at 16 weeks' follow-up.

New evidence is limited because only one small study was identified; the results should be replicated in larger studies before an impact on current recommendations can be considered. However, this intervention to increase the range of foods eaten is consistent with current recommendations helping families and cares with personal care of the child or young person with autism.

Surveillance proposal

We propose to not update the guideline on managing autism in children and young people to address interventions for restricted diet because results seen in new evidence need replicating in larger studies.

Dietary supplements and complementary therapies for children with autism

Background

In developing the guideline on managing autism in children and young people, a range of interventions were considered, including dietary supplements and acupuncture:

- The guideline states ‘do not use omega-3 fatty acids to manage sleep problems in children and young people with autism’ (CG170-1.6.3). This was based on results of a meta-analysis showing negative effect on sleep outcomes. In 2016 surveillance of the guideline on managing autism in children and young people three RCTs were identified indicating that omega 3 fatty acids had no effect on the core features of autism and worsened behaviours.
- The guideline does not include recommendations on vitamin D or folinic acid for managing autism because only one inconclusive study on multivitamin supplements was identified during guideline development. No evidence on vitamin D or folinic acid was identified in previous surveillance.
- Evidence from 2 RCTs assessing acupuncture on overall autistic behaviours (full guideline, page 286) showed significant effect of acupuncture or electroacupuncture compared with sham acupuncture or electroacupuncture or when used as an adjunct to a conventional educational programme. No evidence on acupuncture was identified in previous surveillance.

Evidence and intelligence review

Omega-3 fatty acid supplementation

Three systematic reviews (181–183) assessed RCT evidence for omega-3 fatty acid supplementation in autism (see table: Omega-3 supplements for children with autism). None of these systematic reviews reported the age of participants so the results may also apply to adults with autism.

Although these systematic reviews were all published in 2017 and included a similar number of studies and participants, there were notable inconsistencies in the findings for social behaviour outcomes, with no effect on social responsiveness reported in one study (182), worsening of social skills reported in another study (181) yet, the third review reported improved social interaction (183). An RCT (184) indicated no effect of omega-3 supplementation on social communication or social motivation.

The systematic reviews and a further 2 RCTs indicated inconsistent effects across a range of other autism-related outcomes:

- improvements were reported for lethargy (181,182), hyperactivity (182), stereotypy (182), repetitive and restrictive behaviour (183), irritability (185), and daily living (181)
- worsening was reported for externalising behaviour (181)
- no effects were seen for sensory sensitivity (omega-3 and omega-6 supplementation) (186) and global functioning (182).

Because of the inconsistent results seen in the new evidence on omega-3 supplementation there is no anticipated impact on current recommendations.

Vitamin D

Three RCTs (185,187,188) investigated the effect of vitamin D supplementation in children with autism (see table: Vitamin D supplements for children with autism). Results indicated that, compared with placebo, vitamin D resulted in:

- improvements in clinical symptoms (187), self-care (188) and irritability (185)
- no effect on stereotypy (188)

In one of the studies (187), vitamin D was also assessed when combined with omega-3 supplementation. All groups in this study received parent training. Vitamin D plus omega-3 supplementation improved clinical symptoms compared with placebo. Vitamin D plus omega-3 supplementation improved visual and auditory responses compared with vitamin D plus placebo. Vitamin D plus omega-3 supplementation reduced anxiety scores compared with omega-3 plus placebo. The positive results reported in the abstract for the different arms of the study were for a variety of outcome measures, which may indicate inconsistent effects overall if findings of no effect were not reported in the abstract. Additionally, because this study had 4 arms, the number of participants receiving each combination of treatments was small.

Overall, the evidence base for vitamin D in children and young people with autism consists of small studies that report on varied outcomes. As such, there is no consistent evidence of effect and findings will need replication in larger studies. Therefore, an update to the guideline is not proposed.

Folinic acid

An RCT (189) (n=48) assessed 12 weeks of folinic acid (2 mg per kg daily, maximum of 50 mg daily) compared with placebo in children with autism and language impairment. Folinic acid improved verbal communication compared with placebo. Folinic acid is not licensed for the treatment of autism in children. New evidence indicates potential benefits, but because of small sample sizes, results will need replication in larger studies to determine whether folinic acid supplementation has a place in clinical practice. Therefore, we do not propose to update the guideline.

Acupuncture

A systematic review (190) (14 RCTs, n=968) investigated scalp acupuncture compared with behavioural interventions in children with autism. Scalp acupuncture:

- reduced overall Childhood Autism Rating Scale scores in children under 3 years and in those over 3 years old.
- reduced overall Autism Behaviour Checklist scores.
- improved psychoeducation profile (PEP-3) scores in communication, physical ability and behaviour.

However, there was significant heterogeneity in the analyses, but the causes of heterogeneity could not be fully explored because there were too few studies for subgroup analysis. The authors concluded that further high quality RCTs of scalp acupuncture are needed. Although the results are promising, because of the methodological issues reported, the new evidence is insufficient to impact on recommendations.

Surveillance proposal

We propose to not update existing recommendations to address dietary supplements or complementary therapies for children and young people with autism. Findings on dietary supplements need replication in larger studies and new evidence on acupuncture had unexplained heterogeneity in analyses so additional evidence is needed.

Data tables for other interventions for children with autism

Table: Omega-3 supplements for children with autism

Reference	Study type	Number of participants	Number of included studies	Intervention	Comparator	Outcome	Impact of intervention
Cheng et al. (2017) (182)	SR	194	6	Omega-3 supplementation	Placebo	Global assessment of functioning	No impact with intervention
Cheng et al. (2017) (182)	SR	194	6	Omega-3 supplementation	Placebo	Hyperactivity	Improvement with intervention
Cheng et al. (2017) (182)	SR	194	6	Omega-3 supplementation	Placebo	Lethargy	Improvement with intervention
Cheng et al. (2017) (182)	SR	194	6	Omega-3 supplementation	Placebo	Social responsiveness	No impact with intervention
Cheng et al. (2017) (182)	SR	194	6	Omega-3 supplementation	Placebo	Stereotypy	Improvement with intervention
Horvath et al. (2017) (181)	SR	183	5	Omega-3 supplementation	Placebo	Lethargy	Improvement with intervention
Horvath et al. (2017) (181)	SR	183	5	Omega-3 supplementation	Placebo	Adverse events	No effect of intervention
Horvath et al. (2017) (181)	SR	183	5	Omega-3 supplementation	Placebo	Externalising behaviour	Worse with intervention
Horvath et al. (2017) (181)	SR	183	5	Omega-3 supplementation	Placebo	Social skills	Worse with intervention
Horvath et al. (2017) (181)	SR	183	5	Omega-3 supplementation	Placebo	Vineland adaptive behaviour scale - daily living	Improvement with intervention
Mazahery et al. (2017) (183)	SR	107	4	Omega-3 supplementation	Placebo	Repetitive and restrictive behaviour	Improvement with intervention
Mazahery et al. (2017) (183)	SR	107	4	Omega-3 supplementation	Placebo	Social interaction	Improvement with intervention
Boone et al. (2017) (186)	RCT	31	NA	Omega-3 plus omega-6 fatty acid supplementation	Placebo	Sensory sensitivity	No impact with intervention

Mazahery et al. (2019) (185)	RCT	111	NA	Omega-3 supplementation	Placebo	Irritability	Improvement with intervention
Parellada et al. (2017) (184)	RCT	68	NA	Omega-3 supplementation	Placebo	Social communication	No impact with intervention
Parellada et al. (2017) (184)	RCT	68	NA	Omega-3 supplementation	Placebo	Social motivation	No impact with intervention

Table: Vitamin D supplements for children with autism

Reference	Study type	Number of participants	Number of included studies	Intervention	Comparator	Outcome	Impact of intervention
Fang et al. (2018) (187)	RCT	48	NA	Vitamin D plus parent training	Placebo plus parent training	Clinical symptoms assessed by the Childhood Autism Rating Scale (CARS)	Improvement with intervention
Fang et al. (2018) (187)	RCT	48	NA	Vitamin D plus omega-3 supplementation plus parent training	Placebo plus parent training	Clinical symptoms assessed by the Childhood Autism Rating Scale (CARS)	Improvement with intervention
Fang et al. (2018) (187)	RCT	48	NA	Vitamin D plus omega-3 supplementation plus parent training	Vitamin D plus parent training	Visual and auditory responses	Improvement with intervention
Fang et al. (2018) (187)	RCT	48	NA	Vitamin D plus omega-3 supplementation plus parent training	Omega 3 supplementation plus parent training	Anxiety scores	Improvement with intervention
Kerley et al. (2017) (188)	RCT	42	NA	Vitamin D3	Placebo	Aberrant Behaviour Checklist - Stereotypy	No effect of intervention
Kerley et al. (2017) (188)	RCT	42	NA	Vitamin D3	Placebo	DD-GAS self-care	Improvement with intervention
Mazahery et al. (2019) (185)	RCT	111	NA	Vitamin D	Placebo	Aberrant Behaviour Checklist - Irritability	Improvement with intervention

Training interventions for parents, carers and teachers of children with autism

Background

The guideline on managing autism in children and young people (NICE guideline CG170) recommends considering 'a specific social-communication intervention for the core features of autism in children and young people that includes play-based strategies with parents, carers and teachers to increase joint attention, engagement and reciprocal communication in the child or young person (CG170-1.3.1)'. During guideline development, 3 studies reported positive effects of parental interventions for the core features of autism including reciprocal social communication. However, because only a small body of low quality evidence was available, the recommendation was based largely on guideline committee consensus. The guideline also included a research recommendation on teacher-, parent- and peer-mediated psychosocial interventions in pre-school children with autism.

During 2016 surveillance of this guideline, 3 RCTs and one systematic review of parent interventions for the core features of autism showed positive effects on joint attention, engagement and reciprocal communication, so were assessed as being consistent with the guideline.

During guideline development, 4 studies assessing parent training alone or with other treatments on behaviour that challenges showed inconsistent results. Some positive effects were seen, but often evidence of effect was uncertain. The guideline committee was unable to recommend parent training specifically for behaviour that challenges. However, the guideline recommends psychosocial interventions for behaviour that challenges (CG170-1.4.7 to CG170-1.4.9), and noted that multidisciplinary reviews should take into account the support and training that families, carers or staff may need to implement the intervention effectively (CG170-1.4.6).

.

During 2016 surveillance of this guideline an RCT (n=180) reported that parent training significantly reduced irritability (Aberrant Behaviour Checklist – irritability) and reduced scores on the home situations questionnaire, a measure of behavioural compliance. This RCT partly answered a research recommendation on managing behaviour that challenges in children and young people with autism

Evidence and intelligence review

Parent-mediated interventions

Topic experts and patient groups indicated an increase in published research on parent-training interventions, one of which met criteria for inclusion in the surveillance review (191). An observation that availability of parent support programmes has increased was tempered by a concern that commercial parent training schemes are being marketed but may not be supported by robust evidence.

We identified new evidence on parent training that reported effects on core features of autism.

An RCT (192) (n=48) assessed parent training plus at-home clinician intervention compared with delayed intervention in children with autism and language delay. After 24 weeks, the group receiving active treatment had greater improvement in 'functional utterances'.

An RCT (193) (n=63 parent-toddler pairs) assessed a parent-mediated intervention (social ABCs) compared with usual care. At 24 weeks, the parent intervention improved children's functional vocal responsiveness and vocal initiations and parent smiling.

New evidence (192,193) is therefore consistent with current recommendations to consider a specific social-communication intervention for the core features of autism in children and young people.

Long-term follow-up (194) from a study of parent-mediated social communication intervention (PACT) was conducted at a median of 5.75 years

after the original endpoint of the trial. The primary results from this study, showing benefits of parent training were considered during guideline development (191). The long-term results were covered in an NIHR alert: Parent-focused therapy has some long-term benefits for children with autism. The NIHR alert concluded that 'the results indicate that healthcare professionals should consider early psychosocial therapy in young children with autism, in line with NICE guidance'.

A systematic review (195) (7 studies including 2 RCTs) investigated the impact of remote parent-mediated training in social behaviour and communication skills for parents of children with autism. Results indicated that remote parent training improved parents' knowledge and adherence to the intervention as well as improving social behaviour and communication skills in children with autism. Remote training largely consisted of self-guided websites with or without therapist assistance, training videos, training manuals and video conferencing. The authors reported that the results had a 'high risk of bias' because of small sample sizes and that standardised outcome measures were not consistently used. Therefore, an update to consider the role of remotely-delivered parent training intervention is not warranted.

We also identified new evidence assessing the effect of parent training on behaviour that challenges.

A systematic review (196) (8 RCTs, n=653) reported that parent training (no details of specific interventions provided in abstract) improved child disruptive behaviour compared with controls (no detail in abstract). However, the authors noted significant heterogeneity in the effect seen across individual studies.

An RCT (197) (n=202) assessed a therapist training programme for delivering individualised mental health interventions including parent-mediated and child focused strategies to reduce challenging behaviours. The control group was care as usual, followed by therapist training. The mental health interventions were aimed at children with autism aged 5-13 years. Results indicated that individualised mental health interventions led to greater improvement in

behaviour intensity and problems (measured with the Eyberg Child Behavior Inventory).

An analysis of a study identified in 2016 surveillance of the guideline on managing autism in children and young people reported on additional outcomes. The primary report (198) from this RCT (n=180) indicated that parent training improved disruptive behaviour and irritability compared with parent education in children with autism and behaviour that challenges. The additional report (199) indicated that parent training improved daily living, and this effect was maintained for 24 weeks after the intervention stopped.

New evidence (196,197,199) is therefore consistent with current recommendations to take into account parent and carer's training needs.

We also identified several ongoing trials of parent training interventions:

- ComAlong Toddler - Parental course to help the child to communicate (ISRCTN13330627)
- Improving autistic children's social communication with parents in everyday settings (ISRCTN25378536)
- Managing repetitive behaviours parent group study (ISRCTN15550611)
- REACH-ASD Trial: A Randomised Controlled Trial of Psychoeducation and Acceptance & Commitment Therapy for Parents of Children recently diagnosed with ASD (ISRCTN45412843)

We will check regularly for publication of results from these studies and assess their impact on recommendations.

Teacher-mediated interventions

An RCT (200) (n=39) assessed behaviour analytic therapy compared with usual care. The intervention was delivered by schoolteachers and direct care staff following Promoting the Emergence of Advanced Knowledge Direct Training (PEAK-DT) curriculum. Children with autism in the PEAK-DT group gained more language skills after a year than those receiving treatment as usual.

An RCT (201) investigated the effectiveness of a social engagement intervention called ‘remaking recess’ with and without implementation support with 31 children with autism and 28 school staff. Children in the implementation support group had higher social network inclusion and friendship nominations than children in the intervention-only group and experienced reduced solitary engagement. Treatment fidelity improved for both groups following training of teaching staff.

The new evidence (200,201) finding benefits of teacher-mediated psychosocial interventions is therefore consistent with current recommendations to consider a social-communication intervention for the core features of autism.

Surveillance proposal

We propose not to update recommendations about psychosocial interventions for children and young people with autism, including interventions for behaviour that challenges, because new evidence supports current recommendations.

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