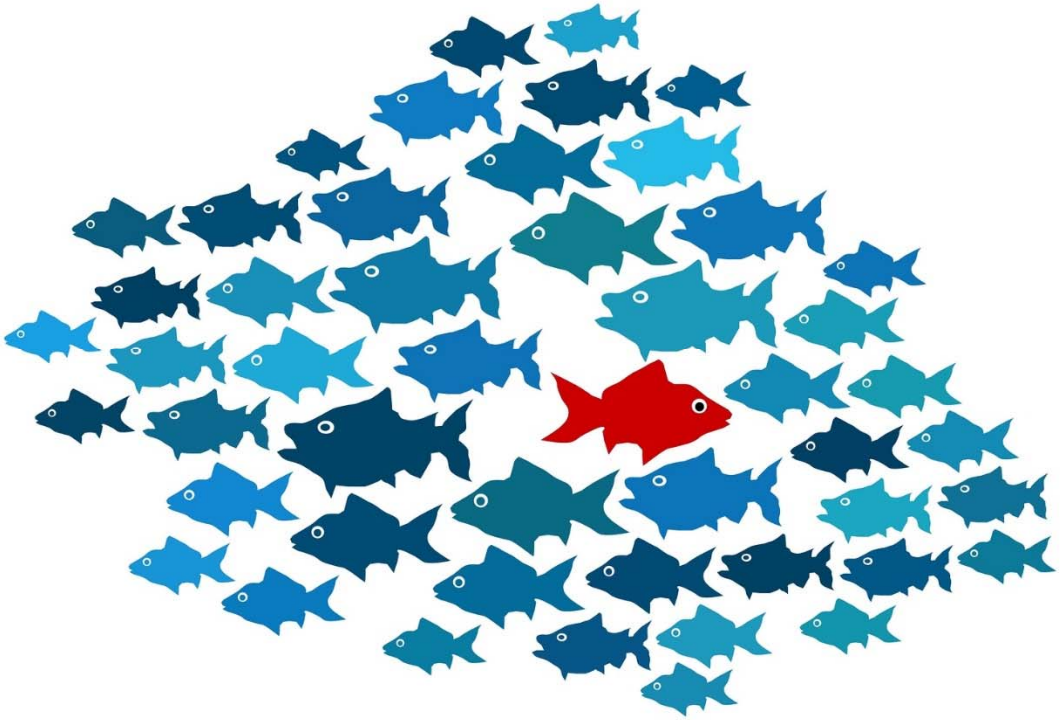
KCE REPORT 233

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

MANAGEMENT OF AUTISM IN CHILDREN AND YOUNG PEOPLE: A GOOD CLINICAL PRACTICE GUIDELINE



KCE REPORT 233
GOOD CLINICAL PRACTICE

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MANAGEMENT OF AUTISM IN CHILDREN AND YOUNG PEOPLE: A GOOD CLINICAL PRACTICE GUIDELINE

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Disclaimer:

- **The external experts and stakeholders were consulted about a (preliminary) version of the scientific report. Their comments were discussed during meetings. They did not co-author the scientific report and did not necessarily agree with its content.**
- **Subsequently, a (final) version was submitted to the assessors and the validators. The validation of the report results from a consensus or a voting process between the assesoosrs and the validators. The assessors and validators did not co-author the scientific report and did not necessarily all three agree with its content.**
- **Finally, this report has been approved by common assent by the Executive Board.**
- **Only the KCE is responsible for errors or omissions that could persist. The policy recommendations are also under the full responsibility of the KCE.**

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This document is available on the website of the Belgian Health Care Knowledge Centre.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AAC	Augmentative and Alternative Communication
AACAP	American Academy of Child & Adolescent Psychiatry
ABA	Applied Behaviour Analysis
ABC	Autism Behaviour Checklist
ADDM	Autism and Developmental Disabilities Monitoring
ADHD	Attention Deficit Hyperactivity Disorder
ADHD-RS	Attention Deficit Hyperactivity Disorder-Rating Scale
ADIS-C	Anxiety Disorders Interview Schedule-Child Version
ADIS-P	Anxiety Disorders Interview Schedule-Parent Version
ADOS	Autism Diagnostic Observation Schedule
AGREE	Appraisal of Guidelines, Research and Evaluation
ANESM	Agence Nationale de l'Evaluation et de la Qualité des Etablissements et Services Sociaux et Médico-sociaux
ASD	Autism Spectrum Disorder
AWIPH	Agence Wallonne pour l'intégration de personnes handicapées
BASC	Behavioural Assessment System for Children
CAMHS	Child And Adolescent Mental Health Services
CATS	Children's Automatic Thoughts Scale
CBCL/1.5-5	The Child Behaviour Checklist/1.5-5
CEBAM	Belgian Centre for Evidence-Based Medicine
CBT	Cognitive Behavioural Therapy
CDC	Centre of Disease Control
CGI-I	Clinical Global Impression-Improvement
COCOF	Commission Communautaire Française
COMB	Combined CBT and Melatonin
CSHQ	Children's Sleep Habits Questionnaire
CPG	Clinical Practice Guideline

COMPASS	Collaborative Model for Promoting Competence and Success
CTRS-R:S	Conners' Teacher Rating Scales-Revised: Short
DMSA	Dimercaptosuccinic acid chelation therapy
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition
DSM-5	Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition
DTT	Discrete Trial Training
DTVP-2	Developmental Test of Visual Perception, 2nd edition
EBI	Early Behavioural Intervention
EBM	Evidence Based Medicine
EBP	Evidence Based Practice
EIBI	Early Intensive Behavioural Intervention
EIBT	Early Intensive Behavioural Treatment
EIDP	Early Intervention Developmental Profile
ERT	Emotion Recognition Training
ESDM	Early Start Denver Model
FRT	Face-to-face Recognition Training
GCP	Good Clinical Practice
GDG	Guideline Development Group
GGC/COCOM	Gemeenschappelijke gemeenschapscommissie/Commission communautaire commune
GI	Gastrointestinal
GIS	Gastrointestinal Symptom Score
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HAS	Haute Autorité de la Santé
HBOT	Hyperbaric Oxygen Therapy
HCSP	Haut Conseil de la Santé Publique
HTA	Health Technology Assessment
IBI	Intensive Behavioural Intervention

ICD	International Classification of Disease
INAMI – RIZIV	National Institute for Health and Disability Insurance (NIHDI)
IQ	Intellectual Quotient
KCE	Federaal Kenniscentrum voor de Gezondheidszorg- Centre Fédéral d' Expertise des Soins de Santé - Belgian Health Care Knowledge Centre
LEAP	Learning Experience and Alternative Program for Preschools and their Parents
LFI!	Let's Face It!
LOA	Level of Agreement
MASC	Multidimensional Anxiety Scale for Children
MSEL	Mullen Scales of Early Learning
NICE	National Institute for Health and Care Excellence
NIHDI	National Institute for Health and Disability Insurance (RIZIV – INAMI)
OCD	Obsessive-Compulsive Disorder
PACT	Preschool Autism Communication Trial
PDDBI	Pervasive Development Disorder Behaviour Inventory
PDD-NOS	Pervasive Developmental Disorder Not Otherwise Specified
PECS	Picture Exchange Communication System
PedsQL TM	Pediatric Quality of Life Inventory
P-ESDM	Parent Mediated ESDM
PGI-R	Parental Global Impressions-Revised
PHARE	Personne Handicapée Autonomie Recherchée
PICO	Participants–Interventions–Comparator–Outcomes
PSDP	Preschool Developmental Profile
PROMPT	Prompts for Restructuring Oral Muscular Phonetic Targets
RCT	Randomized Controlled Trial
RCMAS	Revised Children's Manifest Anxiety Scale
RIT	Reciprocal Imitation Training
RPMT	Responsive Education and Prelinguistic Milieu Training
PRT	Pivotal Response Treatment

SCAS	Spence Children's Anxiety Scale
SCAS-P	Spence Children's Anxiety Scale - Parent version
SDQ	Strengths and Difficulties Questionnaires
SNRI	Selective Serotonin and Noradrenalin Reuptake Inhibitor
SSC	Sense and Self-Regulation Checklist
SSRI	Selective serotonine reuptake inhibitor
SNRI	Serotonine norepinephrine reuptake inhibitor
SR	Systematic Review
SULP	Social Use of Language Programme
TEACCH	Treatment and Education of Autistic and Communication-Handicapped Children
TAII	Technology-aided instruction and intervention
TAU	Treatment as usual
TBD	To be determined
ToM	Theory of Mind
VABS	Vineland Adaptive Behaviour Scales
VAPH	Vlaams Agentschap voor Personen met een Handicap
VGC	Vlaamse Gemeenschaps Commissie

SCIENTIFIC REPORT

1 INTRODUCTION

1.1 Background

In this guideline the terms 'autism' and 'autism spectrum disorder (ASD)' will be used interchangeably. According to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) published in 2013, children and adolescents, who are diagnosed with autism or ASD share two sets of characteristics.[1]

- Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history:
  - Deficitis in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interests, emotions, or affect; to failure to initiate or respond to social interactions.
  - Deficits in nonverbal communicative behaviors used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures; to a total lack of facial expressions and nonverbal communication.
  - Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behavior to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers.
- Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least two of the following, currently or by history:
  - Stereotyped or repetitive motor movements, use of objects, or speech.
  - Insistence on sameness, inflexible adherence to routines, or ritualized patterns or verbal nonverbal behavior.
  - Highly restricted, fixated interests that are abnormal in intensity or focus.
  - Hyper- or hyporeactivity to sensory input or unusual interests in sensory aspects of the environment.

Symptoms must be present in the early developmental period, and must cause clinically significant impairment in social, occupational, or other important areas of current functioning. It is important to note that definitions vary in the subsequent DSM editions and that this affects the outcomes of epidemiological studies. More specifically, pervasive developmental disorder not otherwise specified (PDD-NOS) and Asperger syndrome were included in the diagnosis of autism according to the fourth edition (DSM-IV).

ASD can have multiple causes and it is often not possible to determine one definite cause of autism in a child. Genetics are known to play a role in most children with autism[2] and specific genes, affecting neurological development have been identified in a subgroup of children with autism.[3] ASD is considered a neuro-developmental disorder and although treatment can improve certain behavioural aspects, the disorder cannot be 'cured'. The range of severity and intellectual function is large: from the severely impaired person with classical autism to a 'high-functioning' individual. Thus an equally wide range of support and interventions are required for this heterogeneous condition.

A recent systematic review of epidemiological surveys worldwide estimated a prevalence of ASD of 62/10 000 (1/161 persons, or +- 68 900 cases in Belgium calculated from a population of approximately 11 million (January, 2014).[4,5] Other sources report higher incidence numbers. For example, in a recent study from the Centre of Disease Control (CDC)'s Autism and Developmental Disabilities Monitoring (ADDM) Network based in the US estimated a prevalence rate of autism spectrum disorder of about 1 in 68 children.[6] About 45-50% of persons with ASD have an additional diagnosis of intellectual disability (IQ<70) (double diagnosis).[7] ASD is about 4 times more prevalent in males than females.[8]

1.2 The need for a guideline

Several groups introduced a request to the Belgian Health Care Knowledge Center for a GCP on the management and treatment of children and adolescents with ASD. These were the parent organisations of children and adolescents with ASD, the National Institute for Health and Disability Insurance (NIHDI), the Hoge Gezondheidsraad/Conseil Supérieur de la Santé (HGR – CSS) and professionals caring for persons with a double diagnosis of mental health disorder such as ASD.

The aim of the guideline is to provide a base for harmonizing treatment in Belgium in order to provide the best possible outcomes for children and adolescents with autism, their families and caregivers. Several players both at federal, regional and local levels are involved in the organisation of care for persons suffering from ASD. A separate chapter will elaborate on the Belgian context and needs.

With the development of behavioural therapies in Anglo-Saxon countries there has been a shift in treatment approaches. Therefore, the need for an evidence-based guideline for the treatment of autism in children and adolescents is real.

1.3 Scope

The research questions from the NICE 2013 guideline were proposed to the scoping group and unanimously accepted without any changes.

The scope of the guideline focuses on two main questions:

1. What is the current scientific evidence for psychosocial interventions, educational, pharmacological and biomedical treatments for children and young people with ASD, with or without a double diagnosis ASD, intellectual disability or other associated features?
2. What is good clinical practice (GCP) management for children and young people with ASD and their families?

Aspects that are to be taken into account are:

- developmental stages at different ages,
- different levels of severity and intellectual functioning,
- comorbidities,

- variable context of care provision (at home, at school, in specialised care settings, in ambulatory or residential care).

In the context of this report, the word 'care' should be interpreted broadly, including services and support provided by professionals from the health care sector, social care sector, disability sector or the educational sector. The word 'care' also refers to the more broader term 'intervention'. The type of intervention was based on the denominator used in the NICE guideline. For example, some interventions could have been classified as biomedical whereas they were found under pharmacological (e.g. antioxydants).

Additionally, due to the fact that very many different professionals are involved in the care for autistic children it can be considered to use the term Evidence Based Practice (EBP) as an alternative to Evidence Based Medicine (EBM).

1.4 Remit of the guideline

1.4.1 Overall objectives

This guideline provides recommendations based on current scientific evidence for treatment and support of children and adolescents with autism and their family. ASD is a complex condition. Therefore, addressing six domains, as defined by NICE, allows to discriminate outcomes. Per domain specific scores may be described. The objective of treatment is to improve outcomes specific to a particular domain of ASD, and thereby improving the overall outcome for the child or adolescent with ASD. Caregivers are encouraged to interpret these recommendations in the context of the individual situation and to take into account the values and preferences of the children and adolescents and of their families.

1.4.2 Specific aims

The specific aims of the guideline are to address the concerns of the groups who introduced the request for a GCP. Organisation of care is beyond the scope of this guideline but it is hoped that the present document will guide political decisions regarding a National Autism Plan (http://www.laurette-onkelinx.be/production/content.php?ArticleId=100&PressReleaseId=531&SetLangID=NL).

1.4.3 Target users of the guideline

This guideline is intended to be used by all care providers involved in the management of children and adolescents (until their 19th birthday) with autism in the primary health care sector (including general practitioners), in the secondary and tertiary health care sector (including medical specialists), in social care services, in disability services and in the educational sector. The implementation of the proposed strategies will depend on the collaboration by care providers and policy makers; therefore the guideline is certainly intended to be a roadmap for change and improvement. Finally, this guideline is of particular interest for children and adolescents with autism and for their families because their benefit is our goal. The views and preferences of the parents were actively taken into account. Due to pragmatic reasons it was considered that they were the best representatives of the children and adolescents with ASD.

The recommendations are based on existing evidence and may not always be in line with the current criteria for reimbursement of therapeutic interventions by the federal government or by the federated entities, who are invited to consider adaptation of reimbursement/financing criteria based on these guidelines.

1.5 Statement of intent

Clinical Practice Guidelines (CPGs) are designed to improve the quality of care and decrease the use of unnecessary or harmful interventions. This guideline has been developed by clinicians, health care professionals and researchers for use within the Belgian context in the primary, secondary and tertiary health care sector, in social care services, in disability services and in the educational sector. The recommendations are not intended to indicate an exclusive course of action or to serve as a standard of care. Standards of care are determined on the basis of all relevant data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Variations, which take into account individual circumstances, professional judgement and the choice of the person with ASD, may also be appropriate. The information in this guideline is not a substitute for proper diagnosis, treatment or the provision of advice by an appropriate professional. It is advised, however, that significant deviations from the national guideline should be fully documented

in the file of the person with ASD at the time the relevant decision is taken and in collaboration with the child/adolescent and the family.

1.6 Funding and declaration of interest

The KCE is a federal institution which is financed for the largest part by the National Institute for Health and Disability Insurance (NIHDI, RIZIV – INAMI) but also by the Federal Public National Institute for Health and Disability Insurance (NIHDI, RIZIV – INAMI), the Federal Public Service of Health, food chain safety and environment, and the Federal Public Service of social security. The development of clinical practice guidelines is part of the legal mission of the KCE. Although the development of the guidelines is paid by KCE budget, the sole mission of the KCE is providing scientifically valid information. The KCE has no interest in companies (commercial or not, e.g. hospital, university), associations (e.g. professional association, syndicate), individuals or organisations (e.g. lobby group) on which the guidelines could have a positive or negative impact (financial or other).

The Guideline Appendices contain information about the affiliations of all members of the KCE expert team (section 1.5), members of the Guideline Development Group (GDG) (section 1.1), members of the stakeholder panel (section 1.2), external experts (section 1.3) as well as the affiliations of the external assessors and the CEBAM (Belgian Centre for Evidence-Based Medicine) validators of the report (section 1.6).

All professionals and other persons involved in the GDG or the peer-review process, all members of the stakeholder panel and all validators completed a declaration of interest form. The information of possible conflicts of interest is published in the colophon of this report. All members of the KCE Expert Team make yearly declarations of interest and further details of these are available on request.

2 METHODOLOGY

2.1 Introduction

The KCE guideline is drawn up according to codified principles, based on scientific information from the international literature. This guideline was developed based on the ADAPTE methodology. Further details about KCE and the guideline development methodology are available at https://kce.fgov.be/content/kce-processes.

2.2 General Approach

The present CPG was developed by adapting international CPGs to the Belgian context (www.kce.fgov.be). This approach was structured in a formal methodology by the ADAPTE group, an international group of guideline developers and researchers.[9] In addition and to ensure consensus on the modified recommendations a vote was conducted using the Delphi method (http://www.rand.org).

The ADAPTE methodology generally consists of three major phases (www.adapte.org):

1. **Set-up Phase:** outlines the necessary tasks to be completed prior to beginning the adaptation process (e.g. identifying necessary skills and resources).
2. **Adaptation Phase**: Assists guideline developers in moving from selection of a topic to identification of specific clinical questions; searching for and retrieving guidelines; assessing the consistency of the evidence therein, their quality, currency, content and applicability; decision making around adaptation and preparing the draft adapted guideline. In this case each recommendations from NICE and HAS was discussed during the GDG meetings and a modified 'KCE recommendation' was drafted after the meeting (ADAPTE step 17 option 5). The tables in the report document the recommendations by NICE and HAS for each domain. The comments made by the GDG during the meetings can be found in the Appendix for each domain.
3. In order to ensure over 85% agreement with the proposed formulation of 'KCE guidelines' a Delphi vote was subsequently organised (see further).

4. **Finalization Phase**: Guides guideline developers by getting feedback on the document from stakeholders, consulting with the source developers of guidelines used in the adaptation process, establishing a process for review and updating of the adapted guideline and the process of creating a final document.

2.3 The Guideline Development Group and the Stakeholder Panel

This guideline was developed in collaboration with a multidisciplinary group of practising clinicians, various professionals involved in care for the target group, representatives of parents and user organisations and KCE experts. The composition of the Guideline Development Group (GDG) and the Stakeholder panel is documented in the appendices (section 1.1). We searched Belgian websites related to care for autism and contacted professionals in the field to compile a list of relevant persons including child psychiatrists, neuropediatricians, psychologists, masters in educational sciences, various therapists, researchers in the field of autism, representatives of the educational system and disability care and representatives of parents and user organisations. Guideline development, review expertise, support and facilitation were provided by the KCE Expert Team.

2.3.1 The GDG

The GDG members were invited based on their scientific and clinical expertise. The eight national reference centres for autism, were invited to send representatives including child psychiatrists, neuropediatricians, psychologists, masters in educational sciences, speech therapists, occupational therapists, physical therapists, nurses or researchers. Representatives from the educational sector, disability care and parents' association were included. The GDG group was presided by a child psychiatrist. The twenty GDG members who attended at least one GDG meeting were granted co-authorship. Two persons invited to participate in the GDG did not attend any meeting but provided feedback by e-mail. They are named 'external expert' (see appendices section 1.3). Their comments were discussed at the GDG meetings. The only group lacking despite invitation were nurses and social workers.

The roles assigned to the GDG were:

- to define the research questions, in close collaboration with the KCE experts;
- to provide feedback on the selection of studies and identify further relevant manuscripts which may have been missed;
- to provide feedback on the content of the guideline;
- to provide feedback on the draft recommendations.

2.3.2 The stakeholders

The stakeholders were invited based on their affiliations with : 1) scientific associations for physicians, psychologists, speech therapists, occupational and physical therapists, 2) institutions supported by NIHDI – RIZIV – INAMI conventions, 3) the educational sector and disability care, 4) parents' associations, 5) administration and policy makers. They were selected by searching Belgian websites to find associations of professionals involved in the care for autism and by contacting user organisations and professionals in the field. The composition of the Stakeholder panel is documented in the appendices. It includes representatives of the professional associations of child psychiatrists, neuropediatricians, pediatricians, general practitioners, psychologists, and therapists; representatives of the educational system and disability care; representatives of parents and user organisations, and representatives of administrative bodies. One person could not attend the meeting but provided feedback by e-mail. This person is named 'external expert' and the comments were discussed at the meeting (see appendices).

The stakeholders were consulted at the end of the guideline production process to provide any evidence that may have been missed as well as their opinions on the clarity, completeness and acceptability of the recommendations.

2.4 Search for Evidence

In order to identify published clinical practice guidelines (CPGs) on autism, OVID Medline, the National Guideline Clearing House (http://www.guideline.gov/) and Guidelines International Network (http://www.g-i-n.net/) were searched for both national and international CPGs. In addition, relevant Belgian websites (see section 6.3) were searched as well. The initial search was performed without restrictions on date and language. Subsequently, based on the initial screening of titles and abstract, it was decided to select only references from the last five years (2008-current). All searches for guidelines were performed on June 24th, 2013. A list of the searched websites and a detailed search strategy can be found in appendices (section 2.1). Based on title and abstract and after removal of duplicates, 5 guidelines were retained for full text evaluation.

Additionally, 5 guidelines/documents were identified by the guideline development group (GDG). Two were excluded: the first one was a Swedish health technology assessment report (HTA),[10] and the second a practical implementation document based on the guideline by the Haute Autorité de la Santé (HAS).[11] The remaining 8 guidelines were retained for appraisal of the methodological quality.[12, 13, 14, 15, 16, 17, 18, 19]

2.5 Quality Appraisal

The AGREE II instrument was used to evaluate the methodological quality of the identified CPGs (http://www.agreetrust.org/). Each of the eight documents were scored by two independent researchers (GV and KH or GV and ME) and discussed in case of disagreement. Special attention was given to the criterion 'Rigor of development'. For the full AGREE II appraisals, see section 3.2 in the appendices. The appraisal with AGREE II resulted in 2 high[13],[14] and 2 moderate[12],[16] quality guidelines. The New Zealand guideline[14] was eliminated because the final search date for some guideline parts was 2004, the 'Pediatrics' guideline[16] was eliminated because the scope was too limited and because all included research questions were covered by the NICE guideline.

We finally retained two guidelines: a guideline elaborated in collaboration by the Haute Autorité de la Santé (HAS) and the Agence Nationale de l'Evaluation et de la Qualité des Etablissements et Services Sociaux et Médico-sociaux (ANESM) (2012)[12] and the most recent guideline published by the National Institute for Health and Care Excellence in UK.[13] The NICE guideline had the highest quality scores and had search literature up to January 2013. A decision to maintain the HAS guideline, although of moderate quality, was taken due to geographical and political reasons. The HAS guideline included statements on psychoanalysis whereas this topic was not included in the NICE guideline. Since the use of psychoanalysis is a controversial issue in the Walloon region, including the HAS guideline should increase the acceptability of the present guideline. Additionally, a decision was taken to include the New Zealand Supplementary Paper on Gastrointestinal Problems in Young People with Autism Spectrum Disorder, with search dates 1 January 2004 until August 27, 2012 to specifically address the domain on associated gastrointestinal medical problems. It was decided to prioritise and follow the structure of the NICE guideline because of its comprehensiveness and superior score on AGREE II.

2.6 In- and exclusion criteria

Clinical questions based on the overall scope of the guideline were translated into in- and exclusion criteria using the PICO (Participants–Interventions–Comparator–Outcomes) framework (Table 1). These inclusion and exclusion criteria are similar to the NICE document.

Table 1 – In- and exclusion criteria

Selection criteria	Inclusion criteria
Population	Children and adolescents (0-18 years) with ASD, their family and carers. All different levels of severity and intellectual functioning are included.
Intervention	Non-pharmacological or pharmacological intervention performed in any setting, including the primary, secondary and tertiary health care sector, the educational sector, social care services, and disability care. Ambulatory as well as residential care is included.
Outcome	Outcomes follow the structure of the NICE guideline with an impact on core features of autism assigned as a critical outcome.
Design	Guidelines based on one or more of the following types of study design: meta-analysis, SR (Systematic review) including SR as part of a HTA , RCT (randomized controlled trial), controlled clinical trials, observational studies.
Language	English, Dutch, French

2.7 Research Questions

A list of possible research questions was prepared by KCE based on the two retained recent international guidelines. The final selection of research questions was made during an initial scoping meeting at KCE on October 8th, 2013. The scoping group consisted of professionals involved in the care for children and adolescents with autism and of representatives of parents and user organisations. Members from the GDG as well as members from the stakeholder panel participated in the scoping meeting. The list of all persons who participated in the scoping meeting can be found in the appendices, section 1.4.

This CPG addresses the following domains and research questions.

Domain 1: Experience of care and the organisation and delivery of care

- What services and treatments are effective in providing a positive experience of care for children and young people with autism and their families and carers?
- What are the key problems associated with the experience of care for children and young people with autism and their families and carers?
- For children and young people with autism, and their families and carers, what would help improve the experience of care?
- What information and day-to-day support is effective in supporting children and young people with autism and their families and carers?
- What information and day-to-day support do children and young people with autism and their families and carers want?
  What are the essential elements that allow integration across services/agencies for the optimal organisation and delivery of care to children and young people with autism and their families and carers?
- What are the essential elements that assist in the transition into adulthood services for young people with autism?
- What are the effective ways of monitoring progress in children and young people with autism?
- What alterations need to be made to routine and acute healthcare for children and young people with autism to ensure access for those with autism?
- For children and young people with autism, and their families and carers, is the experience of care and the organisation and delivery of

care different for looked after children, immigrant groups, or children with regression in skills?

Domain 2: Interventions aimed at core features of autism

- For children and young people with autism, what are the benefits of psychosocial, pharmacological or biomedical interventions for the core features of autism (overall autistic behaviours, impaired reciprocal social communication and interaction, restricted interests and rigid and repetitive behaviours) when compared with alternative management strategies?
- For children and young people with autism and their families and carers, is the engagement with or effectiveness of interventions aimed at the core features of autism different for looked after children, immigrant groups or children with regression in skills?
- For children and young people with autism is the effectiveness of interventions aimed at the core features of autism moderated by the nature and severity of the condition or the presence of coexisting conditions (including mental and behaviour, neurodevelopmental, medical or genetic and functional problems and disorders)?
  For children and young people with autism is the effectiveness of interventions aimed at the core features of autism mediated by the intensity of the intervention, the duration of the intervention, the length of follow-up or programme components?

Domain 3: Interventions aimed at behaviour that challenges

- For children and young people with autism, what are the benefits of psychosocial, pharmacological or biomedical interventions for anticipating, preventing or managing behaviour that challenges or poses a risk, when compared with alternative management strategies?
- For children and young people with autism and their families and carers, is the engagement with or effectiveness of interventions aimed at reducing behaviours that challenges or poses a risk different for looked after children, immigrant groups, or children with regression in skills?
- For children and young people with autism is the effectiveness of interventions aimed at reducing behaviour that challenges or poses a risk moderated by the nature and severity of the condition? Including the presence of coexisting conditions (e.g. mental and behaviour, neurodevelopmental, medical or genetic and functional problems and disorders), age, gender?, the presence of sensory differences, IQ, language level, family/carer contextual factors (e.g. socioeconomic status, parental education, parental mental health, sibling with special education needs)?
- For children and young people with autism is the effectiveness of interventions aimed at reducing behaviour that challenges or poses a risk mediated by the intensity of the intervention, the duration of the intervention, the length of follow-up or programme components?

Domain 4: Intervention aimed at associated features of autism and co-existing conditions

- For children and young people with autism, what are the benefits of psychosocial, pharmacological or biomedical interventions for coexisting problems or disorders (including adaptive behaviour, speech and language problems, IQ and academic skills, sensory sensitivities, motor skills, common coexisting mental health problems and common functional problems) when compared with alternative management strategies?
- For children and young people with autism, and their families and carers, is the engagement with or effectiveness of interventions aimed at coexisting problems or disorders different for looked after children, immigrant groups, or children with regression in skills?
- For children and young people with autism is the effectiveness of interventions aimed at coexisting problems or disorders moderated by the nature and severity of the condition, the presence of coexisting conditions (including, mental and behaviour, neurodevelopmental, medical or genetic, and functional, problems and disorders), age, gender, the presence of sensory differences, IQ, language level, family/carer contextual factors (for example, socioeconomic status, parental education, parental mental health, sibling with special education needs)?

- For children and young people with autism is the effectiveness of interventions aimed at coexisting problems or disorders mediated by the intensity of the intervention, the duration of the intervention, the length of follow-up or programme components?

Domain 5: Interventions aimed at improving the impact of the family

- For children and young people with autism, what are the benefits of psychosocial, pharmacological or biomedical interventions for improving the impact on the family when compared with alternative management strategies?
- For children and young people with autism and their families and carers, is the engagement with or effectiveness of interventions aimed at improving the impact of the family different for looked after children, immigrant groups, or children with regression in skills?
- For children and young people with autism is the effectiveness of interventions aimed at improving the impact on the family moderated by the nature and severity of the condition, the presence of coexisting conditions (including, mental and behaviour, neurodevelopmental, medical or genetic and functional, problems and disorders), age, gender, the presence of sensory differences, IQ, language level or family/carer contextual factors (for example, socioeconomic status, parental education, parental mental health, sibling with special education needs)?
- For children and young people with autism is the effectiveness of interventions aimed at improving the impact on the family mediated by the intensity of the intervention, the duration of the intervention, the length of follow-up or programme components?

Domain 6: Adverse events associated with interventions

- What are the potential harms associated with psychosocial, pharmacological or biomedical interventions for children and young people with autism? (Considerations will be given to the particular management and support of looked after children, immigrant groups, and children with regression in skills).

2.8 Data extraction and evidence summary

For every clinical question, the evidence base and recommendations were extracted from each selected guideline and summarized in text form. Data extraction was performed by one researcher and checked by a second researcher. It is noteworthy that the NICE guideline included only SR and RCTs published in English. The HAS provided an additional analysis of the French literature and of non-randomized studies. The structure of the NICE guideline provides the backbone of the current report. The HAS report is summarized under the appropriate headings but mention is made of different subheadings in order to respect slightly different definitions. HAS worked in agreement with l'Agence Nationale de l'Evaluation et de la Qualité des Etablissements et Services Sociaux et Médico-sociaux (ANESM). The NICE guideline used the critical outcomes defined by their guideline development group to structure the guideline chapters and the results of the literature, and this structure has been taken over in the current report. The guideline is based on the diagnostic criteria available at the time of development (DSM-IV-TR). At the time of the production of the NICE guideline, DSM-5 had not yet been published.

2.9 Formulation of recommendations

NICE used GRADE in formulating recommendations.[20, 21] HAS used a score A for level 1 evidence (RCTs or meta-analyses), a score B for level 2 evidence (low level RCT, non-randomised studies and cohort studies) and a score C for level 3 and 4 evidence (comparative studies with bias, retrospective or case studies).

However in both guidelines evidence was scarce and evidence levels could mostly not be attributed. Since the ADAPTE method was applied on two existing guidelines and the great majority of recommendations were expert based, it was not possible to use GRADE for allocating levels of evidence or strengths of recommendation. The final KCE recommendations for management and treatment of ASD are consensus based and therefore their level of evidence is low.

According to the KCE process, research recommendations were issued for domains with poor or conflicting evidence, and recommendations without grading, based on expert consensus, were issued for domains lacking EBM evidence. In this process it was ensured that no final recommendation would

conflict with recommendations for which there is evidence. It should be noted that 'no recommendation' refers to the lack of solid scientific proof and or consensus. This could be modified based on scientific research or consensus.

Based on the two guidelines, a first summary of recommendations made by NICE and HAS was prepared by the KCE team (see tables by domain in the report).These tables also summarize the evidence on which the respective recommendations were made by NICE and HAS.The tables were circulated to the GDG three weeks prior to the face-to-face meetings held on January 13, February 24, March 31 and April 28 2014.

GDG members were asked to comment on the tables before and during the meeting. The comments are documented in the tables by domain in the Appendix. After the GDG meeting and based on the comments a 'KCE recommendation' was drafted and submitted to the GDG for a vote using the Delphi method to reach consensus (http://www.rand.org). The GDG members could fill out the questionnaire online by means of Lime survey (https://www.limesurvey.org). The GDG members indicated for each recommendation whether they agreed, disagreed or felt unable to answer. Subsequently they received feedback during the next meeting in the form of a statistical representation of the group response, after which the process repeated itself. 'The goal is to reduce the range of responses and arrive at something closer to expert consensus''.[22]

In the first round the GDG members answered to closed answer categories (I agree, I disagree, I feel unable to answer) and could give their comments to each recommendation. Comments to the recommendations were listed before and discussed during GDG meetings. Mostly the discussion resulted in reformulations of the commented recommendation. In the second round the same or revised recommendations were presented to the GDG members, with the same closed answer categories, but without space for comments. Only recommendations for which the level of agreement was 85% or lower were presented in the second round. This was done for four packages of recommendations, for some packages more than two rounds were necessary. Those recommendations for which no consensus of more than 85% was reached after the third round, were discarded and considered not to be valid. The results of all survey rounds for the four packages of recommendations, as well as the comments made by the GDG, can be found in the Appendix.

This method enabled us to map the degree of consensus in an objective and documented way. Every voice was heard in the same way. It allowed to focus meetings on the recommendations for which no consensus was reached. A limitation of this methodology was that although all GDG members were invited for each Delphi survey, not all of them replied to each survey. Therefore the actual sample was not the same for each package of recommendations.

All recommendations are summarized in section 5.1. Recommendations are organized by domain and obtained at least 85% consensus. The GDG also identified specific areas for which research is needed and issued specific research recommendations in section 1.1. In order to particularly address the scope relating to the Belgian context, additional expert consensus recommendations that emerged during the previous discussions were drafted and discussed during a 4th GDG meeting on April 28, 2014. These recommendations/statements are presented in section 6.4.

2.10 External review by stakeholders

All the recommendations prepared by the GDG, as well as the summary of the evidence of the NICE and the HAS guideline, were circulated to the stakeholders. On May 26, 2014, thirty-one stakeholders participated in a meeting and discussed the clarity, completeness and acceptability of the recommendations. All invited panellists were asked to score whether they agreed, disagreed or felt unable to answer using an online survey tool. If panellists disagreed with the recommendation they were asked to provide an explanation supported by appropriate scientific evidence. All recommendations that obtained less than 85 % agreement were discussed. The wording of a number of recommendations was improved based on the discussion with these experts, and after obtaining the GDG's approval. In the appendices an overview is provided of how the stakeholder's comments were taken into account. Additional concerns were reported under the sections 'other considerations'. The stakeholders also identified potential barriers and facilitators related to the use of this guideline.

2.11 Final validation

As part of the standard KCE procedures, a two-step validation of the report was conducted prior to its publication. The first external assessment, was performed by two internationally reputable scientific experts who critically reviewed the content of the report (cf. names in the colophon). Their assessment was discussed on 2 September 2014. The second part of the validation, chaired by the Belgian Centre for Evidence-Based Medicine (CEBAM) focussed on methodology making use of the AGREE II checklist. (cf. names in the colophon). This final validation was performed on September 10, 2014. The validation of the report results from a consensus or a voting process between the validators.

3 DEFINITIONS

In this paragraph a short description is presented for some of the psychosocial, behavioural and educational interventions discussed in the selected guidelines. These descriptions are produced by the authors of this guideline but are mainly based on the NICE and HAS guidelines. When appropriate a specific reference is mentioned.

3.1.1 General definitions

Pharmacological interventions: interventions using drugs in their licensed indication

Biomedical intervention: intervention based on the application of the principles of the natural sciences and especially biology and biochemistry. Drugs can also be categorized as a biomedical intervention, if they are used for other than their primary (licensed) indication.

Psychosocial intervention: generic term encompassing all types of interventions aiming at improving the psychological functioning and wellbeing of an individual, as well as his/her integration in society. In this report the term psychosocial intervention covers a broad scope: i.e. it *includes* behavioural, developmental and educational interventions. Thus, we made no distinction in the labelling of the several non-drug interventions in order to avoid over categorization and adhere to a comprehensive discussion.

- **Behavioural intervention**: aims at encouraging appropriate behaviour and discouraging inappropriate behaviour. Therapists, teachers and/or parents break down the desired behaviours into small, achievable tasks which are then taught in a very structured manner. Behavioural programmes typically involve a range of different strategies. Examples are discrete trial training (DTT), pivotal response training (PRT) and early intensive behavioural intervention (EIBI) (see further), which are designed to ensure that newly acquired skills are applied in the child's day-to-day environment.[23]
- **Developmental intervention:** Developmental interventions are designed to target the core deficits within the individual rather than his or her outward behaviours. Therapists, teachers and/or parents work with the individual's own interests or actions to slowly build

engagement, interaction, communication, affection and then specific skills such as logical reasoning, symbolic thinking etc.[24]

- **Educational intervention:** education has been defined as the fostering of acquisition of skills or knowledge to assist a child to develop independence and personal responsibility. This includes not only academic learning but also socialization, adaptive skills, language, communication and reduction of behaviour problems.[25] The term educational intervention has various interpretations. In practice it includes any intervention which is delivered in an educational setting (such as a nursery, a school or a college) or which aims to educate i.e. teach or develop the recipients of the intervention. Some educational interventions are aimed at preschool children and their parents and actually take place in the family home. There is a large overlap between educational interventions and other types of intervention, especially behavioural and developmental interventions. Most educational interventions use one or more behavioural or developmental techniques.[24]
- **Parent training:** A number of interventions involve the training of parents. Parent training is not an intervention in itself. It should be viewed as a mode of treatment delivery.

3.1.2 Specific interventions

AAC

Augmentative and alternative communication (AAC) is an umbrella term that encompasses the communication methods used to supplement or replace speech or writing for those with impairments in the production or comprehension of spoken or written language. ACC can for example include facial expressions or gestures, point to pictures or writing. Children with severe speech or language challenges may use AAC strategies to supplement existing speech or replace speech that is not functional. Special augmentative aids, such as picture and symbol communication boards and electronic devices, are available to assist the process. AAC strategies can be a permanent aid or a temporary addition to an autistic child's communication.

ABA

Applied behaviour analysis (ABA) is a general approach to intervention that can involve a wide range of behavioural strategies such as discrete trial training (DTT). It is intended to be used to change behaviours across multiple domains. Behavioural approaches to intervention (also called behaviour modification or behaviour therapy) can take many different forms and include strategies such as discrete trial learning, pivotal response training, incidental teaching, shaping, modelling and prompting of behaviours, backward and forward chaining, time out and extinction. The essential principle, however, is that all behaviours are affected by their consequences (which may be negative or positive). While behavioural principles affect everyone's daily activities, ABA involves a systematic study of the factors that may be causing problem behaviours (who, where, when triggers) or limiting skill acquisition, detailed assessment of the behaviour(s) and assessment of potential rewards and maintaining factors. This analysis is then used to formulate hypotheses about the behaviour, its antecedents, triggers, causes and maintaining factors and then modifying any or all of these in order to effect behavioural change. NICE considered ABA as an applied science rather than as a specific intervention.

AIT

Auditory integration training - also known as AIT - involves a person listening to a selection of music that was electronically modified. There are several different kinds of auditory integration training including the Berard Method, the Listening Program, Samonas Sound Therapy and the Tomatis Method. AIT is based on the concept that some individuals, including some children with autism, are hypersensitive (over-sensitive) or hyposensitive (under-sensitive) to certain sound frequencies. This is believed to cause a variety of perceptual problems - such as an inability to concentrate or to understand other people, irritability or lethargy. AIT is designed to improve the person's ability to process sounds by're-educating' the brain'.[24]

CBT

Cognitive behavioural therapy (CBT) is a type of psychotherapy. In CBT therapists focus on the impact a patient's present dysfunctional thoughts have on current behaviour and future functioning. CBT is aimed at evaluating, challenging and modifying a patient's dysfunctional beliefs (cognitive restructuring). In this form of treatment, the therapist mostly emphasizes homework assignments and outside-of-session activities. Therapists exert an active influence over therapeutic interactions and topics of discussion, use a psycho-educational approach and teach patients new ways of coping with stressful situations. There are two main types of CBT: (a) CBT in which cognitive restructuring is the core element of the treatment and (b) CBT in which cognitive restructuring is an important component, but in which at least two other components (such as behavioural activation, social skills training, relaxation or coping skills) also have a prominent place.[26]

COMPASS

The collaborative model for promoting competence and success (COMPASS) is a parent-teacher collaborative model aiming at enhancing the competence of the student with autism as well as the person working with the student. COMPASS builds on comprehensive, ongoing assessment before decisions are reached. Information is gathered by formal and informal means and by input from people who knows the individual, to balance challenges and support mechanisms, and ultimately reach consensus for building a successful individualized program.[27]

DTT

Discrete trial training focuses specifically on developing skills in a hierarchical manner (using chaining, shaping and fading techniques), systematic identification of reinforcers, continuous monitoring of progress and generalisation to progressively less structured and more natural environments.[23]

IBI/EIBI

The generic terms intensive behavioural intervention (IBI) and early intensive behavioural intervention (EIBI) refer to behavioural interventions that are intensive and comprehensive. The intensity of a program relates to the number of hours of treatment the child receives per week (up to 40 hours) as well as the intensity of training, curriculum, evaluation, planning and coordination. EIBI or and early intensive behavioural intervention training (EIBT) begins at the age of four years or younger. There are different models: some emphasizes instruction at home with discrete trial training (DTT), other models provide instruction in classrooms; some emphasize teaching methods other than discrete trial training, such as incidental teaching. (http://www.asatonline.org/treatment/treatments/eibi)

ERT

Emotion recognition training (ERT) is the use of various methods designed to teach emotion recognition skills to children with autism with a focus on components of facial expressions.

ESDM

The Early Start Denver Model (ESDM) was developed for intensive delivery of a comprehensive early behavioural intervention for children with autism ages 12 to 48 months. It is a refined and adapted extension of the Denver Model intervention for preschoolers with autism ages 24 to 60 months. The model emphasizes lively, dynamic interactions involving a strong positive affect aiming to lead children to seek out social partners as participants in favourite activities. The technique of 'sensory social routines' was developed to highlight an engaging dyadic exchange, initiated by the child and continued through nonverbal, and later, verbal communications.[28]

P-ESDM is a parent-mediated form of ESDM.

FRT

Face Recognition Training (FRT) training includes a Let's Face It! (LFI!) computer-based intervention. The LFI! Program comprised of seven interactive computer games that target the specific face impairments associated with autism, including the recognition of identity across image

changes in expression, viewpoint and features, analytic and holistic face processing strategies and attention to information in the eye region.[29]

Facilitated communication

Facilitated communication - also known as supported typing - is a form of alternative and augmentative communication in which someone physically supports an autistic person and helps him to point at pictures or words. Facilitated communication is based on the idea that many of the difficulties faced by autistic people are due to movement difficulties rather than to social or communication difficulties. The communication partner - usually called a facilitator - physically supports the autistic person so that he can point to pictures, symbols, letters and/or words using a computer keyboard or letter/picture books. By doing this, the autistic person can demonstrate what he wants to communicate. [24]

HBOT

Hyperbaric oxygen therapy (HBOT) is the medical use of oxygen at a level higher than atmospheric pressure. The equipment consists of a pressure chamber, which may be of rigid or flexible construction and a means of delivering 100% oxygen. The treatment is performed to a predetermined schedule by trained personnel who monitor the patient and may adjust the schedule as required.

Joint-attention training

Joint attention is the process by which an infant learns to recognize the direction of an adult's gaze, orient their own gaze to follow it and then look in the same direction. Joint engagement is the process in which an infant and someone else do the same thing at the same time. There are numerous interventions which are designed to improve joint attention and/or joint engagement amongst other skills in people on the autism spectrum including some behavioural and developmental interventions. There are also some programmes which specifically target joint attention and joint engagement.[24]

Kata (exercise training)

Kata is a Japanese word describing detailed choreographed patterns of movements practiced either solo or in pairs. Kata are used in many traditional Japanese arts but are most commonly known for the presence in the martial arts, including aikido, judo, jujutsu and karate.

LEAP

LEAP is an abbreviation of Learning Experience - An Alternative Program for Preschoolers and Parents. LEAP is a developmentally-integrated preschool program for typically developing children and peers with autism. It aims to offer a comprehensive parent education program providing real help in real-world home and community settings. Replication sites exist in school districts throughout the United States.

Neurofeedback

Neurofeedback consists in recording patients' electroencephalographic (EEG) activity, showing them their oscillatory brain activity as it is recorded (using bar graphs to reflect the amplitude of a particular frequency) and training the patients to 'move up or down' their brain activity while observing the amplitude of their own brain waves.[13]

PACT

Parent-mediated Communication-focused Treatment (PACT) refers to a parent-child communication-focused intervention in children aged 2 years to 4 years, 11 months with autism. The rationale behind the PACT intervention is that these children respond with enhanced communicative and social development if parents are able to adapt their communication to their child's specific impairments. The intervention consists of one-to-one clinic sessions with therapist and parents and children. The aim of the intervention is firstly to increase parental sensitivity and responsiveness to the autistic child's particular pattern of communication using direct work with parents and video feedback methods. Then, the further incremental development of the child's communication is encouraged by introducing a range of strategies such as action routines, matching language to the child's understanding, and the use of pauses. After an initial orientation meeting, families attend fortnightly 2 hour clinic sessions for 6 months followed by monthly booster sessions for

6 months (maximum 18). In-between sessions, families are asked to do 30 minutes of daily home practice.[30]

PECS

The Picture Exchange Communication System (PECS) is used to teach learners to communicate in a social context. Using PECS, learners are initially taught to give a picture of a desired item to a communicative partner in exchange for the item. There are six phases of PECS's instruction: (1) 'how' to communicate, (2) distance and persistence, (3) picture discrimination, (4) sentence structure, (5) responsive requesting, and (6) commenting.[31]

Peer-mediated training

In peer-mediated training typically developing (normal) children ('peer buddies') are involved in the treatment program, e.g. in social skills groups or in free-play sessions (for further details see the full NICE guideline p256-261).

PRT

Pivotal response treatment (PRT) aims at developing 'pivotal' behavioural skills, motivates and enables to respond to multiple cues.[32] Pivotal response training aims to foster generalisation and focuses on pivotal aspects of behaviour such as motivation and responsivity to multiple stimuli. It includes components such as child choice, turn-taking and other maintenance strategies, and makes use of naturalistic settings and teaching procedures to enhance language, play and social behaviour.[23]

RIT

Reciprocal Imitation Training (RIT) is a naturalistic imitation intervention developed to teach young children with autism to imitate during play.[33]

Social Communication Interventions

The GDG involved in the NICE guideline placed great emphasis on properly defining the term 'social communication' interventions. The following definition is taken from the PACT study.[30]

'Social communication interventions are a kind of psychosocial intervention that act to make specific and theoretically-based alterations in a child's dyadic communication environment in order to improve the child's social communication, attention and language. They are most usually used to improve core autism features in preschool children with diagnosed autism, but are also used to enhance social adaptation in young school age children.'

'Common features of the interventions preschool are the creation of a pattern of dyadic communication within play that tends to follow the child's lead and interest in activities, talks about what the child is doing, repeating back or expanding on what the child says, giving sensitively timed corrective feedback, sitting close to the child and making eye-contact, and making environmental adjustments to engage the child. In the early school years a similar communication environment is established but adapted into the school and peer setting.'

'The interventions typically will build on an assessment of the current developmental level of the child with staged goals in line with social communication developmental theory.'

SULP

Social use of Language Programme (SULP) is an independently researched programme, offered with manuals and teaching sets. It claims to be 'a cohesive framework within which to enhance personal, emotional and social development from a communication and thinking skills perspective'.[34]

TEACCH

Treatment and Education of Autistic and Communication-Handicapped Children (TEACCH) is a training program for individuals of all ages and skill levels with ASD. TEACCH builds on a philosophy that recognizes autism as a lifelong condition and does not aim to cure but to respond to autism. Strategies used are designed to address the difficulties faced by all people with autism and be adaptable to whatever style and degree of support is required. TEACCH methodology is rooted in behaviour therapy (more recently combining cognitive elements) guided by theories suggesting that behaviour typical of people with autism results from underlying problems in perception and understanding. The strategies put forward by TEACCH do not work on the behaviour directly, but on its underlying reasons, such as lack of understanding of what the person is expected to do or what will happen to them next, and sensory under- or over-stimulation. Working from

the premise that people with autism are predominantly visual learners, intervention strategies are based around physical and visual structure, schedules, work systems and task organisation. Individualised systems aim to address difficulties with communication, organisation, generalisation, concepts, sensory processing, change and relating to others.[35]

TAII

Technology-aided instruction and intervention (TAII) (e.g. Teach Town) are those in which technology is the central feature of an intervention that supports the goal or outcome for the student. Technology is defined as 'any electronic item/equipment/application/or virtual network that is used intentionally to increase/maintain, and/or improve daily living, work/productivity, and recreation/leisure capabilities of adolescents with autism spectrum disorders'. TAII incorporates a broad range of devices, such as speech-generating devices, smart phones, tables, computed-assisted instructional programs and virtual networks. The common features of these interventions are the technology itself (as noted) and instructional procedures for learning to use the technology or supporting its use in appropriate contexts.[31]

Teach Town

Computer-assisted educational intervention developed to teach children with autism to learn real world social and communications skills, and to support their emotional development. The Basics version is developed for children who are developmentally 2 to 7 years old; it exists in a version for parents and a version for teachers.[36]

Theory of Mind training

Theory of Mind (ToM) is a theory based on the fact that the mind is not directly observable. It consists of the ability to attribute mental states (beliefs, desires, intentions etc.) to yourself and others and to understand that others have mental states that can differ from one's own. Deficits in this ability typically occur in people with autism spectrum disorders. 'ToM-training' encompasses a variation of treatments aiming at improving social skills in ASD by improving social cognitions and ToM.[37]

4 MANAGEMENT OF CHILDREN AND YOUNG PEOPLE WITH AUTISM

4.1 Experience of care and the organization and delivery of care

4.1.1 NICE

4.1.1.1 Methods

The methods used in the NICE review for this chapter differed from the main methodology as described in section 2.6 to 2.8. In this chapter, a systematic search was performed in a broad selection of databases for primary qualitative studies and surveys published after 1992 dealing with first-hand experience of care of children and young people with autism, and their families and carers; no particular outcome was specified. For details see the full NICE guideline section 4.2.1 page 60-63 and see NICE guideline Appendix 7. Each included study was reviewed and broad themes were identified and coded using a matrix. This matrix was formed by creating a table with the eight dimensions of person-centred care developed by the Picker Institute Europe, down the vertical axis, and key points on a pathway of care as specified by the NICE GDG, across the horizontal axis (see Table 2). The Picker Institute's dimensions of patient-centred care were chosen because they are well established, comprehensive and based on research.

Table 2 – Dimensions of the NICE matrix used to analyse qualitative data on experience of care

NICE matrix: vertical axis and horizontal axis dimensions	
Dimensions of person-centred care (vertical axis)	1. Involvement in decisions and respect for preferences 2. Clear, comprehensible information and support for self-care 3. Emotional support, empathy and respect 4. Fast access to reliable health advice 5. Effective treatment delivered by trusted professionals 6. Attention to physical and environmental needs 7. Involvement of, and support for, family and carers 8. Continuity of care and smooth transitions
Key-points on a pathway of care (horizontal axis)	• Access; • Information and support; • Assessment and referral in crisis; • CAMHS (Child and adolescent mental health services); • Transition (CAMHS to adult mental health); • Community services (e.g. leisure programmes); • Therapeutic intervention; • Primary care; • Secondary care; • Social care; • Residential care: short breaks; • Residential care: long term; • Educational setting: mainstream; • Educational setting: specialist; • Educational setting: home education; • Themes that apply to all points on the pathway.

The NICE GDG agreed initial recommendations based on the findings from their review of qualitative evidence. These initial recommendations were presented to an expert advisory group as part of a validation process and then feedback from these groups was integrated with the initial findings. Next, the recent legislation regarding services for people with autism spectrum conditions in England and Wales was taken into consideration to further inform the final guideline recommendations. Since this is context-specific information which is considered to be out of scope for the present report, the initial version of the recommendations based on the findings from the review of qualitative evidence will be used in this report instead of the final NICE guideline recommendations related to experience of care and the organization and delivery of care.

4.1.1.2 Evidence

NICE[13] extracted information from 214 qualitative studies and surveys; 34 publications (16%) concerned service user experience and 180 publications (84%) concerned family and carer experience. For each cell of the matrix, the results were presented in a narrative way, using quotes from the original study. For details see the full NICE guideline section 4.2.4 to 4.2.11 pages 63-171. Three studies (Meirsschaut 2010, Moyson 2011, Renty 2006) were conducted in Belgium and are therefore of specific relevance to the Belgian situation.[38-40] These studies are discussed here in more detail; they covered 9/128 cells of the matrix developed by NICE (see 4.1.1.1, Table 2).

The three themes identified in the study by Meirsschaut (2010)[38] were:

- access to effective treatment delivered by trusted professionals,
- providing information and support while involving/ supporting family and carers;
- involving/supporting family and carers by residential care (short breaks).

Carers discussed their frustration with travel and paperwork, and with long waiting lists (Meirsschaut 2010),[38] see also Renty (2006).[40]

Carers highlighted the importance of being given information about autism in the post-diagnosis period, including: what autism is (Meirsschaut 2010).[38]

Carers described an unmet need for respite services (Meirsschaut 2010).[38]

The two themes identified in the study by Moyson (2011)[39] were:

- providing information and support while involving/ supporting family and carers,
- effective treatment delivered by trusted professionals in specialist educational settings.

Siblings described positive experiences with support groups and valued the opportunity to share their experiences with other siblings (Moyson 2011).[39] Siblings spoke positively about the specialist education their sister/brother with autism was experiencing: '*You know, I'm glad he can go to that special school for children like him. The teachers there know exactly how to treat him. (11-year-old brother of boy with autism)*' (p 49 Moyson 2011).[39]

The seven themes identified in the study by Renty (2006)[40] were:

- providing information and support while involving/ supporting family and carers,
- continuity of care and smooth transitions from CAMHS to adult mental health,
- effective treatment delivered by trusted professionals in mainstream educational settings,
- effective treatment delivered by trusted professionals in specialist educational settings,
- involving/supporting family and carers in mainstream educational settings,
- continuity of care and smooth transitions in mainstream educational settings,
- effective treatment delivered by trusted professionals for therapeutic interventions.

Carers discussed their frustration with travel and paperwork, and with long waiting lists (Renty 2006).[40]

A recurring theme in the carer experience of care was a gap in services for children and young people with autism without a coexisting learning disability (IQ>70) and this was particularly emphasised as a barrier to accessing services, support and education (Renty 2006).[40]

Problems with varying eligibility thresholds across services were also discussed as a barrier to access by carers (Renty 2006).[40]

Carers wanted the following to be available promptly post-diagnosis: information about services available (Renty 2006).[40]

Carers also wanted to be offered the opportunity for follow-up support: '*The pediatrician who conducted the disclosure interview assured us that we were ever allowed to take contact with her to ask questions…During the disclosure interview we were flooded with information. Because the disclosure of a diagnosis brings about a lot of emotions, we did not remember all that was said. Furthermore, a lot of questions arise a few days after the disclosure interview. Therefore, it is so important that you can call someone to answer those questions'* (p 377 Renty 2006).[40]

Carers discussed the importance of continuity of support between child and adult mental health services for the well-being of their child: *'Now she [daughter] consults an excellent child psychiatrist. Next month she will be 18 years old, thus she has to find a new psychiatrist. That won't be easy for her. Continuity of support is essential for L.'s wellbeing'* (p 379 Renty 2006).[40]

Professional understanding of autism (in mainstream educational settings): carers emphasised the importance that teachers and teaching assistants have an understanding of autism (Renty 2006).[40]

Carers spoke positively about experiences where they had been included and listened to (in mainstream educational settings): '*I think the extensive personal experiences that we have with our child are very important. The teacher says that if we have a different opinion, we may always suggest alternatives for the benefit of our child's development. We act in close cooperation'* (p 379-380 Renty 2006).[40]

Carers spoke about the need for honest communication with the school, and highlighted this as important because of a lack of communication from their child about their school day (Renty 2006).[40]

Carers discussed positive experiences of using a daily home-school diary: *'We have daily contact with the teacher either by an exercise book or by our son's diary. I am very pleased with that. The teacher writes down how D. is doing and in which activities he participated. That's very important. If there are problems in school, the teacher writes how she has dealt with it'* (p 379 Renty 2006).[40]

Carers spoke about problems for their child caused by high turnover of educational staff: *'Currently, the school has to deal with a large turnover of staff. It always takes a long time for our son before he becomes acquainted with these new people'* (p 380 Renty 2006).[40]

Carers emphasised the importance that teachers and teaching assistants have an understanding of autism, and they were satisfied that specialist educational provision met this need: *'The teacher has a lot of knowledge of ASD and that is very important. That is one of the advantages of attending a specialized school: they know what our son needs and have the know-how to respond to his needs'* (p 380 Renty 2006).[40]

Parents and carers were also asked to rate their experience of autism-specific support, including special education facilities and home-based interventions. Of the 244 participants in this study, 59% received autism focused support with their mean satisfaction reported as 4.12 out of 5 (5 being very satisfied). The 244 carers were also asked to rate satisfaction in relation to mainstream nursery, primary and secondary schools. On a scale where 5 is excellent, the mean scores were 3.28, 3.12 and 3.43 respectively (Renty 2006).[40] Similarly, within the same study, carers were asked to rate their child's education provision in terms of the quality of support and education the child received. Out of a possible score of 10, the mean score received from the parents was 5.8 (Renty 2006).[40] Finally, 244 carers were asked to rate how satisfied they were with the school meeting their child's needs. On a scale where 5 indicated 'very satisfied', secondary schools received an average score of 4, followed by special education nursery school (average: 3.95) and primary school (average: 3.75) (Renty 2006).[40]

4.1.1.3 NICE Recommendations regarding the experience of care of children and young people with autism and their families and carers

Based on the review of the qualitative evidence for the experience of care of children and young people with autism and their carers and siblings the NICE GDG agreed on the initial recommendations, which are presented in Table 3.

4.1.2 HAS guideline

HAS proposed the following question: 'How to optimally organize and coordinate educational and therapeutic interventions for children and adolescents with autism?' The following subheadings were formulated: 'How to synchronize interventions within one structure? How to synchronize interventions in different care structures?'

None of the 17 guidelines reviewed by HAS offered an answer to the research question. Therefore the French literature was reviewed for four domains to which the research question was applied. All types of reports and questionnaires were included in order to document the local situation, and all recommendations were based on these reports and expert consensus. In this regard, the HAS document differs greatly from NICE.

The HAS recommendations were subdivided in four domains:

- Stakes and principles of action
- Sensitive transition periods
- Tools for insuring a coherent intervention
- Education and support of caretakers

The recommendations are presented in Table 3. For full and detailed descriptions, please refer to the HAS document.

Table 3 – Summary of recommendations by NICE and HAS guidelines on organization and delivery of care

NICE guideline Recommendation	HAS guideline Recommendation
All staff working with children and young people with autism should have an understanding of autism.	
In all settings, professionals should take into account the physical environment in which children and young people with autism are supported and cared for and make reasonable and appropriate adjustments. Where it is not possible to adjust or adapt the environment, processes should be adjusted to limit the negative impact of the environment.	
Children and young people with autism should have access to a key worker approach in order to manage and coordinate treatment, care and support, including the management of transitions, for the child or young person with autism and their family and carers.	
Children and young people with autism should be offered evidence-based intervention aimed at preparation and coping strategies to facilitate access to community services, including the skills to access public transport, employment and leisure facilities.	
Children and young people with autism, and their family and carers, should have easy access to short breaks.	
Children and young people with autism, and their family and carers, should be provided with post-diagnosis information about services available and support, for example a family support worker.	
Treatment and care of children and young people with autism should involve shared decision making and a collaborative approach that takes into account service user preferences.	
All children and young people with autism should have access to healthcare and social care services, including mental health services, and access should not be restricted based on a child's intellectual ability, autism diagnosis, or any other eligibility criteria.	
Stakes and principles of action	
	Need of a coherent multidisciplinary approach.

	Define rules for multi (trans) disciplinary approach in the same or in different institutions.
	Rules should define work plan including timing and identify coordinator.
	Rules should be formalised within an institution, in conventions with other professionals, in networks.
	The rules should be known by all professionals.
	The rules/action plan should be part of the personalised reimbursement and educational plan.
Tools for improving coherent intervention	
	Develop a personalised program based on evaluation with appropriate tools and on observation in daily life, and in agreement with the patient, the parents and all professionals involved.
	Assign the task of coordinator to one of the professionals in order to guarantee the coherence and continuity of care.
	A medical doctor or director of an institution will be responsible for overseeing or delegating the coordination task.
	A file (case record, dossier) is the source document for communication.
	The file should contain all relevant information on the patient: personalised project, evaluations, treatment plan, and specific interventions.
	Sharing the file necessitates parental consent, in line with the rules of duty of professional confidentiality.
	In professional communication, it is recommended to use the International Classification of Diseases (ICD-10) and the International Classification of Functioning, Disability and Health for Children and Youth (ICF-CY).
	A go-between notebook is recommended to support communication between the professionals and the parents and child.
	Upon transfer between institutions (medical/social) a contact person (referent) should be kept.
	Networking, collaboration and regular meetings should be organized between professionals.

	The Reference centres for Autism have a specific role in supporting the networking.
	Institutions, especially hospitals, should offer protocols to facilitate first contacts.
	A medical examination by the medical doctor chosen by the parents should be offered at least yearly.
Sensitive transition periods	
	Diagnostic and therapeutic teams should collaborate closely. Professionals who intervene only occasionally should consult the team.
	Therapeutic teams should take part in the first information session with parents.
	Transition periods e.g. transfer from one type of care/education to another or from childhood to adulthood require particular attention and should be prepared. Continuity of care should be assured.
	Crisis situations require specific evaluation and intervention. Necessary information should be communicated among professionals, also in case hospitalization is inevitable. Specific education of professionals about crisis situations is necessary.
Education and support for professionals	
	Continuous education (every 2 to 3 years) is needed for all professionals.
	Therapeutic teams should be accompanied by an external expert for debriefings once per month or per trimester.
	Professionals should not work in isolation but share experiences with peers or be supervised.
	New professionals should be coached.
	Awareness and support should be offered to professionals to prevent burn-out.

4.2 Interventions aimed at the core features of autism

4.2.1 Psychosocial interventions for core features of autism

4.2.1.1 Evidence

The evidence reported by NICE and HAS is summarized and presented in Table 4 and recommendations were derived from the evidence.

NICE[13] extracted clinical evidence from 39 RCTs on this topic. For the direct and indirect effects of psychosocial interventions on overall autistic behaviours, data were extracted from 7 RCTs, for the direct and indirect effects of psychosocial interventions on the core autism feature of impaired reciprocal social communication and interaction data were extracted from 33 RCTs and for the indirect effects of psychosocial interventions on the core autism feature of restricted interests and rigid and repetitive behaviours data were extracted from 5 RCTs. More detailed information on the studies can be found in the full NICE guideline from section 5.2.2 page 205-283 and in NICE guideline Appendix 12b.

HAS[12] described global intervention programmes (section 5.3, p 90-188) based on 12 SRs from 2000-2010 and a Canadian review on studies published prior to 2001. All included children were under 6 years of age. No studies comparing global interventions (e.g. ABA vs. TEACCH) could be identified but studies comparing ABA or TEACCH to personalised, parental or educational intervention were reviewed. Further, studies comparing behavioural intervention vs. educational support as well as various other developmental interventions were discussed. None of the included subjects had high IQs.

Besides global intervention programmes, HAS also considered specific interventions. It considered interventions aimed at improving communication and at improving social interactions separately. On the topic of communication, HAS discussed the results of 2 SRs, 6 comparative clinical studies (of which 2 are RCT 's included by NICE) and 5 clinical reports that did not meet the inclusion criteria (no comparison, less than10 patients included). On the topic of social interactions 10 SRs were reviewed, 8 comparative studies (of which 4 RCTs included by NICE) and 2 comparative studies not meeting the inclusion criteria. More detailed information on the studies can be found in the full HAS guideline from section 5.4.1 to section 5.4.2 page 188-224.

HAS also reported separately on patients with Asperger syndrome. Evidence was extracted from 5 SRs and 13 clinical studies on interventions including highly functioning patients with Asperger's syndrome. More detailed information on the studies can be found in the full HAS guideline in section 5.4.6 page 240-255.

HAS reported that no evidence was available for Rett syndrome.

It should be notes that play–based strategies are limited to young children and that the recommendations do not apply to adolescents.

4.2.1.2 Effect of psychosocial interventions on overall autistic behaviours

NICE[13] concluded that there was low quality evidence of an effect in favour of the educational interventions (COMPASS and LEAP) when compared with treatment as usual or manual-only control, respectively. There was low to very low quality evidence for the behavioural intervention (ESDM) parent training and a social-communication intervention (Child's Talk) and the evidence was inconclusive.

Since all studies on global psychosocial interventions included subjects with IQs below average, HAS[12] considered IQ as an indicator of adaptive capacities and an interesting outcome of these interventions, rather than focusing on autistic behaviour. HAS concluded that systematic interventions improve IQ, language and ability to communicate more than personalised, less intensive and educational support, but not all children respond to these approaches. Early (at preschool age) and long term (2 to 3 years) interventions were beneficial in about 50% of children with autism and mental retardation. The longest post-interventional follow-up was 4 years. Expert consensus specified that none of the global interventions should be presented as a cure for autism.

HAS[12] reported a lack of scientific evidence regarding psychoanalysis and institutional psychotherapy.

4.2.1.3 *Effect of psychosocial interventions on the core autism feature of impaired reciprocal social communication and interaction*

NICE[13] concluded that although many studies have examined the effects of psychosocial interventions on the core autism feature of impaired reciprocal social communication and interaction, due to differences in comparators and outcome measures, very little meta-analysis was possible. From the few meta-analyses possible with better quality evidence, there was small to moderate effects in favour of caregiver- or preschool-teacher-mediated social-communication interventions on social interaction (as measured by the ADOS), communication acts, parent-child joint attention and parent-child joint engagement, for young children with autism (mean ages of 1-4 years). There was also very low quality evidence from a meta-analysis for a moderate effect of peer-mediated social-communication interventions on peer-child joint engagement for older children (mean ages of 8-9 years). Based on low to very low quality evidence it was not possible to draw conclusions about the relative benefit of parent training, AAC, animal-based, arts-based, behavioural or cognitive interventions. As to the educational interventions for the core autism feature of impaired reciprocal social communication and interaction, the NICE GDG considered the LEAP intervention to be potentially promising, but further blinded evaluation was considered necessary before a treatment recommendation could be made.

HAS[12] concluded regarding the specific topic of communication that all interventions with non-verbal or verbal children provide encouraging results. Especially for non-verbal children the methods should be incorporated into more comprehensive interventions. The PROMPT (Prompts for Restructuring Oral Muscular Phonetic Targets) and the Denver method are beneficial for communication. Different domains (e.g. attention, speech, interaction) should be trained simultaneously. Computer assisted programs facilitate language acquisition.

HAS concluded regarding social interaction that most studies report favourable effects especially in children less than 6 years of age with one on one interaction. The acquisition of social skills is specific and not interchangeable. It is difficult to assess whether a child acquires a social competence or a behavioural skill. Interventions should lead to social competence. Different patient profiles and different reaction patterns complicate the evaluation of interventions. However, the lack of knowing the best intervention should not prevent the use of interventions.

Regarding the specific subgroup of children and adolescents with Asperger's syndrome, HAS concluded that some studies obtain favourable results for training to recognize emotions or for CBT aiming at improving social relationships. The effect of CBT interventions on anxiety in the specific subgroup of children and adolescents with Asperger's syndrome are promising. Anxiety is considered to be a co-morbid disorder. HAS experts mention that CBT requires a good level of language before it can be applied. Regarding other individual psychotherapeutic approaches, experts have heavily criticised the psychoanalytical approach, due to the lack of scientific evidence of efficacy.

HAS reported that no evidence was available for Rett syndrome, thus no specific conclusions or recommendations could be offered.

4.2.1.4 *Effect of psychosocial interventions on the core autism feature of restricted interests and rigid and repetitive behaviours*

NICE[13] concluded that there was very little evidence for psychosocial interventions aimed at the core autism feature of restricted interests and rigid and repetitive behaviours. Based on a single trial, there was low quality evidence for a small effect of parent training (as an adjunct to antipsychotics) on compulsions. In contrast, the evidence (low to very low quality) for behavioural interventions, cognitive interventions and social-communication interventions was inconclusive.

HAS[12] did not discuss restricted interests and rigid and repetitive behaviours separately but defined other domains such as cognitive, emotions (included in section 4.3 on behaviour that challenges) and sensory-motor functioning (see full HAS guideline section 5.4.4 page 236). Sensory-motor functioning is also discussed in section 4.4.5. HAS issues general conclusions on early global interventions and personalised programs based on expert consensus.

4.2.2 Pharmacological interventions for core features of autism

NICE[13] extracted clinical evidence from 12 RCTs on this topic. For the direct and indirect effects of pharmacological interventions aimed at overall autistic behaviours, data were extracted from 8 trials; one trial examined the indirect effects of antioxidants on the core autism feature of impaired reciprocal social communication and interaction; 6 trials examined various pharmacological interventions aimed at the core autism feature of restricted interests and rigid and repetitive behaviours. More detailed information on the studies can be found in the full NICE guideline from section 5.3.2 page 289-307 and in NICE guideline Appendix 12b.

HAS[12] evaluated pharmacological interventions for all features of autism: core features and associated behaviour per class of pharmacological agents. Their advice is based on international recommendations (n=3), meta-analyses and literature reviews (n= 11), controlled clinical studies (n= 97) and other types of studies such as observational studies and case reports (n>150) (see HAS full guideline annexe 2). The following drug classes were reviewed: first generation antipsychotics (haloperidol), second generation antipsychotics (risperidone), SSRIs (fluvoxamine, fluoxetine, and citalopram), psych stimulant drugs such as dopamine reuptake inhibitors (methylphenidate) and norepinephrine reuptake inhibitors (SNRIs) (atomoxetine) and anticonvulsants.

For the effect of interventions on conditions coexisting with autism, rather than on the core features of autism, see chapter 4.4. For common coexisting mental health problems: see section 4.4.6.

4.2.2.1 Effect of pharmacological interventions on overall autistic behaviours

NICE[13] concluded that evidence was limited for pharmacological interventions aimed at overall autistic behaviours. There was low quality evidence from a single trial for a non-statistically significant treatment effect of anticonvulsant drugs (divalproex sodium) on overall autistic behaviours. There was also no evidence for a significant positive treatment effect of antidepressant drugs (fluoxetine) on overall autistic behaviours. However, there was evidence for a number of significant adverse events associated with antidepressants. There was moderate quality evidence from a single study (n participants=40) for a large and statistically significant effect of the combination of cyproheptadine (not available anymore in Belgium) and haloperidol relative to the combination of placebo and haloperidol for overall autistic behaviours. Only one meta-analysis (with two trials, total n participants=124) was possible and suggested a large positive treatment effect of antipsychotic drugs (risperidone) on overall autistic behaviours based on very low quality evidence. Moreover, there was evidence for significant harms associated with antipsychotic drugs, including increased risk of any adverse event, weight gain, prolactin concentration, leptin level, and tachycardia (see also section 4.6 Adverse Events). Based on low quality evidence there was no statistically significant effect of SNRI drugs (atomoxetine) relative to placebo for overall autistic behaviours.

HAS[12] concluded that the low level of evidence regarding the efficacy of drug treatments is in sharp contrast with the rate of prescriptions. The core features of autism cannot be treated with drugs. Associated problems (behaviour, psychosis, epilepsy) may be an indication for pharmacological treatment. The use of psychopharmaca should be second line and not systematic. HAS underlines that parents should receive written information on possible adverse events of pharmacological intervention and that their consent should be obtained, unless the life of the patient or his/her surroundings is at stake.

4.2.2.2 Effect of pharmacological interventions on the core autism feature of impaired reciprocal social communication and interaction

NICE[13] concluded that evidence was limited for pharmacological interventions aimed at the core autism feature of impaired reciprocal social communication and interaction. Results from a single small study provided low quality evidence of no significant benefits or harms associated with antioxidant drugs (N-acetylcysteine) for social impairment as an indirect outcome.

4.2.2.3 *Effect of pharmacological interventions on the core autism feature of restricted interests and rigid and repetitive behaviours*

NICE[13] concluded that evidence was limited for pharmacological interventions aimed at the core autism feature of restricted interests and rigid and repetitive behaviours. Evidence from the antidepressant meta-analysis of 2 trials (total N participants=188) revealed no clear evidence for positive treatment effects and significant harms associated with antidepressant drugs (fluoxetine, citalopram). There was also moderate quality evidence from one of these 2 studies (citalopram, N participants=149) for a placebo effect with antidepressant drugs on restrictive behaviours. Conversely, there was evidence from three trials (total N participants=415) of antipsychotic drugs, of moderate quality, for a small effect of risperidone (2 trials) or aripiprazole (1 trial) on compulsions. However, there was also evidence for significant harms associated with antipsychotic drugs, including increased risk of any adverse event, weight gain, prolactin concentration, leptin level and tachycardia (see also section 4.6 Adverse Events).

HAS[12] reports on 3 RCTs addressing irritability, rigid and repetitive behaviour and hyperactivity. The drugs studies were haloperidol, risperidone and aripiprazole. Although beneficial effects are reported on the outcome, adverse events were frequent. Based on expert consensus, HAS recommends these drugs as second line and temporary treatment only (see also section 4.3.3).

4.2.3 *Biomedical intervention for core features of autism*

NICE[13] extracted clinical evidence from 27 RCTs on this topic. Data were extracted from 24 studies for direct and indirect effects of biomedical interventions on overall autistic behaviours; data were extracted from 12 studies for direct and indirect effects of biomedical interventions on the core autism feature of impaired reciprocal social communication and interaction and from 8 studies for direct and indirect effects of biomedical interventions on the core autism feature of restricted interests and rigid and repetitive behaviours. More detailed information on the studies can be found in the full NICE guideline from section 5.4.2 page 307-373 and in NICE guideline Appendix 12b.

HAS[12] reports on biomedical treatments and other pharmacological therapies including: naltrexone (international recommendations n=2, SRs n=2), choline esterase inhibitors (2 RCTs), alpha 2 adrenergic agonists (one international recommendation and 3 RCTs), secretin (international recommendations n=4, 2 SRs, 1 RCT), immunotherapy (international recommendations n=3,1 RCT), chelating agents (international recommendations n=2,1 RCT), antibiotics (no evidence), antifungals (international recommendations n=2), vitamins (international recommendations, 1 Cochrane review SR, 1 RCT), diets excluding gluten or casein (international recommendations, the French food safety agency (AFFSA), 1 Cochrane review), omega 3 acids (international recommendations, 1 SR, 1 RCT), dextrometrophan (1 RCT), famotidine (1 RCT), amantadine (1 RCT), benzodiazepines and antihistaminic drugs (one international recommendation). More detailed information on the studies can be found in the full HAS guideline pages 293-297 and 305.

For the effect of interventions on features associated with autism, rather than on the core features of autism, see chapter 4.4. For the associated feature of sensory sensitivities: section 4.4.4, motor difficulties: section 4.4.5 and common medical problems (gastro-intestinal problems): section 4.4.7.

4.2.3.1 *Effect of biomedical interventions on overall autistic behaviours*

NICE[13] concluded that evidence was limited for biomedical interventions aimed at overall autistic behaviours. There was low to very low quality evidence from small single trials for acupuncture, massage, multivitamin/mineral supplement, omega-3 fatty acid supplement, gluten- and casein-free diet and neurofeedback. The one trial examining effects of chelation on overall autistic behaviours found no evidence for any statistically significant effect.

HAS[12] did not conclude in favour of any of the biomedical or other pharmacological interventions. There was no categorisation according to the different features of autism.

4.2.3.2 *Effect of biomedical interventions on the core autism feature of impaired reciprocal social communication and interaction*

NICE[13] concluded that there was low to very low quality evidence from single small studies for effects of a gluten- and casein-free diet or neurofeedback on the core autism feature of impaired reciprocal social communication and interaction. There was also evidence for small to moderate placebo effects of secretin on communication and social interaction consistent with improvement across both groups but greater improvement in the placebo group. Based on low quality evidence, the results were inconclusive with regard to complementary interventions, medical procedures (HBOT), nutritional interventions and sensory interventions.

4.2.3.3 *Effect of biomedical interventions on the core autism feature of restricted interests and rigid and repetitive behaviours*

NICE[13] concluded that there was low quality evidence from a single small trial for effects of an exercise intervention on the core autism feature of restricted interests and rigid and repetitive behaviours. There was also very low quality evidence from a single study for indirect effects of neurofeedback on stereotyped behaviour. There was evidence for a large effect of a gluten- and casein-free diet on unusual or bizarre behaviours, however, evidence was inconsistent and when a blinded outcome measure (ADOS) was examined, no significant effects of a gluten- and casein-free diet were observed. Based on low to very low quality evidence, it was not possible to reach a conclusion about the effect of secretin, medical procedures and sensory interventions.

4.2.4 *Recommendations regarding interventions aimed at the core features of autism*

An overview of all recommendations from the included guidelines for the domain of core features of autism is presented below and in Table 4.

4.2.4.1 *Recommendations regarding psychosocial interventions*

NICE 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 and that strategies should:

- be adjusted to the child or young person's developmental level
- aim to increase the parents', carers', teachers' or peers' understanding of, and sensitivity and responsiveness to, the child or young person's patterns of communication and interaction
- include techniques of therapist modelling and video-interaction feedback
- include techniques to expand the child or young person's communication, interactive play and social routines.

The intervention should be delivered by a trained professional. For preschool children consider parent, carer or teacher mediation. For school-aged children consider peer mediation.

HAS issues general and specific recommendations. Also, since studies are limited to children under 4 years of age, recommendations are made based on literature in the younger group and based on clinical profiles and expert advice in older children.

In children under 4 years of age, global early intervention, within 3 months of diagnosis, is recommended. Whenever global intervention cannot be initiated in a timely fashion, specific intervention for speech and communication should be a first and intermediate step. General recommendations regarding quality standards are given (HAS pp 24-25). The recommended interventions are ABA (grade B), ESDM (grade B) and TEACCH (grade C). Developmental and behavioural approaches should not be mutually exclusive.

For subjects over 4years old, the HAS recommendations are entirely expert based. In children with severe symptoms and low developmental level it is recommended to continue a personalised project including a global intervention and various other support measures (educational, specific therapeutic, environmental...) as needed by the patient and the parents. Children with a satisfactory developmental level should be supported to attend regular school. Specific personalised support measures (global intervention program, educational...) should be organised. In case of heterogeneous development, interventions should be tailored to the situation.

Based on the lack of scientific evidence and the absence of expert consensus no recommendations could be made regarding psychoanalysis and institutional psychotherapy.

Specifically, HAS and ANESM recommend that even in non-verbal children every personalized programme includes communication. Collaboration should be established between the professional caretakers and the parents.

The development of oral communication skills necessitates (see also section 4.4.2 on Speech and language problems)

- a personal relationship between the (caring) adult and the child
- the use of specific techniques to establish interpersonal contact and augment communication
- that the caretakers and the parents integrate the acquired skills into daily life

Specific recommended interventions are:

- speech therapy (based on expert consensus) to promote the emergence of spoken language or any other means of communication (sign, picture, symbol, writing, etc..) (see also section 4.4.2 Speech and language problems).
- personalised educational, behavioural and developmental interventions as described for improving social interactions.

The development of social interactions necessitates a personal programme in close collaboration with the parents and with clear goals. There is low quality evidence to advice that a programme should be implemented as soon as communication appears problematic and even before a firm diagnosis is made. Interventions aimed at play, imitation and social behaviour should be proposed early on and the parents should be trained. The child should be assisted in every aspect of daily life: school, shopping etc. These interventions can be part of a more comprehensive approach.

Specific recommended interventions are:

- educational, behavioural and developmental interventions being part of a comprehensive early approach (see global approach)
- expert consensus recommends individual or personal sessions, at any age, to stimulate interpersonal exchange. The type of intervention should be adapted to the level of functioning.

For children with a high developmental level (Asperger syndrome), HAS and ANESM recommend that clear goals should be set regarding emotional functioning. Specific recommended interventions are:

- CBT (grade B)
- Role play (grade C)
- Conversation groups (expert consensus)
- Individual psychotherapy (expert consensus)

4.2.4.2 Recommendations regarding pharmacological, biomedical and dietary interventions

NICE recommends not using the following interventions for the management of core features of autism in children and young people:

- antipsychotics
- antidepressants
- anticonvulsants
- exclusion diets (such as gluten- or casein-free diets).

HAS recommends to limit the use of drugs to the following indications:

- pain
- associated epilepsy
- associated somatic disease

HAS states that pharmacological intervention may be considered for associated conditions (depression, behavioural problems, sleep disturbances) but this will be discussed in the appropriate section. None of the biomedical interventions are recommended.

4.2.4.3 Recommendations regarding interventions that should not be used for autism in any context

NICE recommends not using the following interventions to manage autism in any context in children and young people:

- secretin
- chelation
- hyperbaric oxygen therapy

HAS recommends not to use the following global interventions:

- Son Rise ®
- 3i method
- Feuerstein method
- Padovan or neurofunctional reorganisation method
- Floortime or Greenspan method, unless it is integrated in a global approach
- Doman-Delacato method
- Tomatis method (auditive integration therapy)

More detailed information on these interventions can be found in the full HAS guideline pages 185-187.

HAS recommends not to use the following biomedical interventions to manage problems related to autism in children and young people:

- carbon dioxide, oxygen gas treatment
- secretin
- immunotherapy
- chelation
- antibiotics
- antifungals
- vitamins
- omega 3 acids
- gluten-free or casein-free diets
- dextrometrophan
- famotidine
- amantadine
- sedatives (benzodiazepines and antihistaminics)

Table 4 – Summary of recommendations by NICE and HAS guidelines on core features of autism

Intervention	NICE guideline	NICE Recommendation	HAS guideline	HAS Recommendation
Psychosocial interventions				
Psychosocial, *overall autistic behaviour*	Behavioural interventions • ESDM	Insufficient evidence, no recommendation provided	<u>Under 4 yrs. of age</u> • ABA • ESDM • TEACCH <u>Over 4 yrs. of age</u> • Personalised programs	 Grade B Grade B Grade C Expert consensus
Psychosocial, *overall autistic behaviour*	Educational interventions • LEAP • COMPASS	Insufficient evidence, no recommendation provided		
Psychosocial, *overall autistic behaviour*	Parent training	Insufficient evidence, no recommendation provided		
Psychosocial, *overall autistic behaviour*			<u>Asperger syndrome</u> • CBT • Role play • Conversation groups • Individual psychotherapy	 Grade B Grade C Expert consensus Expert consensus
Psychosocial, *overall autistic behaviour*	Social-communication intervention • Child's Talk	Insufficient evidence, no recommendation provided		
Psychosocial, *overall autistic behaviour*			Psychoanalysis, institutional psychotherapy	No consensus

Intervention	NICE guideline	NICE Recommendation	HAS guideline	HAS Recommendation
Psychosocial, *impaired reciprocal social communication and interaction*	Animal-based intervention • horseback riding	Insufficient evidence, no recommendation provided		
Psychosocial, *impaired reciprocal social communication and interaction*	Arts-based intervention • relational music therapy	Insufficient evidence, no recommendation provided		
Psychosocial, *impaired reciprocal social communication and interaction*			Early global intervention	Grade B
Psychosocial, *impaired reciprocal social communication and interaction*	Behavioural interventions • ESDM • P-ESDM • reciprocal imitation training	Insufficient evidence, no recommendation provided		
Psychosocial, *impaired reciprocal social communication and interaction*	Cognitive interventions • ERT • FRT • ToM	Insufficient evidence, no recommendation provided		
Psychosocial, *impaired reciprocal social communication and interaction*	Educational interventions • LEAP • TeachTown: Basics	Insufficient evidence, no recommendation provided		
Psychosocial, *impaired reciprocal social communication and interaction*	Parent training	Insufficient evidence, no recommendation provided		
Psychosocial, *impaired reciprocal social communication and interaction*	Picture Exchange Communication System Training • ACC	Insufficient evidence, no recommendation provided		

Intervention	NICE guideline	NICE Recommendation	HAS guideline	HAS Recommendation
Psychosocial, *impaired reciprocal social communication and interaction*	Social-communication Interventions* • EBI/EIBI + joint attention training • LEGO therapy • social skills groups	Recommended		
Psychosocial, *restricted interests and rigid and repetitive behaviours*	Behavioural intervention • ESDM • P-ESDM	Insufficient evidence, no recommendation provided		
Psychosocial, *restricted interests and rigid and repetitive behaviours*	Cognitive intervention • enhanced ERT	Insufficient evidence, no recommendation provided		
Psychosocial, *restricted interests and rigid and repetitive behaviours*	Parent Training	Insufficient evidence, no recommendation provided		
Psychosocial, *restricted interests and rigid and repetitive behaviours*	Social-communication intervention • PACT	Insufficient evidence, no recommendation provided		
Psychosocial, *cognitive domain*			Early global intervention stimulate child's interest speech therapy, psychomotor therapy, psychotherapy educational support caretakers' collaboration structured environment	Grade B if initiated before 4 yrs. of age
Psychosocial, *sensory-motor domain*			Not therapeutic but beneficial for personal and social enjoyment:	

Intervention	NICE guideline	NICE Recommendation	HAS guideline	HAS Recommendation
			physical activity musical therapy therapy involving animals	Expert consensus
Pharmacological interventions				
Pharmacological, *overall autistic behaviour*	• anticonvulsants • antidepressants • antipsychotics (with or without antihistamines) • SNRIs	Not recommended Not recommended Not recommended Insufficient evidence, no recommendation provided	• antipsychotics • SSRI's • dopamine reuptake inhibitors • SNRI's • anticonvulsants	Not recommended
Pharmacological, *impaired reciprocal social communication and interaction*	Pharmacological intervention • antioxidants	Insufficient evidence, no recommendation provided		
Pharmacological, *restricted interests and rigid and repetitive behaviours*	Pharmacological interventions • antidepressants • antioxidants • antipsychotics	Not recommended	• antipsychotics	Not recommended
Biomedical interventions				
Biomedical, *overall autistic behaviour*	Complementary interventions • acupressure • acupuncture • electro-acupuncture • Qigong massage	Insufficient evidence, no recommendation provided		
Biomedical, *overall autistic behaviour*	Hormone therapy	Not recommended	Hormone therapy	

Intervention	NICE guideline	NICE Recommendation	HAS guideline	HAS Recommendation
	• porcine secretin • synthetic porcine secretin • synthetic human secretin		• secretin	Not recommended
Biomedical, *overall autistic behaviour*	Medical procedures • chelation • HBOT	Not recommended	Medical procedures • chelation • immunotherapy	Not recommended
Biomedical, *overall autistic behaviour*	Nutritional interventions • multivitamin + mineral supplement • L-carnosine/L carnitine • omega-3 fatty acid • gluten- and casein-free diet	Insufficient evidence Insufficient evidence Insufficient evidence Not recommended	Nutritional interventions • multivitamin + mineral supplement • omega-3 fatty acid • gluten- and casein free diet	Not recommended
Biomedical, *overall autistic behaviour*	Sensory interventions • neurofeedback • auditory integration training	Insufficient evidence, no recommendation provided	Sensory interventions • auditory integration training	Not recommended
Biomedical, *overall autistic behaviour*			Other drugs • antibiotics • antifungals • dextrometorphan • famotidine • amantadine • benzodiazepines	Not recommended

Intervention	NICE guideline	NICE Recommendation	HAS guideline	HAS Recommendation
			• antihistaminic drugs Other drugs • naltrexone • cholinesterase inhibitors • alpha 2 adrenergic agonists	Insufficient evidence, no recommendation provided
Biomedical, *impaired reciprocal social communication and interaction*	Complementary interventions • electro-acupuncture	Insufficient evidence, no recommendation provided		
Biomedical, *impaired reciprocal social communication and interaction*	Hormone therapy • porcine secretin • synthetic porcine secretin	Not recommended		
Biomedical, *impaired reciprocal social communication and interaction*	Medical procedure • chelation • HBOT	Not recommended		
Biomedical, *impaired reciprocal social communication and interaction*	Nutritional interventions • multivitamin + mineral supplement • L-carnosine/ L-carnitine • omega-3 fatty acid • gluten- and casein-free diet	Insufficient evidence Insufficient evidence Insufficient evidence Not recommended		
Biomedical, *impaired reciprocal social communication and interaction*	Sensory intervention • neurofeedback	Insufficient evidence, no recommendation provided		

Intervention	NICE guideline	NICE Recommendation	HAS guideline	HAS Recommendation
Biomedical, *restricted interests and rigid and repetitive behaviours*	Hormone therapy • porcine secretin • synthetic porcine secretin	Not recommended		
Biomedical, *restricted interests and rigid and repetitive behaviours*	Medical procedures • chelation • HBOT	Not recommended		
Biomedical, *restricted interests and rigid and repetitive behaviours*	Motor intervention • Kata exercise training	Insufficient evidence, no recommendation provided		
Biomedical, *restricted interests and rigid and repetitive behaviours*	• L-carnosine/ L-carnitine • Gluten- and casein-free diet	Insufficient evidence Not recommended		
Biomedical, *restricted interests and rigid and repetitive behaviours*	Sensory intervention • neurofeedback	Insufficient evidence, no recommendation provided		

** includes caregiver-mediated or preschool-teacher mediated as well as peer-mediated and/or therapist mediated interventions*

4.2.5 From evidence to recommendations

The evidence as well as the NICE and HAS recommendations presented in Table 4 were sent to the GDG and discussed in a face-to-face meeting. The comments made by the GDG can be found in Appendix 5. Based on this discussion, the KCE prepared a first draft of KCE recommendations. These were re-submitted to the GDG, to start the Delphi process as described in section 2 (Methodology). The results of the subsequent Delphi rounds can be found in Appendix 6.

4.3 Interventions aimed at behaviour that challenges

The NICE and HAS guideline both discussed behaviour that challenges in a separate chapter. NICE[13] defined it as a constellation of behaviours that frequently occur in people with developmental disorders, including intellectual disability and autism, but are unusual in other populations. These patterns of behaviour are extremely variable, and can include: physical aggression towards self (self-injury); severe levels of 'habitual behaviours' such as rocking and head-banging; physical aggression towards others; destruction of property; temper outbursts; high levels of oppositional behaviour and defiance; and verbal aggression. HAS[12] used the term

'problematic behaviour' for behaviour that causes difficulties of a certain intensity, frequency or duration, or that includes a danger for the person with autism or his environment, and that affects this person's learning process, adaptation and social integration.

4.3.1 Evidence – psychosocial interventions

NICE[13] extracted clinical evidence from 13 trials on this topic. Four of these studies examined the efficacy of psychosocial interventions on behaviour that challenges as a direct outcome (target of intervention), and nine provided data on behaviour that challenges as an indirect outcome. More detailed information on the studies can be found in the full NICE guideline from section 6.2.1 page 386-410 and in NICE guideline Appendix 12c.

HAS[12] reviewed 5 SRs on interventions aimed at challenging behaviour, and 5 additional, non-controlled studies on very small numbers of children that were not part of the SRs. More detailed information on the studies can be found in the full Has guideline p 225-232 section 5.4.3. An overview is provided in Table 5.

4.3.2 Effect of psychosocial interventions on behaviour that challenges

NICE[13] concluded that there was low to very low quality evidence from single studies for significant effects of horseback riding, behavioural intervention, CBT and parent training on behaviour that challenges. The only meta-analysis possible was for social skills groups (two studies) and there was low to very low quality evidence for moderate effects on parent-rated behaviour that challenges.

HAS[12] concluded that evaluating behavioural difficulties and using an appropriate behavioural treatment program seems effective. HAS further elaborated on expert discussion on the use of isolation chamber, as well as on the packing technique, which appears to be used in France only. The packing technique implies that the child is wrapped in cold, wet towels (for more information, see HAS report p 233). The recommendations are consensus based: to avoid challenging behaviour by improving communication, by adapting the environment and by anticipating triggers. Furthermore HAS and Anesm recommend to rule out co morbidity and physical pain and to analyse factors that favour, trigger and sustain difficult behaviour. In order to implement desirable behaviour, psycho-educational and behavioural techniques are recommended or any intervention that improves self-image. It is stated that the use of isolation chambers should be exceptional and it is recommended not to use the packing technique, except in a research setting that complies with the requirements of the Haut Conseil de la santé publique (HCSP).

4.3.3 Evidence - pharmacological interventions

NICE[13] extracted clinical evidence from 18 trials on this topic. Fifteen of these studies examined the efficacy of pharmacological interventions on behaviour that challenges as a direct outcome (target of intervention), and three provided data on behaviour that challenges as an indirect outcome. More detailed information on the studies can be found in the full NICE guideline from section 6.3.1 page 410-441 and in NICE guideline Appendix 12c.

HAS[12] discussed pharmacological intervention in general for core features and associated conditions. We here specifically report on the recommendations regarding challenging behaviour and hyperactivity. HAS considered the diagnosis of Autism and ADHD as mutual exclusive. However, HAS described the results of RCTs on the efficacy of methylphenidate for symptoms of attention deficit and hyperactivity in children and adolescents with autism in the section on pharmacological treatment of severe behavioural difficulties (see full HAS report p 286-289 and 303). These results are discussed below and presented in Table 5. Adverse events are discussed in section 4.6.

4.3.4 Effect of pharmacological interventions on behaviour that challenges

NICE[13] concluded that there is evidence for positive treatment effects of antipsychotic drugs on behaviour that challenges. The majority of the evidence on the use of antipsychotics for behaviour that challenges in children and young people with autism compared risperidone or aripiprazole with placebo, and there is moderate to low quality evidence for treatment effects on irritability, lethargy, stereotypic behaviour, hyperactivity, inappropriate speech and parent-defined target behaviours that challenge. However, there are also robust data suggestive of adverse events

associated with risperidone or aripiprazole, in particular, weight gain, prolactin concentration and tachycardia. It is also important to note that these trials were run over short time periods and very little is known about the long-term effects of antipsychotic drugs in children and young people with autism.

There was insufficient or inconclusive evidence with regard to the effects of anticonvulsants (topiramate, divalproex), antioxidants (N-acetylcysteine), antivirals (amantadine), or opioid antagonists (naltrexone). There was evidence that antidepressants (citalopram) are associated with harms, but no benefit. There was evidence that antihistamines (cyproheptadine), cognitive enhancers (piracetam), and methylxanthines (pentoxifylline) used as an adjunct to an antipsychotic drug, may improve behaviour that challenges. However, this was based on only one small trial for each drug.

HAS[12] stated that pharmacological treatment can be used as second line and always temporary treatment when (behavioural) problems counteract the child's integration and aptitude for first line psycho social intervention. No preferential therapeutic strategy could be recommended for treatment of behavioural problems such as auto mutilation, agressivity, repetitive behaviour or hyperactivity that severely affects the quality of life of the patient and the immediate environment (see HAS document p 302-303). Haloperidol is the sole drug with market authorization in France. The results of available RCT s performed in children (n>10) up to September 2011 for the outcomes of interest and with a follow-up period of 10 to 12 weeks (6 months for one study) are reported for haloperidol, risperidone, aripiprazole and methylphenidate (see Table 5). Adverse events are discussed in a separate chapter.

4.3.5 *Evidence – biomedical interventions*

NICE[13] extracted clinical evidence from 15 RCTs on this topic. Six of these studies examined the efficacy of biomedical interventions on behaviour that challenges as a direct outcome (target of intervention), and nine provided data on behaviour that challenges as an indirect outcome. More detailed information on the studies can be found in the full NICE guideline from section 6.3.1 page 441- 462 and in NICE guideline Appendix 12c.

HAS[12] discussed biomedical interventions for challenging behaviour together with core features. We therefore refer the reader to the section on core features of autism.

4.3.6 *Effect of biomedical interventions on behaviour that challenges*

NICE[13] concluded that there was single study data for positive treatment effects of massage or a multivitamin and mineral supplement on behaviour that challenges. However, the evidence was very limited and further randomised placebo-controlled studies are required to corroborate the existing evidence for massage and dietary supplements in children and young people with autism.

There was insufficient evidence to reach a conclusion about the effect of electro-acupuncture, hormone treatment (secretin), medical procedures (HBOT and DMSA (chelation therapy with dimercaptosuccinic acid)), nutritional or sensory interventions on behaviour that challenges.

Table 5 – Summary by NICE and HAS guidelines on behaviour that challenges

Intervention	NICE guideline	NICE Recommendation	HAS guideline	HAS Recommendation
Psychosocial interventions				
First-line treatment:	If no coexisting mental health or behavioural problem, physical disorder or environmental problem has been identified as triggering or maintaining the behaviour that challenges, offer the child or young person a psychosocial intervention (informed by a functional assessment of behaviour) as a first-line treatment	Recommended (mainly based on expert consensus)	Expert opinion: In case of challenging behaviour that is dangerous for the child or the environment: use psycho-educational-behavioural techniques 'CBT'	Expert consensus: recommended
First-line treatment: *Functional assessment*	The functional assessment should identify: factors that appear to trigger the behaviour patterns of behaviour the needs that the child or young person is attempting to meet by performing the behaviour The consequences of the behaviour (that is, the reinforcement received as a result of the behaviour).	Recommended (mainly based on expert consensus)	Expert consensus: Assess co morbidity Identify sources of physical pain Identify triggers	Expert consensus: recommended
First-line treatment: *Psychosocial interventions*	Psychosocial interventions for behaviour that challenges should include: clearly identified target behaviour a focus on outcomes that are linked to quality of life assessment and modification of environmental factors that may contribute to initiating or maintaining the behaviour a clearly defined intervention strategy that takes into account the developmental level and coexisting problems of the child or young person a specified timescale to meet intervention goals (to promote modification of intervention strategies that do not lead to change within a specified time)	Recommended (mainly based on expert consensus)		

Intervention	NICE guideline	NICE Recommendation	HAS guideline	HAS Recommendation
	a systematic measure of the target behaviour taken before and after the intervention to ascertain whether the agreed outcomes are being met consistent application in all areas of the child or young person's environment (for example, at home and at school) Agreement among parents, carers and professionals in all settings about how to implement the intervention.			
			Expert opinion: Isolation chamber	Use only in exceptional cases Ensure continued support and respect for the child
			Expert opinion: Packaging technique	Recommended not to use
Pharmacological interventions				
	Consider antipsychotic medication 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	Recommended		
	Antipsychotic medication should be initially prescribed and monitored by a pediatrician or psychiatrist who should: identify the target behaviour decide on an appropriate measure to monitor effectiveness, including frequency and severity of the behaviour and a measure of global impact	Recommended (mainly based on expert consensus)		

Intervention	NICE guideline	NICE Recommendation	HAS guideline	HAS Recommendation
	review the effectiveness and any side effects of the medication after 3–4 weeks Stop treatment if there is no indication of a clinically important response at 6 weeks.			
	If antipsychotic medication is prescribed: • start with a low dose • use the minimum effective dose needed • Regularly review the benefits of the antipsychotic medication and any adverse events.	Recommended (based on evidence and expert consensus)		
	When choosing antipsychotic medication, take into account side effects, acquisition costs, the child or young person's preference (or that of their parent or carer where appropriate) and response to previous treatment with an antipsychotic.	Recommended (based on evidence and expert consensus)		
	When prescribing is transferred to primary or community care, the specialist should give clear guidance to the practitioner who will be responsible for continued prescribing about: • the selection of target behaviours • monitoring of beneficial and side effects • the potential for minimally effective dosing • the proposed duration of treatment • Plans for stopping treatment.	Recommended (mainly based on expert consensus)		
			RCT with positive outcome on irritability, stereotypic behaviour and hyperactivity haloperidol vs. placebo (n=126)	Expert consensus: Recommend as second line and temporary treatment

Intervention	NICE guideline	NICE Recommendation	HAS guideline	HAS Recommendation
			risperidone vs. placebo and risperidine vs. haloperidol (n=89) aripiprazole vs. placebo (n=213)	
			RCT with positive outcome on hyperactivity methylphenidate vs. placebo	Expert consensus: Recommend as second line and temporary treatment
Biomedical interventions				
	Trials included massage, multivitamin and mineral supplement, electro-acupuncture, hormone treatment (secretin), medical procedures (HBOT and DMSA), nutritional and sensory interventions	Insufficient evidence, no recommendations provided		

4.3.7 From evidence to recommendations

The evidence as well as the NICE and HAS recommendations presented in Table 5 were sent to the GDG and discussed in a face-to-face meeting. The comments made by the GDG can be found in Appendix 5. Based on this discussion, the KCE prepared a first draft of KCE recommendations. These were re-submitted to the GDG, to start the Delphi process as described in section 2 (Methodology). The results of the subsequent Delphi rounds can be found in Appendix 6

4.4 Interventions aimed at associated features of autism and coexisting conditions

This chapter deals with all associated features and coexisting conditions as defined by the NICE and HAS guidelines.

The guidelines are not completely aligned in the topics they have addressed. For instance the adaptive behaviour, as addressed by NICE, includes every-day skills such as effective language, self-care etc. and reflects social competence, independence and autonomy in everyday settings. This topic is not addressed by HAS. On the other hand, HAS added a section on sexuality that was not addressed by NICE.

4.4.1 Impairments in adaptive behaviour

4.4.1.1 Psychosocial interventions aimed at impairments in adaptive behaviour

Evidence

NICE[13] extracted relevant clinical evidence from 15 RCTs on this topic. Five of these studies examined the efficacy of psychosocial interventions on adaptive behaviour as a direct outcome (target of intervention), and ten provided data on adaptive behaviour as an indirect outcome. Interventions were compared to treatment as usual (TAU).Three behavioural intervention trials examined effects on adaptive behaviour as a direct outcome and one behavioural intervention trial examined indirect effects on adaptive behaviour. One cognitive-behavioural intervention trial examined effects of CBT on adaptive behaviour as an indirect outcome. Two parent training studies examined effects on adaptive behaviour as a direct outcome and three parent training trials examined indirect effects of parent training on adaptive behaviour. Finally, five social-communication intervention trials examined effects on adaptive behaviour as an indirect outcome. More detailed information on the studies can be found in the table presented below, in the full NICE guideline from section 7.2.2 page 497-518 and in NICE Appendix 17 (evidence profiles) and 13 (forest plots).

HAS[12] did not discuss impaired adaptive behaviour separately. Interventions on communication and social interactions are part of the core features.

A summary is provided in Table 6.

Effect of psychosocial interventions on adaptive behaviour

Based on low to very low quality evidence, NICE concluded that it is not possible to draw conclusions about the relative benefit of any of the psychosocial interventions (behavioural interventions, cognitive-behavioural interventions, parent training, social-communication interventions) on adaptive behaviour as an indirect outcome.

4.4.1.2 Pharmacological interventions aimed at impairments in adaptive behaviour

Evidence

NICE[13] extracted relevant clinical evidence from 2 RCTs on this topic. Both of these studies examined the efficacy of pharmacological interventions on adaptive behaviour as an indirect outcome (not the target of the intervention) and both were antipsychotic trials comparing aripiprazole with placebo. More detailed information on the studies can be found in the full NICE guideline from section 7.2.4 page 518 - 521 and in NICE Appendix 17 (evidence profiles) and 13 (forest plots).

HAS[12] did not address this issue.

Effect of pharmacological interventions on adaptive behaviour

NICE concluded that here was evidence for small to moderate and statistically significant effects of aripirazole on adaptive behaviour as measured by the Pediatric Quality of Life Inventory (PedsQL) total score and emotional functioning and cognitive functioning subscales. However, the quality of this evidence was low to very low due to risk of bias concerns (unclear blinding of outcome assessment), small sample size, and considerable to substantial heterogeneity (for the total score estimate). There was also evidence for statistically significant harms associated with the use of antipsychotics (see 4.6 on adverse events). Consequently, the NICE GDG concluded that there was insufficient evidence to provide recommendations.

4.4.1.3 Biomedical interventions aimed at impairments in adaptive behaviour

Evidence

NICE[13] extracted relevant clinical evidence from 12 RCTs on this topic. None of these studies examined the efficacy of biomedical interventions on adaptive behaviour as a direct outcome (target of intervention), with all 12 providing data on adaptive behaviour as an indirect outcome. Of these 12 RCTs, four studies were complementary therapies trials, two were hormone trials, three were medical procedures studies, and three were nutritional intervention trials. More detailed information on the studies can be found in the full NICE guideline from section 7.2.4 page 522 - 536 and in NICE Appendix 17 (evidence profiles) and 13 (forest plots).

HAS[12] did not address this issue.

Effect of biomedical interventions on adaptive behaviour

NICE concluded, based on low to very low quality evidence, that it is not possible to draw conclusions about the relative benefit of biomedical interventions (complementary therapies, hormones, medical procedures, and nutritional interventions) on adaptive behaviour as an indirect outcome and, consequently, that there was insufficient evidence to make a recommendation about the use of biomedical interventions for adaptive behaviour in children and young people with autism.

Table 6 – Summary of recommendations by NICE and HAS guidelines on associated features of autism and coexisting conditions: impairments in adaptive behaviour

Psychosocial interventions			
NICE guideline	**NICE Recommendation**	**HAS guideline**	**HAS Recommendation**
Behavioural interventions • EIBI or EBI vs. TAU • EIBI vs. Parent Training • Home-based EBI vs. Centre-based EBI	Insufficient evidence, no recommendation provided		
Cognitive-behavioural interventions • CBT vs. Wait-list	Insufficient evidence, no recommendation provided		
Parent training • Parent training vs. TAU • Combined Parent training and Early Intervention Programme vs. Early Intervention Programme alone • Parent and day-care staff training vs. Standard day-care • Combined parent training and anti-psychotic vs. antipsychotic alone	Insufficient evidence, no recommendation provided		
Social-Communication interventions • Caregiver-mediated social communication intervention vs. TAU • Social skills group vs. TAU • LEGO therapy vs. SULP	Insufficient evidence, no recommendation provided		
Pharmacological interventions			
NICE guideline	**NICE Recommendation**	**HAS guideline**	**HAS Recommendation**
• Aripiprazole vs. placebo	Insufficient evidence, no recommendation provided		

Biomedical interventions			
NICE guideline	**NICE Recommendation**	**HAS guideline**	**HAS Recommendation**
Complementary interventions • Acupuncture/electroacupucture vs. Sham • Acupuncture/electroacupucture and educational programme vs. educational programme Hormone interventions • Secretin vs. placebo Medical procedure interventions • Long-term chelation (7 rounds of DMSA) vs. Short-term chelation (1 round of DMSA and 6 rounds of placebo) • HBOT vs. attention-placebo Nutritional interventions • Omega-3 fatty acids vs. placebo • Omega-3 fatty acids vs. healthy diet control • Gluten-free and casein-free diet vs. TAU	Insufficient evidence, no recommendation provided		

4.4.2 Speech and language problems

Although communication impairments, in the broadest sense, are a core deficit in autism, the level of structural language abilities in children with autism varies widely and many children with autism show significant delays in the acquisition of language. Although the majority of individuals with autism do develop speech, core deficits in speech and communication tend to persist, even in those with good spoken language. Examples are poor vocabulary, problems with grammar and discourse, and speech impairments. When children with autism have problems with phonology and/or syntax they may be diagnosed as having an additional language or speech disorder.[13]

In the chapter on speech and language, NICE[13] reported specifically on study outcomes in the following three domains: verbal/non-verbal communication or use of PECS, receptive language, expressive language. This is in contrast with the chapter on the core autism feature of impaired reciprocal social communication and interaction, where only results from (sub-)scales addressing this core feature were included.

HAS[13] did not make the same distinction based on study outcomes. It included one section on communication interventions (see full HAS report p188-202), which will be discussed in detail below. It will also be briefly summarized in section 4.2.1.1 and 4.2.1.3 on interventions for the core autism feature of impaired reciprocal social communication and interaction.

4.4.2.1 Psychosocial interventions aimed at speech and language problems

Evidence

NICE[13] extracted relevant clinical evidence from 21 RCTs on this topic. Six of these studies examined the efficacy of psychosocial interventions on speech and language as a direct outcome (target of intervention), and 15 provided data on speech and language as an indirect outcome. Two alternative and augmentative communication (AAC) intervention trials examined effects on speech and language as a direct outcome. Two arts-based intervention trials examined effects on speech and language as a direct outcome. Four behavioural intervention trials examined effects on speech and language as an indirect outcome. One educational intervention trial examined effects on speech and language as a direct outcome, and one study examined effects on speech and language as an indirect outcome. One parent training trial examined direct effects on speech and language, and three trials examined indirect effects of parent training on speech and language. Finally, seven social-communication intervention trials examined effects on speech and language as an indirect outcome. More detailed information on the studies can be found in the full NICE guideline from section 7.3.2 page 542 - 571 and in NICE Appendix 17 (evidence profiles) and 13 (forest plots).

The HAS[12] extracted evidence from three reviews, six RCT and five observational studies. One review studied the facilitated communication, PECS, Makaton and sign language. The second review included RCTs dealing with interventions on recognition of face emotions, attention or motivation, lexical production in oral language, sign language and PECS on speech and language. The third one analysed the effect of ABA. Two RCTs studied the effect of PECS on language and communication skills. One RCT analysed the effect of an extra curriculum targeting socially engaged imitation, joint attention and affect sharing. Another RCT analysed the effect of Reciprocal Imitation Training (RIT) on imitation skills. Impact on language of joint attention versus play interventions, Denver model intervention versus Prompts of Restructuring Oral Muscular Phonetic Targets (PROMPT) or RIT are studied in the three last RCTs. Observational studies considered the following interventions: educational intervention, usage of speech-generating device, MEHRIT (social-communication-based intervention), ABA + Pivotal response treatment (PRT) and parental training. More detailed information on the studies can be found in the full HAS guideline from section 5.4.1. Page 188 – 202. A summary is provided in Table 7.

Effect of psychosocial interventions on speech and language problems

NICE[13] concluded that there was limited low to very low quality evidence for positive treatment effects of an AAC intervention e.g. PECS vs. Responsive Education and Prelinguistic Milieu Training (RPMT) on speech and language for children with autism. Based on the review of the PECS data, the NICE GDG decided that given the paucity of data and lack of blinded outcome assessment the evidence was not sufficient to warrant making a recommendation about the use of PECS in children and young people with autism. However, as the GDG agreed that the evidence was promising, the group proposed a research recommendation for further RCTs to be conducted to examine the effects of PECS on speech and language in children with autism. This research recommendation reads as follows: Is Picture Exchange Communication Systems (PECS) effective in improving spontaneous requesting in non-verbal children with autism across a range of contexts that demonstrate generalisation of skills? Based on moderate to very low quality evidence it was not possible to reach a conclusion about arts-based interventions, behavioural interventions, educational interventions, parent training and social-communication interventions targeted at speech and language problems.

HAS[12] concludes that PECS is a technique integrated in numerous interventions. Recent evaluations of PECS have become rare. All the studied interventions are effective for verbal and non-verbal children. PROMPT and the Denver model intervention achieve satisfactory results. Introduction of joint attention or symbolic play in the ABA intervention show a beneficial effect for communication development in 3-4 years old non-verbal children. Interventions using computer-mediated communication facilitate the attention and the interest in children in preschool age and in primary school age. The techniques of 'facilitated communication' where adults guide the child / adolescent's arms without speaking, did not show any evidence of efficacy and are judged inappropriate for child / adolescents with autism. The 'facilitated communication' should not be confused with provision of technical support or support for communication (pictures, pictograms).

4.4.2.2 Pharmacological interventions aimed at speech and language problems

Evidence

NICE concluded that only one pharmacological intervention study met criteria for full-text retrieval, but this study could not be included in the review as data could not be extracted due to cross-over design and unavailability of either first phase data or results of paired-sample t-tests.

HAS did not address this issue.

4.4.2.3 Biomedical interventions aimed at speech and language problems

Evidence

NICE[13] extracted relevant clinical evidence from 16 RCTs on this topic. Two of these studies examined the efficacy of biomedical interventions on speech and language as a direct outcome (target of intervention), and 14 provided data on speech and language as an indirect outcome.
Two complementary therapies trials examined effects on speech and language as a direct outcome. One of these was a foreign language paper; however, data and study characteristics were extracted from a systematic review. An additional two complementary intervention trials examined indirect effects on speech and language. Four hormone trials examined effects on speech and language as an indirect outcome. Two medical procedures trials examined effects on speech and language as an indirect outcome. Four nutritional intervention trials examined indirect effects on speech and language. Finally, two sensory intervention trials examined effects on speech and language as an indirect outcome. More detailed information on the studies can be found in the full NICE guideline from section 7.3.5 page 571 - 588 and in NICE Appendix 17 (evidence profiles) and 13 (forest plots).

HAS[12] did not address this issue.

Effect of biomedical interventions on speech and language problems

NICE concluded that there was evidence for placebo/negative treatment effects on speech and language associated with auditory integration training and neurofeedback. In the case of auditory integration training, narrative review suggests improvement in both experimental and control groups but greater improvement in the attention-placebo condition. However, for neurofeedback, results reported suggest a worsening over time for the experimental group and an improvement over time for the treatment as usual group. In reviewing the placebo/negative treatment effects associated with auditory integration training and neurofeedback, the GDG decided that these should not be recommended for the treatment of speech and language problems in children and young people with autism. Based on moderate to very low quality evidence it was not possible for the NICE GDG to reach a conclusion about complementary interventions (acupuncture/ acupressure), hormones, medical procedures and nutritional interventions.

HAS did not address this issue.

Table 7 – Summary of recommendations by NICE and HAS guidelines on associated features of autism and coexisting conditions: speech and language problems

Intervention domain: Speech and language problems

Psychosocial interventions			
NICE guideline	**NICE Recommendation**	**HAS guideline**	**HAS Recommendation**
ACC interventions • PECS vs. TAU • PECS vs. RPMT	Insufficient evidence, no recommendation provided. However, the evidence is promising and therefore a research recommendation is provided (see text).		
		• PECS	Personalized project should: • Include functional objectives in the field of verbal or non-verbal communication • Be implemented in collaboration with parents and other care providers • Be implemented even before certain diagnosis (grade C).
Arts-based interventions • Music therapy vs. TAU	Insufficient evidence, no recommendation provided		
Behavioural interventions • EIBI vs. TAU • EBI vs. TAU • EIBI vs. Parent training • Home-based EBI vs. Centre-based EBI	Insufficient evidence, no recommendation provided		
Educational interventions • Teach Town + IBI vs. IBI (only)	Insufficient evidence, no recommendation provided However based on promising		

• LEAP training vs. Manual-only control	results of the LEAP intervention research recommendation provided.		
Parent training • Parent Training vs. TAU • Parent and day-care staff training vs. Standard day-care	Insufficient evidence, no recommendation provided		
Social-Communication interventions • Caregiver-mediated social communication intervention vs. TAU • Social skills group vs. TAU • Joint attention training and EBI/EIBI vs. EBI/EIBI only	Insufficient evidence, no recommendation provided	• socially engaged imitation, engaged imitation, joint attention and affect sharing • joint attention vs. play interventions • Denver model vs. PROMPT • Denver model vs. RIT	The development of functional communication requires: • Individualized relationship • Specific techniques implemented for the development of joint attention through simulation introducing progressive changes (grade C) • Endorsement by parents and caretakers in daily live. Recommended interventions are: • Speech therapy sessions (expert opinion) • Schedule to be determined by needs, constraints and priorities: for <6yrs old 2-4x/week • Educational, behavioural and individualized intervention implemented within the framework of early, global and coordinated (expert opinion) • AAC applied to various daily surroundings (grade C)

			• Provide training for parents • Do NOT exclude children >6yrs old even if not verbal • Provide exercises at school
		• Based on one SR	It is recommended not to use the techniques of 'facilitated communication'

Pharmacological interventions			
NICE guideline	**NICE Recommendation**	**HAS guideline**	**HAS Recommendation**
No evidence found	No recommendation		
Biomedical interventions			
NICE guideline	**NICE Recommendation**	**HAS guideline**	**HAS Recommendation**
Complementary interventions • Acupuncture/acupressure and language therapy vs. Language therapy alone • Acupuncture/electroacupuncture vs. Sham • acupuncture/ electroacupuncture	Insufficient evidence, no recommendation provided		
Hormone interventions • Secretin vs. Placebo	Insufficient evidence, no recommendation provided		
Medical procedure interventions • Long-term chelation (7 rounds of DMSA) vs. Short-term chelation (1 round of DMSA and six rounds of placebo) • HBOT vs. attention-placebo	Insufficient evidence, no recommendation provided		
Nutritional interventions • Omega-3 fatty acids vs. Placebo	Insufficient evidence, no recommendation provided		

• Omega-3 fatty acids vs. healthy diet control • Multivitamin/mineral supplement vs. Placebo • L-carnosine supplement vs. Placebo		
Sensory interventions • Auditory integration training vs. Attention-placebo	Do not use auditory integration training	
Sensory interventions Neuro-feedback vs. TAU	Do not use neurofeedback to manage speech and language problems in children and young people with autism	

4.4.3 IQ, academic skills and learning

IQ as an outcome here reflects measurements assessed by various scales.

4.4.3.1 Psychosocial interventions aimed at IQ, academic skills and learning

Evidence

NICE[13] extracted relevant clinical evidence from 10 RCTs on this topic. One of these studies examined the efficacy of psychosocial interventions on IQ or academic skills as a direct outcome (target of intervention), and nine provided data on IQ or academic skills as an indirect outcome. One of the behavioural intervention trials examined effects on IQ as a direct outcome and two behavioural intervention trials examined indirect effects on IQ and academic skills. One educational intervention trial examined effects on IQ as an indirect outcome. Four parent training trials examined indirect effects on IQ. Finally, two social-communication intervention trials examined effects on IQ as an indirect outcome. More detailed information on the studies can be found in the table presented below, in the full NICE guideline from section 7.4.2 page 592-601 and in NICE Appendix 17 (evidence profiles) and 13 (forest plots).

The HAS [12] extracted evidence from 6 non randomized studies and 1 RCT on the effect of ABA with IQ as a direct outcome. Two controlled trials assessed a school integration program (Children's Toddler School) and its effect on IQ. More detailed information can be found in the full HAS guideline in section 5.3.2 page 95-99.

A summary is provided in Table 8.

Effect of psychosocial interventions on IQ, academic skills and learning

Based on low to very low quality evidence, NICE concluded that it is not possible to draw conclusions about the relative benefit of psychosocial interventions (behavioural interventions, parent training, and social-communication interventions) on IQ and academic skills as an indirect outcome. However, low quality evidence from one relatively large trial suggests that an educational intervention (LEAP) may produce a large effect in terms of IQ (indirect outcome).

HAS concluded that there is unclear evidence on the relationship between psychosocial interventions and IQ.

4.4.3.2 *Pharmacological interventions aimed at IQ, academic skills and learning*

Evidence

NICE [13] extracted relevant clinical evidence from one single RCT on this topic. This study on antipsychotics provided data on academic skills as an indirect outcome. Detailed information on the study can be found in the full NICE guideline from section 7.4.4 page 601-602 and in NICE Appendix 17 (evidence profiles) and 13 (forest plots).

HAS [12] did not address this issue.

Effect of pharmacological interventions on IQ, academic skills and learning

There was no evidence for a statistically significant effect of risperidone on academic skills as an indirect outcome (measured by the Classroom Analogue Task) and NICE concluded, based on the low to very low quality evidence, that it is not possible to draw conclusions about the relative benefit of pharmacological interventions (antipsychotic drugs) on IQ and academic skills.

4.4.3.3 *Biomedical interventions aimed at IQ, academic skills and learning*

Evidence

NICE[13] extracted relevant clinical evidence from five RCTs on this topic. Two of these studies examined the efficacy of biomedical interventions on IQ or academic skills as a direct outcome (target of intervention), and three provided data on IQ or academic skills as an indirect outcome. Two complementary therapy trials examined effects on IQ as a direct outcome. One hormone trial examined effects on IQ as an indirect outcome. One nutritional intervention trial examined indirect effects on IQ. Finally, one sensory intervention trial examined effects on IQ as an indirect outcome.
More detailed information on the studies can be found in the table presented below, in the full NICE guideline from section 7.4.6 page 603-607 and in NICE Appendix 17 (evidence profiles) and 13 (forest plots).

HAS [12] did not address this issue.

Effect of biomedical interventions on IQ, academic skills and learning

NICE did not find evidence for statistically significant effects of acupuncture/electro-acupuncture or secretin on IQ. There was no evidence for a statistically significant effect of a multivitamin/mineral supplement on cognition. Additionally, there was no evidence for a statistically significant effect of auditory integration training on performance IQ. Consequently, based on low to very low quality evidence NICE did not find it possible to draw conclusions about the relative benefit of biomedical interventions (acupuncture, hormones, nutritional interventions, and sensory interventions) on IQ and academic skills.

Table 8 – Summary of recommendations by NICE and HAS guidelines on associated features of autism and coexisting conditions: IQ, academic skills and learning

Intervention domain: IQ, academic skills and learning

Psychosocial interventions			
NICE guideline	**NICE Recommendation**	**HAS guideline**	**HAS Recommendation**
Behavioural interventions • EIBI or EBI vs. TAU • EIBI vs. Parent training	Insufficient evidence, no recommendation provided		
Educational interventions • LEAP training vs. manual-only control	Insufficient evidence, no recommendation provided. However, promising results so research recommendation provided.		
Parent training • Parent Training vs. TAU • Combined parent training and early intervention centre programme vs. early intervention centre programme	Insufficient evidence, no recommendation provided		
Social-Communication interventions • Caregiver-mediated social communication intervention vs. TAU • Joint attention training and EIBI vs. EIBI	Insufficient evidence, no recommendation provided		
		Partial or total school integration • Expert opinion	Offer full-time schooling in mainstream or adapted environment.
		Partial or total school integration • Expert opinion	Recommended: • Progressively increase time at school • Provide mentor with training in autism

			• Inform peers if child/adolescent and parents agree
		Partial or total school integration • Expert opinion	• adolescent may benefit from coaching during traineeship or jobsearch
Pharmacological interventions			
NICE guideline	**NICE Recommendation**	**HAS guideline**	**HAS Recommendation**
Pharmacological interventions • Risperidone vs. placebo	Insufficient evidence, no recommendation provided		
Biomedical interventions			
NICE guideline	**NICE Recommendation**	**HAS guideline**	**HAS Recommendation**
Complementary interventions • Acupuncture/electroacupuncture vs. Sham • acupuncture/ electroacupuncture Hormone interventions • Secretin vs. Placebo Nutritional interventions • Multivitamin/mineral supplement vs. Placebo Sensory interventions • Auditory integration training vs. Attention-placebo	Insufficient evidence, no recommendation provided (for all listed intervention types)		

4.4.4 Sensory sensitivities

Sensory sensitivities vary considerably between individuals with autism and can have a significant impact on the daily lives of children with autism. They may be implicated in rigid behaviours and stereotypical and/or self-stimulatory behaviours such as spinning, hand flapping or rocking. Other examples are extreme reactions to certain sights, sounds and textures, and difficulties to adjust to new environments. Eating problems are also often associated with sensory problems, e.g. insistence on eating only colours or types of food, or hyper-sensitivity to taste, smell or texture[13].

4.4.4.1 Psychosocial interventions aimed at sensory sensitivities

Evidence

NICE [13] extracted relevant clinical evidence from 2 RCTs on this topic. Both studies provided data on sensory sensitivities as an indirect outcome. One animal-based trial examined effects on sensory sensitivities as an indirect outcome. One educational intervention trial examined indirect effects on sensory sensitivities. More detailed information on the studies can be found in the table presented below, in the full NICE guideline from section 7.5.2 page 609 - 612 and in NICE Appendix 17 (evidence profiles) and 13 (forest plots).

HAS[12] extracted evidence from 2 systematic reviews. The first dealt with auditory integration training and other sound therapies for autism spectrum disorders (Berard, Tomatis, Samonas methods). The second SR dealt with several types of therapies for children with autism spectrum disorders (auditory integration training, sensory integration training, massage, and acupuncture). More details information on these systematic reviews can be found in the full HAS guideline from section 5.4.4. pages 236-239. It is noteworthy that NICE discussed massage and auditory integration training under the section 'biomedical interventions' (see 4.4.4.3).

For effects of these interventions (e.g. massage) on motor outcomes, see section 4.4.5 (Motor difficulties).

A summary is provided in Table 9.

Effect of psychosocial interventions on sensory sensitivities

NICE [13] concluded that there was single study evidence for a large and statistically significant effect of horseback riding on the sensory seeking subscale of the Sensory Profile, but non-significant effects for the total score and the sensory sensitivity subscale. The confidence in the significant effect estimate was very low due to risk of bias concerns (non-blind parent-rated outcome measure), small sample size and high risk of selective reporting bias (data not reported for all subscales of the Sensory Profile scale). There was no evidence for a statistically significant effect of Teach Town (as an adjunct to IBI) on auditory processing as an indirect outcome, as measured by the Brigance Inventory of Child Development. The GDG concluded that there was insufficient evidence to recommend any of the interventions reviewed for sensory sensitivities in children and young people with autism.

Two RCTs included in the systematic reviews retrieved by HAS did not show effectiveness of auditory integration (low quality of evidence). Thus, scientific evidence on the efficacy and safety of sensory integration, massage, music therapy or animal based therapies is lacking.

4.4.4.2 Pharmacological interventions aimed at sensory sensitivities

Evidence

NICE did not identify relevant studies on this topic.

HAS did not address this issue.

4.4.4.3 Biomedical interventions aimed at sensory sensitivities

Evidence

NICE[13] extracted relevant clinical evidence from four RCTs on this topic. Two complementary therapy trials examined effects on sensory sensitivities as a direct outcome. Two sensory intervention trials examined effect on sensory sensitivities as a direct outcome. More detailed information on the studies can be found in the table presented below, in the full NICE guideline from section 7.5.5 page 612 - 618 and in NICE Appendix 17 (evidence profiles) and 13 (forest plots).

HAS[12] did not address this issue.

Effect of biomedical interventions on sensory sensitivities

NICE found evidence from a meta-analysis with two studies for large and statistically significant effects of Qigong massage on sensory impairment as measured by the Pervasive Development Disorder Behaviour Inventory (PDDBI) and the Sense and Self-Regulation Checklist (SSC). However, the confidence in these effect estimates was downgraded to low due to risk of bias concerns (group allocation was not truly randomised and blinding of outcome assessment was either unclear or non-blind) and small sample size. There was no evidence for a statistically significant effect of auditory integration training on sound sensitivity, distress or sensory self-stimulation at 1-month, 3-month, 6-month or 12-month post-intervention follow-up time points. There was single study evidence for a large and statistically significant effect of sensory integration therapy on sensory problems as measured by a study-specific checklist. However, the quality of the evidence was downgraded to low due to risk of bias concerns (unclear blinding of outcome assessment) and small sample size. Based on this the GDG concluded that there was insufficient evidence to recommend any of the interventions reviewed for sensory sensitivities in children and young people with autism. Nevertheless, the GDG felt that a research recommendation should be made about sensory integration therapy.

Table 9 – Summary of recommendations by NICE and HAS guidelines on associated features of autism and coexisting conditions: sensory sensitivities

Intervention domain: *Sensory sensitivities*

Psychosocial interventions			
NICE guideline	**NICE Recommendation**	**HAS guideline**	**HAS Recommendation**
Animal-based interventions • Horseback riding vs. waitlist control	Insufficient evidence, no recommendation provided	Animal based therapies	Insufficient evidence, no recommendation provided
Educational interventions • Combined Teach Town and IBI vs. IBI (only)	Insufficient evidence, no recommendation provided		
		• Expert opinion	Visual impairment should be treated adequately
		• Expert opinion	Significant hypersensitivity should be attenuated or modulated, and the environment adjusted
		Hearing filters • Expert opinion	In case of hyperacusis auditory filters may be proposed
		Psychomotor skills and occupational therapy • Expert opinion	Psychomotor and occupational therapy may be proposed to avoid the over-stimulation or in contrast

			the under-stimulation from noise, light or touch
		Auditory integration (i.e. Tomatis method)	not recommended (grade B)
		Music therapy	Insufficient evidence, no recommendation provided
		Massage	Insufficient evidence, no recommendation provided
		Sensory integration	Insufficient evidence, no recommendation provided

Pharmacological interventions			
NICE guideline	**NICE Recommendation**	**HAS guideline**	**HAS Recommendation**
No evidence found			

Biomedical interventions			
NICE guideline	**NICE Recommendation**	**HAS guideline**	**HAS Recommendation**
Complementary interventions • Qigong massage training vs. Waitlist Sensory interventions • Auditory integration training vs. attention-placebo • Sensory integration therapy vs. TAU	Insufficient evidence, no recommendation provided. However, research recommendation provided for Sensory Integration Therapy.		

4.4.5 Motor difficulties

4.4.5.1 Psychosocial interventions aimed at motor difficulties

Evidence

NICE[13] extracted relevant clinical evidence from six RCTs on this topic. All six of these studies examined the efficacy of psychosocial interventions on motor skills as an indirect outcome of the intervention. One animal-based intervention trial examined indirect effects on motor skills. One behavioural intervention trial examined effects on motor skills as an indirect outcome. One educational intervention trial examined effects on motor skills as an indirect outcome. Two parent training studies examined indirect effects on motor skills. Finally, one social-communication intervention trial examined effects on motor skills as an indirect outcome. More detailed information on the studies can be found in the table presented below, in the full NICE guideline from section 7.6.2 page 619 – 626 and in NICE Appendix 17 (evidence profiles) and 13 (forest plots).

The HAS[12] extracted evidence from a systematic review dealing with therapies for children with autism spectrum disorders. More details on this systematic review for this specific topic can be found in HAS full guideline in section 5.4.4 pages 237-238.

A summary is provided in Table 10.

Effect of psychosocial interventions on motor difficulties

NICE did not find evidence for a statistically significant effect of horseback riding on motor skills as an indirect outcome, as measured by the fine motor/perception subscale of the Sensory Profile. There was single study evidence for a moderate and statistically significant effect of EIBI (ESDM) on motor skills as measured by the VABS. However, the quality of the evidence was low due to risk of bias concerns (unclear blinding of outcome assessment) and small sample size. In addition, a non-significant effect was observed for the blinded outcome measure Mullen Scales of Early Learning (MSEL) of fine motor skills. There was single study evidence for a moderate and statistically significant effect of LEAP intervention on fine motor skills as an indirect outcome, as measured by the MSEL. However, the quality of the evidence was low due to risk of bias concerns (unclear blinding of outcome assessment) and small sample size. There was no evidence for statistically significant effects of parent training or parent and day-care staff training on fine or gross motor skills as an indirect outcome, as measured by the Vineland Adaptive Behaviour Scales (VABS) or Early Intervention Developmental Profile (EIDP)/Preschool Developmental Profile (PSDP). Finally, there was no evidence for a statistically significant effect of a caregiver-mediated social-communication intervention on motor skills as an indirect outcome, as measured by the MSEL or the VABS. Conclusively, The GDG agreed that the results of the LEAP trial were promising, however, would need to be replicated by at least one other study and with blinded outcome assessment. The GDG reached the decision that there was insufficient evidence on which to make a recommendation about the use of any of the reviewed interventions for motor skills in children and young people with autism.

Based on current scientific evidence the HAS did not provide recommendations on efficacy or safety of psychomotor or occupational therapy and animal based therapies.

4.4.5.2 Pharmacological interventions aimed at motor difficulties

Evidence

NICE did not identify relevant studies on this topic.

HAS did not address this issue.

Effect of pharmacological interventions on motor difficulties

NICE did not identify relevant studies on this topic.

4.4.5.3 Biomedical interventions aimed at motor difficulties

Evidence

NICE[13] extracted relevant clinical evidence from three RCTs on this topic. All three of these studies examined the efficacy of biomedical interventions on motor skills as an indirect outcome of the intervention. One hormone trial examined indirect effects on motor skills. Two nutritional intervention trials examined effects on motor skills as an indirect outcome. More detailed information on the studies can be found in the table presented below, in the full NICE guideline from section 7.6.5 page 626 - 630 and in NICE Appendix 17 (evidence profiles) and 13 (forest plots).

HAS[12] did not address this issue.

Effect of biomedical interventions on motor difficulties

NICE did not find evidence for a statistically significant effect of secretin on fine motor skills as an indirect outcome, as measured by the MSEL or Developmental Test of Visual Perception, 2nd edition (DTVP-2). NICE did also not find evidence for a statistically significant effect of an omega-3 fatty acid supplement on fine motor skills as an indirect outcome, as measured by the MSEL. Similarly, there was no evidence for a statistically significant effect of a gluten-free and casein-free diet on motor impairment as an indirect outcome, as measured by the Movement Assessment Battery for Children. Consequently, the GDG reached the decision that there was insufficient evidence on which to make a recommendation about the use of any of the reviewed interventions for motor skills in children and young people with autism.

Table 10 – Summary of recommendations by NICE and HAS guidelines on associated features of autism and coexisting conditions: motor difficulties

Intervention domain: *Motor difficulties*

Psychosocial interventions			
NICE guideline	**NICE Recommendation**	**HAS guideline**	**HAS Recommendation**
Animal-based interventions • Horseback riding vs. waitlist control	Insufficient evidence, no recommendation provided	Animal-based interventions	Insufficient evidence, no recommendation provided
Behavioural interventions • EIBI (EDSM) vs. TAU	Insufficient evidence, no recommendation provided		
Educational interventions • LEAP training vs. manual only control	Insufficient evidence, no recommendation provided. However, promising results so research recommendation provided.		
Parent training • Parent training vs. TAU • Parent and day care staff training vs. standard day care	Insufficient evidence, no recommendation provided		
Social-Communication interventions	Insufficient evidence, no recommendation provided		

• Caregiver-mediated social communication intervention vs. TAU			
		Psychomotor or occupational therapy • Expert opinion	Recommend psychomotor or occupational therapy in case of praxis, postural, tonic or gnostic disorders interfering with daily live (dressing, feeding, leisures) or with school education (writing, reading)
Pharmacological interventions			
NICE guideline	**NICE Recommendation**	**HAS guideline**	**HAS Recommendation**
No evidence found			
Biomedical interventions			
NICE guideline	**NICE Recommendation**	**HAS guideline**	**HAS Recommendation**
Hormone interventions • Secretin vs. placebo Nutritional interventions • Omega-3 fatty acids vs. healthy diet control • Gluten-free and casein- free diet vs. TAU	Insufficient evidence, no recommendation provided.		

4.4.6 Common coexisting mental health problems

Coexisting mental health problems are common in children and young people with autism. The NICE guideline (2011) on diagnosis of autism in children and young people identified the following most commonly reported mental health disorders in children and young people with autism: anxiety 62%; ADHD 41%; obsessive-compulsive disorder (OCD) 37%; depression 13%, and oppositional defiant disorder 7%.[41]

4.4.6.1 Psychosocial interventions aimed at common coexisting mental health problems

Evidence

NICE[13] extracted relevant clinical evidence from four RCTs on this topic. All four of these studies examined the efficacy of psychosocial interventions on coexisting anxiety as a direct outcome of the intervention. All four trials were cognitive-behavioural intervention trials. More detailed information on the studies can be found in the table presented below, in the full NICE guideline from section 7.7.2 page 631 – 642 and in NICE Appendix 17 (evidence profiles) and 13 (forest plots).

HAS[12] did not address this issue. However, HAS briefly discussed the effect of CBT interventions on anxiety in the specific subgroup of children and adolescents with Asperger's syndrome (see also section 4.2.1.3). More details can be found in HAS full guideline in section 5.4.6. pages 240-257.

A summary is provided in Table 11.

Effect of psychosocial interventions on common coexisting mental health problems

NICE found evidence for clinical efficacy of CBT programmes with autism-specific modifications on coexisting anxiety for children with autism. NICE did not find evidence of how other coexisting mental health disorders (including ADHD, OCD, posttraumatic stress disorder, depression and conduct disorder), should be treated differently in autism.
In a meta-analysis with two studies NICE found moderate quality evidence for a large and statistically significant positive treatment response of CBT on anxiety as measured by the number of participants who no longer met DSM-IV criteria for an anxiety disorder and by the number of participants who were rated as 'much improved/very improved' on the Clinical Global Impression-Improvement (CGI-I). There was no evidence to suggest heterogeneity of treatment effect, although this is difficult to detect with only two studies. Meta-analysis with two to three studies also revealed evidence for large and statistically significant effects of compared Cognitive Behavioural Therapy (CBT) on continuous outcome measures of anxiety symptoms as measured by total scores on the self-rated or parent-rated SCAS or MASC and the clinician-rated ADIS-C/P and on the Generalized Anxiety Disorder subscale of the ADIS-P or SCAS-P. However, the confidence in these effect estimates was low to very low due to risk of bias concerns for the self- and parent-rated scales (non-blind outcome assessment), small sample size and inconsistency for the meta-analysis of the total anxiety symptoms scores (considerable to substantial heterogeneity). There was also single study evidence for large and statistically significant effects of CBT on chronic anxiety as measured by the RCMAS, on anxiety relating to a specific phobia as measured by the ADIS-P, for a delayed effect of CBT on OCD symptoms at 6-week post-intervention follow-up but not at post-intervention assessment, on emotional symptoms as measured by the parent- and teacher-rated SDQ, and on self-directed negative thoughts as measured by the CATS. However, the quality of this evidence was low due to risk of bias concerns (non-blind parent- or self-rated outcome measures) and small sample size. Treatment effects were not universally statistically significant, with evidence from two studies for non-significant effects of CBT on the social anxiety and separation subscales of the ADIS-P or SCAS-P. There was also evidence from a single study for non-significant effects of CBT (child-only and child and parent groups combined) on panic or fear of personal injury as measured by the SCAS-P, and from another study for non-significant effects of CBT on outward-directed negative thoughts as measured by the CATS.

Regarding the specific subgroup of children and adolescents with Asperger's syndrome HAS concluded that the effect of CBT interventions on anxiety in the specific subgroup of children and adolescents with Asperger's syndrome are promising. HAS experts mention that CBT requires a good level of language before it can be applied (see also paragraph 4.2.1.3).

4.4.6.2 Pharmacological interventions aimed at common coexisting mental health problems

Evidence

NICE[13] extracted relevant clinical evidence from one RCT on this topic. This study examined the efficacy of a pharmacological intervention on coexisting ADHD symptoms as a direct outcome of the intervention by comparing atomoxetine (SNRI class) with placebo. More detailed information on the study can be found in the table presented below, in the full NICE guideline from section 7.7.4 page 642 – 644 and in NICE Appendix 17 (evidence profiles) and 13 (forest plots).

HAS[12] did not address this issue. HAS considered the diagnosis of Autism and ADHD as mutual exclusive. However, HAS described the results of RCTs on the efficacy of methylphenidate for symptoms of attention deficit and hyperactivity in children and adolescents with autism in the section on pharmacological treatment of severe behavioural difficulties but (see full HAS report p 286-289 and 303). In the present report these results are discussed in section 4.3 (Interventions aimed at behaviour that challenges).

Effect of pharmacological interventions on common coexisting mental health problems

NICE found moderate quality evidence for a small and statistically significant effect of atomoxetine on parent-rated ADHD symptoms as measured by the ADHD-RS based on DSM-IV. However, non-significant effects were observed on all teacher-rated subscales of the CTRS-R:S, on the parent-rated hyperactivity subscale of the ABC and on clinician-rated improvement in ADHD symptoms (CGI-ADHD-I). This study found evidence for statistically significant harms associated with atomoxetine, with participants who received atomoxetine being over three and a half times more likely to experience nausea during the trial and over four times more likely to experience decreased appetite than participants receiving placebo.

Table 11 – Summary of recommendations by NICE and HAS guidelines on associated features of autism and coexisting conditions: common coexisting mental health problems.

Intervention domain: Coexisting mental health problems

Psychosocial interventions			
NICE guideline	**NICE Recommendation**	**HAS guideline**	**HAS Recommendation**
Cognitive-behavioural interventions • CBT vs. TAU	Consider the following for children and young people with autism and anxiety who have the verbal and cognitive ability to engage in CBT: • group CBT adjusted to the needs of children and young people with autism • Individual CBT for children and young people who find group-based activities difficult.		
	Consider adapting the method of delivery of CBT for children and young people with autism and anxiety to include: • emotion recognition training • greater use of written and visual information and structured worksheets • a more cognitively concrete and structured approach • simplified cognitive activities, for example, multiple-choice worksheets • involving a parent or carer to support the implementation of the intervention, for example,		

	involving them in therapy sessions • maintaining attention by offering regular breaks • incorporating the child or young person's special interests into therapy if possible		
Pharmacological interventions			
NICE guideline	**NICE Recommendation**	**HAS guideline**	**HAS Recommendation**
Pharmacological interventions • Atomoxetine vs. placebo	Insufficient evidence, no recommendation provided.		
Biomedical interventions			
NICE guideline	**NICE Recommendation**	**HAS guideline**	**HAS Recommendation**
Nutritional interventions • Omega-3 fatty acids vs. healthy diet control • Gluten-free and casein- free diet vs. TAU • Omega-3 fatty acids vs. Placebo Medical procedure interventions • Long-term chelation (7 rounds of DMSA) vs. Short-term chelation (1 round of DMSA and six rounds of placebo)	Insufficient evidence, no recommendation provided.		

4.4.6.3 *Biomedical interventions aimed at common coexisting mental health problems*

Evidence

NICE[13] extracted relevant clinical evidence from four RCTs on this topic. All of the studies examined the efficacy of biomedical interventions on coexisting mental health problems as an indirect outcome. Two nutritional intervention trials examined indirect effects on ADHD symptoms. Two nutritional intervention trials examined effects on anxiety as an indirect outcome. Finally, one medical procedures trial examined indirect effects on anxiety. More detailed information on the studies can be found in the table presented below, in the full NICE guideline from section 7.7.6 page 645 - 649 and in NICE Appendix 17 (evidence profiles) and 13 (forest plots).

HAS[12] did not address this issue.

Effect of biomedical interventions on common coexisting mental health problems

NICE[13] found no evidence for a statistically significant effect of an omega-3 fatty acid supplement (relative to healthy diet control) on ADHD symptoms as an indirect outcome, as measured by the ADHD subscale of the CBCL/1.5-5. There was also no statistically significant evidence for harms associated with an omega-3 fatty acid supplement when compared with placebo by another trial (see section 4.6 Adverse events). There was single study evidence for a moderate and statistically significant effect of a gluten-free and casein-free diet on the inattention subscale of the ADHD-RS based on DSM-IV, but non-significant effects for the hyperactivity subscale. The confidence in the effect estimate for inattention was low due to risk of bias concerns (non-blind outcome assessment and higher drop-out in the experimental group) and small sample size. This study reported that no participants in either experimental or control groups experienced any adverse events during the trial. NICE also found no evidence for a statistically significant effect of omega-3 fatty acid supplements on anxiety as an indirect outcome, as measured by the BASC or the CBCL/1.5-5. There was also no statistically significant evidence for harms associated with an omega-3 fatty acid supplement when compared with placebo (see chapter on adverse events). In the chelation trial, there was no evidence for a statistically significant effect of chelation on anxiety as an indirect outcome, as measured by the specific fears subscale of the PDDBI. Data could not be extracted from this study for adverse events associated with chelation.

4.4.7 *Common medical and functional problems*

The common medical and functional problems for which evidence was reported in the NICE and HAS guideline are sleep problems and gastro-intestinal problems.

4.4.7.1 *Psychosocial and pharmacological interventions aimed at common medical and functional problems*

Evidence

NICE[13] extracted relevant clinical evidence from three RCTs on this topic. Two of these studies examined the efficacy of psychosocial and/or pharmacological interventions on coexisting sleep problems as a direct outcome (target of the intervention), and one study examined effects on sleep problems as an indirect outcome. One four-armed trial compared CBT, melatonin, and combined CBT and melatonin to placebo and examined direct effects on sleep problems. Another trial also compared melatonin to placebo and examined effects on sleep problems as a direct outcome. Finally, one SNRI trial examined effects on sleep problems as an indirect outcome. More detailed information on the studies can be found in the table presented below, in the full NICE guideline from section 7.8.2 page 661 – 679 and in NICE Appendix 17 (evidence profiles) and 13 (forest plots).

HAS[12] extracted one non-systematic review dealing with eating and sleep disorders and two RCTs studying the impact of behavioural interventions on feeding behaviour in very small group of children (from 1 to 3). More detailed information on these studies can be found in the full HAS guideline from section 5.4.5 page 239-240. HAS also extracted studies on melatonin (international recommendations n=2, SR n=1, HAS recommendation 2010, 3 RCTs and one retrospective study). More detailed information on these studies can be found in the full HAS guideline from section 5.4.5 page 291-293 and 303.

A summary is provided in Table 12

Effect of psychosocial and pharmacological interventions on common medical and functional problems

NICE[13] found single study moderate quality evidence for large and statistically significant effects of CBT (relative to placebo pill) on nap time, bedtime, and sleep efficiency, and moderate and statistically significant effects on sleep onset latency and total sleep time as measured by actigraph. The only non-significant subscale for continuous actigraph data was for wake after sleep onset. However, dichotomous measures based on the actigraph data of positive treatment response for sleep onset latency and sleep efficiency were also non-significant. There was also single study evidence for large and statistically effects of CBT (relative to placebo pill) on the total score for the CSHQ and on CSHQ subscales (bed resistance, sleep onset delay, and night-waking), and for a moderate and statistically significant effect on the daytime sleepiness subscale of the CSHQ. However, the confidence in these effect estimates was downgraded to low due to risk of bias concerns (non-blind parent-rated outcome measure) and small sample size. Non-significant effects were observed for the sleep anxiety, sleep duration, parasomnias, and sleep-disordered breathing subscales of the CSHQ.

There was single study moderate quality evidence for large and statistically significant effects of melatonin (relative to placebo) on sleep onset latency, wake after sleep onset, bedtime, total sleep time, and sleep efficiency, and a moderate and statistically significant effect on nap time, as measured by actigraph. There was also evidence for large and statistically significant effects of melatonin on dichotomous measures based on the actigraph data of positive treatment response for sleep onset latency and sleep efficiency, with participants who received melatonin being over 25 times more likely to show sleep onset latency of less than 30 minutes or reduction of sleep onset latency by at least 50% than participants receiving placebo, and participants receiving melatonin were over 31 times more likely to show at least 85% for sleep efficiency than participants who received placebo.

There was also moderate quality evidence for a large and statistically effects of melatonin (relative to placebo) on the total score for the CSHQ and on CSHQ subscales (bed resistance, sleep onset delay, night-waking, and sleep duration), and for a moderate and statistically significant effect on the daytime sleepiness subscale of the CSHQ. Non-significant effects were observed for the sleep anxiety, parasomnias, and sleep-disordered breathing subscales of the CSHQ. Finally, there was moderate quality data from one trial for a large and statistically significant effect of melatonin (relative to placebo) on sleep onset latency as measured by sleep diary. However, effects on total sleep time were non-significant.

There was single study moderate quality evidence for a large and statistically significant effect of melatonin (relative to CBT), in favour of melatonin, on sleep efficiency, and moderate and statistically significant effects on sleep onset latency, wake after sleep onset, and total sleep time. The only non-significant subscales for continuous actigraph data were for nap time and bedtime. There was also evidence for large and statistically significant effects of melatonin on dichotomous measures based on the actigraph data of positive treatment response for sleep onset latency and sleep efficiency, with participants who received melatonin being over four times more likely to show sleep onset latency of less than 30 minutes or reduction of sleep onset latency by at least 50% than participants receiving CBT, and participants receiving melatonin were over five times more likely to show at least 85% for sleep efficiency than participants who received CBT.

There was also single study evidence for large and statistically effects of melatonin (relative to CBT), in favour of melatonin, on the total score for the CSHQ and on CSHQ subscales (night-waking, sleep duration), and for a moderate and statistically significant effects on the bed resistance and sleep onset delay subscales of the CSHQ. However, the confidence in these effect estimates was downgraded to low due to risk of bias concerns (non-blind parent-rated outcome measure) and small sample size. Non-significant effects were observed for the sleep anxiety, parasomnias, sleep-disordered breathing, and daytime sleepiness subscales of the CSHQ.

One paper narratively reports that no adverse events were reported or observed and none of the participants dropped out because of side effects and in another paper where treatment emergent signs and symptoms were reported and analysed and there was no evidence for statistically significant harms associated with melatonin (see section 4.6 Adverse events).

There was moderate quality evidence for large and statistically significant effects of combined CBT and melatonin (COMB), relative to placebo and in favour of COMB, on all continuous actigraph outcome measures for sleep. There was also evidence for large and statistically significant effects of COMB on dichotomous measures based on the actigraph data of positive

treatment response for sleep onset latency and sleep efficiency, with participants who received COMB being nearly 56 times more likely to show sleep onset latency of less than 30 minutes or reduction of sleep onset latency by at least 50% than participants receiving placebo, and participants receiving COMB were over 41 times more likely to show at least 85% for sleep efficiency than participants who received placebo. There was also evidence for large and statistically effects of COMB (relative to placebo), in favour of COMB, on the total score for the CSHQ and on CSHQ subscales (bed resistance, sleep onset delay, sleep anxiety, night-waking, sleep duration, and daytime sleepiness). The only non-significant effects observed were for the parasomnias and sleep-disordered breathing subscales of the CSHQ. However, it is important to note that for the CSHQ data, unlike the actigraph data, the confidence in effect estimates was downgraded to low due to risk of bias concerns (non-blind parent-rated outcome measure) and small sample size.

There was also evidence for benefits of COMB over CBT-only on sleep onset latency, wake after sleep onset, total sleep time, and sleep efficiency as measured by continuous actigraph data and evidence for large and statistically significant effects of COMB relative to CBT-only on dichotomous measures based on the actigraph data. Participants who received COMB were over nine times more likely to show sleep onset latency of less than 30 minutes or reduction of sleep onset latency by at least 50% than participants receiving CBT-only, and participants receiving COMB were nearly seven times more likely to show at least 85% for sleep efficiency than participants who received CBT-only. In addition, there was evidence for benefits of COMB relative to CBT-only on all but one subscale (sleep-disordered breathing) of the parent-completed CSHQ**.**

Finally, there was also evidence for benefits of COMB over melatonin-only on sleep onset latency, wake after sleep onset, and total sleep time as measured by continuous actigraph data and evidence for a large and statistically significant effect of COMB relative to melatonin-only on a dichotomous measure based on the actigraph data, with participants who received COMB being more than twice as likely to show sleep onset latency of less than 30 minutes or reduction of sleep onset latency by at least 50% than participants receiving melatonin-only. There was also evidence for benefits of COMB relative to melatonin-only on the total sleep problems score as measured by the CSHQ and on CSHQ subscales of bed resistance, sleep onset delay, sleep anxiety, and night-waking.

There was no evidence for statistically significant effects of atomoxetine on sleep problems as an indirect outcome, as measured by a study-specific Sleep Measure Scale. This study did, however, find evidence for statistically significant harms associated with atomoxetine, with participants who received atomoxetine being over three and a half times more likely to experience nausea during the trial and over four times more likely to experience decreased appetite than participants receiving placebo (see chapter on adverse events)

Due to the lack of evidence and the low number of cases, HAS GDG[12] did not consider that any specific interventions could be recommended for eating disorders. HAS concluded that melatonin has a positive effect on sleep disturbances.

4.4.7.2 Biomedical interventions aimed at common medical and functional problems

Evidence

NICE[13] extracted relevant clinical evidence from four RCTs on this topic. One of these studies examined the efficacy of a biomedical intervention on coexisting

sleep problems as an indirect outcome, one study examined the efficacy of a biomedical intervention on both coexisting sleep problems and gastrointestinal symptoms as indirect outcomes, one study examined the efficacy of a biomedical intervention on gastrointestinal symptoms as a direct outcome (target of the intervention), and one study examined effects on gastrointestinal symptoms as an indirect outcome. More detailed information on the studies can be found in the table presented below, in the full NICE guideline from section 7.8.4 page 679 - 685 and in NICE Appendix 17 (evidence profiles) and 13 (forest plots).

HAS[12] did not address this issue.

Effect of biomedical interventions on common medical and functional problems

NICE[13] found no evidence for a statistically significant effect of a multivitamin and mineral supplement on sleep improvement as an indirect outcome, as measured by the PGI-R. Neither was there evidence for statistically significant harms associated with a multivitamin/mineral supplement.

There was statistically significant evidence for a negative treatment effect with omega-3 fatty acids on sleep problems. Narrative review of this effect showed that the omega-3 group worsened from pre- to post-intervention, while the healthy diet control group showed some improvement. Data could not be extracted from this study for adverse events. However, there was no statistically significant evidence for harms associated with an omega-3 fatty acid supplement when compared against placebo by another trial.

There was no evidence for a statistically significant effect of secretin on the number of gastrointestinal problems as an indirect outcome, as measured by a study-specific GI symptoms questionnaire. Data could not be extracted for adverse events associated with secretin.

There was no evidence for a statistically significant effect of immunoglobulin (dosages combined) on gastrointestinal symptoms as measured by the number of participants who showed a positive treatment response, defined as 'moderately or substantially improved' on at least two of last four assessments or 'somewhat improved' for all of last four assessments of the modified gastrointestinal symptom score (GIS) for GI symptoms. This study also examined potential subgroup differences in the treatment response for gastrointestinal symptoms but found no evidence that the treatment effect was moderated by either predominant bowel pattern (diarrhoea, constipation, or alternating) or age (2-11 years or 12-17 years). There was also no statistically significant evidence for harms associated with immunoglobulin (see chapter on adverse events).

Finally, NICE did not find evidence for a statistically significant effect of a multivitamin/mineral supplement on gastrointestinal symptom improvement as an indirect outcome, as measured by the PGI-R. There was also no evidence for statistically significant harms associated with a multivitamin/mineral supplement (see chapter on adverse events).

Table 12 – Summary of recommendations by NICE and HAS guidelines on associated features of autism and coexisting conditions: common medical and functional problems.

Intervention domain: Common medical and functional problems

Psychosocial and pharmacological interventions			
NICE guideline	**NICE Recommendation**	**HAS guideline**	**HAS Recommendation**
Psychosocial and pharmacological interventions: • CBT vs. placebo • Melatonin vs. placebo • Melatonin vs. placebo • COMB vs. placebo • COMB vs. CBT • COMB vs. Melatonin • Atomoxetine vs. placebo	For **sleep problems** offer an assessment that identifies: • what the sleep problem is (for example, delay in falling asleep, frequent waking, unusual behaviours, breathing problems or sleepiness during the day) • day and night sleep patterns, and any change to those patterns • whether bedtime is regular • what the sleep environment is like, for example: o the level of background noise o use of a blackout blind o a television or computer in the bedroom o whether the child shares the room with someone • presence of co morbidities especially those that feature hyperactivity or other behavioural problems • levels of activity and exercise during the day • possible physical illness or discomfort (for example, reflux, ear or toothache, constipation or eczema) • effects of any medication	Melatonin	Recommended for severe sleep disorders resistant to a non-pharmacological approach

	• any other individual factors thought to enhance or disturb sleep, such as emotional relationships or problems at school • The impact of sleep and behavioural problems on parents or carers and other family members.	
	If the child or young person with autism snores loudly, chokes or appears to stop breathing while sleeping, refer to a specialist to check for obstructive sleep apnoea.	
	Develop a sleep plan (this will often be a specific sleep behavioural intervention) with the parents or carers to help address the identified sleep problems and to establish a regular night-time sleep pattern. Ask the parents or carers to record the child or young person's sleep and wakefulness throughout the day and night over a 2-week period. Use this information to modify the sleep plan if necessary and review the plan regularly until a regular sleep pattern is established.	
	Do not use a pharmacological intervention to aid sleep unless: • sleep problems persist despite following the sleep plan • Sleep problems are having a negative impact on the child or young person and their family or carers.	
	If a pharmacological intervention is used to aid sleep it should: • only be used following consultation with a specialist pediatrician or psychiatrist	

	with expertise in the management of autism or paediatric sleep medicine • be used in conjunction with non-pharmacological interventions • Be regularly reviewed to evaluate the ongoing need for a pharmacological intervention and to ensure that the benefits continue to outweigh the side effects and risks.		
	If the sleep problems continue to impact on the child or young person or their parents or carers, consider: • referral to a paediatric sleep specialist, and • Short breaks and other respite care for one night or more. Short breaks may need to be repeated regularly to ensure that parents or carers are adequately supported. Agree the frequency of breaks with them and record this in the care plan.		
		Behavioural interventions on **eating disorders**	Insufficient evidence, no recommendation provided
Biomedical interventions			
NICE guideline	**NICE Recommendation**	**HAS guideline**	**HAS Recommendation**
Nutritional interventions: • Multivitamin/mineral supplement vs. placebo • Omega-3 fatty acids vs. healthy diet control • Secretin vs. placebo • Immunoglobulin vs. placebo	Do not use omega-3 fatty acids to manage **sleep problems** in children and young people with autism.		

4.4.7.3 *New Zealand Guideline Supplementary Paper on Gastrointestinal Problems in Young People with ASD*

Because the brief chapter on common associated medical conditions in NICE and HAS contrasts with the frequent occurrence of these problems, the GDG decided to additionally extract the evidence from the New Zealand Guideline Supplementary Paper on Gastrointestinal Problems in Young People with ASD.[42] Two research questions were addressed:

1. Are gastrointestinal (GI) problems more common in children and young people with ASD than those without ASD?
2. What gastrointestinal signs or symptoms, typical and atypical, should be investigated in children and young people with ASD?

The GI problems that were included as outcomes are: chronic constipation, diarrhoea, faecal incontinence, encopresis, changes to bowel habit, vomiting, nausea, gastro-oesophageal reflux, abdominal pain, discomfort, irritability, bloating and flatulence. Other outcomes, such as food allergies, food intolerance, food selectivity, immunologic dysregulation, intestinal inflammation, metabolic dysfunction, nutritional deficiencies and anatomical abnormalities were excluded.

For the first question 3 SRs and 6 primary studies were analysed. For the second question1 SR and 5 primary studies were analysed. The recommendations of the New Zealand Guideline are reproduced in Table 13. It is noteworthy that feeding problems were not addressed by any of the guidelines.

Table 13 – Conclusions and recommendations issued by the New Zealand Guideline Supplementary Paper on Gastrointestinal Problems in Young People with ASD

1.	Gastrointestinal problems, specifically constipation, chronic diarrhoea, altered bowel habits, and encopresis (faecal soiling), are more common in children and young people with ASD compared with typically developing peers.
2.	When challenging behaviours are evident, people with ASD need to be assessed for co-morbid conditions such as seizures, ADHD, anxiety disorders, depression, and gastrointestinal problems.
3.	Children and young people with ASD should have a full evaluation that includes a thorough assessment of gastrointestinal function. Some children, particularly those with social communication difficulties, may have atypical presentations such as increased anxiety, irritability, disordered sleep patterns, and unusual vocalisations and movements.

4.4.7.4 *Other NICE guidelines on possible associated medical conditions*

For specific medical conditions care givers could refer to the existing NICE guidelines that are available on the NICE website (http://www.nice.org.uk/) including the guidelines on Post Traumatic Stress Disorder (CG26) Depression (CG28), Obsessive Compulsive Disorder (CG31), ADHD (CG72), Constipation (CG99), Epilepsy (CG137) and Antisocial behaviour (CG158). The quality of these supplementary guidelines was not appraised by the KCE.

4.4.8 *Specific interventions related to sexuality for adolescents*

There is no evidence on this topic. However, the GDG of HAS pointed out the issue of sexuality and emotional and affective live as a topic of interest whereas NICE[13] did not address this issue.

Based on expert consensus, HAS[12] recommended to consider the impact of puberty on adolescent's behaviour. The content of the sexual education programs proposed in scholar curricula for adolescents must also be proposed to autistic adolescents. These programs should be provided by trained professionals and they should be adapted taking into account the social interaction and communication features as well as the comprehension and reasoning skills of the adolescents with autism. The purpose is to allow these adolescents to find an adapted behaviour with peers and to acquire autonomy and fulfilment in this domain (see Table 14)

Table 14 – Summary of recommendations by NICE and HAS guidelines on associated features of autism and coexisting conditions: sexuality.

Intervention domain: Sexuality

Psychosocial interventions			
NICE guideline	**NICE Recommendation**	**HAS guideline**	**HAS Recommendation**
		No evidence	Expert consensus: Propose adapted sexual education

4.4.9 From evidence to recommendations

The evidence, as well as the NICE, HAS and New Zealand recommendations presented in Tables 6 to 14, were sent to the GDG and discussed in a face-to-face meeting. The comments made by the GDG can be found in Appendix 5. Based on this discussion, the KCE prepared a first draft of KCE recommendations. These were re-submitted to the GDG, to start the Delphi process as described in section 2 (Methodology). The results of the subsequent Delphi rounds can be found in Appendix 6.

4.5 Interventions aimed at improving the impact on the family

An overview of the recommendations by NICE and HAS is summarized in Table 15.

4.5.1 Psychosocial interventions aimed at improving the impact of autism on the family

4.5.1.1 Evidence

NICE[13] extracted clinical evidence from 6 RCTs on this topic. For the direct effects of psychosocial interventions on the family were from 1 RCT. Indirect effects were extracted from 5 RCTs. More detailed information on the studies can be found in the full NICE guideline from section 8.2.2 page 695-706 and in NICE guideline Appendix 12e.

HAS[12] retrieved 2 observational evaluations of interventions aimed at supporting the family, one described in a Belgian dissertation and one evaluation based on a qualitative study. For more information, see HAS p 29-34.

4.5.1.2 Effect of psychosocial interventions aimed at improving the impact of autism on the family

NICE concluded that there was only one study that analysed the impact of a psychosocial intervention (parent training) on the family as a direct outcome and the quality of evidence was low. A small and statistically significant effect of parent training on parental stress was show in a meta-analysis of 3 other studies, graded as low quality of evidence due to small sample size and risk of bias concerns. Two other studies analysed the impact of a psychosocial intervention (one study: cognitive-behavioural intervention CBT; one study: early behavioural intervention EBI) on the family as an indirect outcome, the quality of evidence was low to very low.

HAS included the Belgian paper 'Guidance psycho-pédagogique' (Psycho-educational guidance), which described a method for individual supportive counselling with parents, and the results that were observed when applying this method.[43] The qualitative study evaluated the efficacy of a group-based formation in the TEACCH program for parents; the study used mothers' testimonies to measure self-esteem and stress.

The HAS concluded that information and psychological support have to be provided to the extended family including parents, sibling, grandparents, uncles, aunts, cousins and close friends (all persons likely to interact with the patient).

4.5.2 Pharmacological interventions aimed at improving the impact of autism on the family

4.5.2.1 Evidence

NICE[13] extracted clinical evidence from 1 RCT on this topic that examined the efficacy of a selective noradrenaline reuptake inhibitor (atomoxetine) on improving the impact of autism on the family as an indirect outcome. More detailed information on the studies can be found in the full NICE guideline from section 8.3.2 page 706-707

HAS[12] did not address this issue.

4.5.2.2 Effect of pharmacological interventions aimed at improving the impact of autism on the family

NICE concluded that there was no statistically significant effect of atomoxetine on parental mental health or parental stress as an indirect outcome, as measured by the General Health Questionnaire GHQ-28 or the Nature of Scientific Inquiry questionnaire (NOSI) However, more nausea and decrease appetite were experienced by the participants in the intervention group.

4.5.3 Biomedical interventions aimed at improving the impact of autism on the family

4.5.3.1 Evidence

NICE[13] extracted clinical evidence from 1 RCT on this topic that examined the efficacy of complementary therapies on improving the impact of autism on the family as an indirect outcome. More detailed information on the studies can be found in the full NICE guideline from section 8.4.2 page 707-709.

HAS[12] did not address this issue.

4.5.3.2 Effect of biomedical interventions aimed at improving the impact of autism on the family

NICE concluded that the RCT showed a moderate and statistically significant effect of training parents in how to administer Qigong massage (intervention based on Chinese medicine) on parental stress as an indirect outcome as measured by the Autism Parenting Stress Index (APSI). The quality of evidence was low.

HAS did not address this issue.

Table 15 – Summary of recommendations by NICE and HAS guidelines on at improving the impact on the family.

Intervention domain: Improving the impact on family

Psychosocial interventions			
NICE guideline	**NICE Recommendation**	**HAS guideline**	**HAS Recommendation**
Behavioural interventions • EBI	Insufficient evidence, no recommendation provided		
Cognitive-behavioural intervention • CBT	Insufficient evidence, no recommendation provided		
Parent training • PEBM Parent education and behaviour management/ PEC parent education and counselling; • training of parents by speech and language therapists; • home TEACCH; • hospital-based seminar, on-site consultations to day care centres, psycho-educational and supportive training	Insufficient evidence, no recommendation provided		

	Observational evaluation, qualitative research and expert opinion	It is recommended to facilitate support of parents and to propose different support modalities: • Information on autism and on interventions; • Support to understand particular challenges experienced by their child with autism; • Psychological support; • Exchange of experience among parents; • Contacts with parents associations or with other persons with autism; Information on and support to get access to professional help; in particular guidance when the child/adolescent needs to be (re-) oriented
	Expert opinion	It is recommended that special attention be paid to signs of suffering and seeking for support expressed by siblings and to propose different modalities: • individual psychological support; • thematic groups 'parents-children-sibling'; • discussion groups; • organized activities with the sibling, etc. These modalities cannot be imposed.

4.5.4 From evidence to recommendations

The evidence as well as the NICE and HAS recommendations presented in Table 15 were sent to the GDG and discussed in a face-to-face meeting. The comments made by the GDG can be found in Appendix 5. Based on this discussion, the KCE prepared a first draft of KCE recommendations. These were re-submitted to the GDG, to start the Delphi process as described in section 2 (Methodology). The results of the subsequent Delphi rounds can be found in Appendix 6.

4.6 Adverse events associated with interventions

NICE[13] provides a separate chapter on harms whereas HAS[12] discusses safety within each section on a specific intervention. In this guideline we adhere to the structure proposed by NICE and we will incorporate the safety data from the HAS document in this structure.

The NICE review only included systematic reviews or randomized controlled trials in which adverse events were reported. The HAS report included recommendations formulated by professional organisations, meta-analyses and reviews, RCTs and controlled trials, observational studies and case series.

NICE discussed a few methodological aspects related to the evaluation of harmful effects of therapeutic interventions.

A causal relationship between a harmful effect and an intervention can be best detected in a randomized controlled trial (RCT) of the intervention against placebo. However, an RCT is usually developed to evaluate treatment efficacy rather than adverse events, and if adverse events are reported, the RCT is often insufficiently powered to detect rare and/or unexpected events. The relatively short duration of an RCT might also prevent long-term adverse events to be detected. Therefore identification of adverse events often depends on observations reported after efficacy trials have been published, but in these reports the causal relationship between the intervention and the adverse event is more difficult to prove.

The failure to record adverse events in interventions employing psychosocial, behavioural and educational methods partly reflects an assumption by researchers that such interventions may not cause adverse events at all; but logically, if an intervention is powerful enough to have wanted effects it is also potentially powerful enough to cause unwanted effects.

Finally, in many of the studies where adverse effects are reported, the primary informant is a parent/caregiver rather than the child or young person whose perspective and experience may be different from that reported by others.

NICE concludes that, given these limitations, their review of adverse events should be considered as limited in both its identification of possible short- and longer-term adverse effects, and also in their causal relationship to the intervention. The relative absence of reported adverse effects' association with non-pharmacological (and supplement) interventions should not be considered as good evidence that such interventions are either safer or more acceptable than other approaches as this may reflect only measurement differences.

4.6.1 Harms associated with psychosocial interventions

NICE[13] did not detect any systematic review or primary study (RCT) involving harms associated with psychosocial interventions as an outcome.

HAS[12] identified no harms in the section on global interventions, neither in the section on specific psychosocial interventions for communication, social interaction, behavioural problems, motor or sensory problems nor in the section on other specific psychosocial interventions. However, regarding the 'packing technique' reference was made to the report by the French HCSP (Haute Conseil de la santé publique)[44] that warns against psychological harm (see Has report p 234).

4.6.2 Harms associated with pharmacological interventions.

4.6.2.1 NICE guideline

NICE[13] extracted clinical evidence from 19 RCTs on this topic. In all trials except one, the comparator was placebo. Adverse events were examined in:

- two anticonvulsant trials (both evaluating divalproex),
- one antidepressant trial (citalopram) and one selective noradrenaline reuptake inhibitor (SNRI) trial (atomoxetine),

- one antihistamine trial (cyproheptadine, not available anymore in Belgium),
- one antioxidant trial (N-acetylcysteine),
- nine antipsychotic trials (5 studies on risperidone of which one study included a low dose scheme; 2 studies on aripiprazole of which one study included a low dose scheme; one trial on haloperidol; and one trial comparing risperidone with haloperidol),
- one antiviral trial (amantidine hydrocholoride),
- one cognitive enhancer trial (piracetam),
- one melatonin trial,
- one opioid antagonist trial (naltrexone).

In all studies adverse events were examined as an indirect outcome of the trial; the results of the trials related to efficacy were described in the chapters on interventions aimed at the core features of autism, at behaviour that challenges and at associated features of autism and coexisting disorders.

More detailed information on the studies can be found in the full NICE guideline in section 9.3.2 page 721-790 and in NICE guideline Appendix 13 and 17 and is summarized in Table 16.

NICE concluded as follows:

- for the antidepressant citalopram: there was evidence from a single study (N participants=149) for statistically significant harms, including: increased energy level; disinhibited, impulsive or intrusive behaviour; decreased attention and concentration; hyperactivity; stereotypy; diarrhoea; any insomnia and initial insomnia or difficulty falling asleep; skin or subcutaneous tissue disorder. NICE evaluated the quality of the evidence as very low.
- for the SNRI atomoxetine: there was evidence from a single study (N participants=97) for an increased risk of nausea and decreased appetite. NICE evaluated the quality of the evidence as very low.
- for the antipsychotics: there was meta-analysis evidence for statistically significant increased risk for the harms. NICE evaluated the quality of the evidence mostly as very low and in some cases as low.
- for low-dose antipsychotics: there was evidence for statistically significant adverse events as follows: clinically relevant (>=7%) weight gain (aripiprazole; 1 study, N participants=103), weight gain measured with a continuous measure (kg) (aripiprazole, risperidone; meta-analysis of 2 studies, N participants=160), and increased appetite (aripiprazole, risperidone; meta-analysis of 2 studies, N participants=168). NICE evaluated the quality of the evidence as very low.

Table 16 – NICE 2013 Conclusion: Meta-analysis evidence for statistically significant increased risk for the following harms associated with antipsychotics

Adverse event	Drug(s) evaluated; number of studies, total n° of participants in all studies	Adverse event	Drug(s) evaluated; n° of studies, total n° of participants in all studies
any adverse event	aripiprazole, risperidone, haloperidol; 5 studies, N=528	somnolence/drowsiness, fatigue	aripiprazole, risperidone; 5 studies, N=588
Clinically relevant weight gain (>=7%)	aripiprazole; 2 studies, N= 313	sedation	aripiprazole, risperidone; 3 studies, N=409
weight gain measured with continuous measure (kg)	aripiprazole, risperidone; 6 studies, N=541	rhinitis	aripiprazole, risperidone; 2 studies, N=295
increased appetite	aripiprazole, risperidone; 5 studies, N=588	fever	aripiprazole, risperidone; 4 studies, N=488
constipation	risperidone; 3 studies, N=275	tachycardia	risperidone; 2 studies, N=179
increased prolactin concentration	risperidone; 2 studies, N=124	drooling	aripiprazole, risperidone; 3 studies, N=413
leptin change score	risperidone; 2 studies, N=104	tremor	aripiprazole, risperidone; 4 studies, N=492
cardiac pulse (beats per min.) change score	risperidone; 1 study, N=78		

4.6.2.2 HAS guideline

HAS[12] provided an overview of existing guidelines, meta-analyses and reviews, RCTs, controlled trials, observational studies and case series. Both efficacy and adverse events were discussed; only the results of the RCTs were presented in Tables (see HAS report: Tables p 276, 283, 286, 289, 291).

The following drugs were included:

- antipsychotics: haloperidol, risperidone, olanzapine, aripiprazole, other;
- antidepressants: the SSRI's fluvoxamine, fluoxetine, citalopram, other;
- drugs used for attention deficit and hyperactivity disorder (ADHD) associated to autism: atomoxetine, methylphenidate;
- anticonvulsants: divalproex, valproate, lamotrigine, levetiracetam.

HAS concluded that there were few RCTs, that the trial size was mostly small and that adverse events were frequent.

It warned against the well-known side effects of psychotropic drugs. The drugs that showed positive effects in RCTs (haloperidol, risperidone, aripiprazole and methylphenidate) all had troublesome side effects (nausea, pain, enuresis, extra-pyramidal signs, cardiac and metabolic effects...). Adverse events seemed more frequent with risperidone than with aripiprazole treatment but a head to head comparison was lacking.

4.6.3 Harms associated with biomedical interventions

NICE[13] extracted clinical evidence from 7 RCTs on this topic. Adverse events were examined in:

- two medical procedure trials (both hyperbaric oxygen therapy HBOT against attention-placebo),
- five nutritional interventions trials (multivitamin/mineral supplement, omega-3 fatty acid supplement, oral human immunoglobulin, or ginkgo biloba against placebo; a gluten-free and casein-free diet against treatment as usual).

In all studies adverse events were examined as an indirect outcome of the trial; the results of the trials related to efficacy were described in the chapters on interventions aimed at the core features of autism, at behaviour that challenges and at associated features of autism and coexisting disorders.

More detailed information on the studies can be found in the full NICE guideline in section 9.4.2 page 790-804 and in NICE guideline Appendix 13 and 17.

NICE concluded that there was evidence from a single study (N=58) for an increased risk of minor-grade ear barotrauma associated with HBOT. NICE evaluated the quality of the evidence as low.

HAS[12] evaluated efficacy and adverse events for several biomedical interventions:

melatonin, naltrexone, choline esterase inhibitors, alpha 2 adrenergic agonists (e.g. clonidine), secretin, immunotherapy, chelating agents, antibiotics, antifungals, vitamins, diets excluding gluten or casein, omega-3 acids, dextrometrophan, famotidine, amantadine and benzodiazepines.

HAS gave an overview of existing guidelines, meta-analyses and reviews, RCTs, controlled trials, observational studies and case series. Only for melatonin, the results of the RCTs were presented in a Table (see HAS report: Table p 293). Melatonin was overall well tolerated; no adverse events were reported in 3 RCTs.

For the other biomedical interventions, HAS concluded that there were no or only few studies available that had evaluated adverse events (and efficacy) associated with these interventions.

4.6.4 Conclusion regarding adverse events associated with interventions

NICE[13] nor HAS[12] formulated specific recommendations regarding adverse events associated with interventions.

HAS recommended that the balance between risk and benefit should systematically been evaluated when psychotropic drugs are used. Parents should receive written information.

The evidence described in paragraph 4.6.1 to 4.6.3 was taken into account in the recommendations regarding psychosocial interventions, pharmacological interventions and biomedical interventions.

Table 17 – Summary of recommendations by NICE and HAS guidelines on adverse events.

Intervention domain Adverse events	NICE guideline	NICE Recommendation	HAS guideline	HAS Recommendation
			Expert opinion: when prescribing psychotropic drugs benefits and risks should be balanced	recommend
			Expert opinion: parents should receive written information on the drugs that are prescribed	recommend

4.6.5 From evidence to recommendations

The evidence as well as the NICE and HAS recommendations presented in Table 17 were sent to the GDG and discussed in a face-to-face meeting. The comments made by the GDG can be found in Appendix 6. Based on this discussion, the KCE prepared a first draft of KCE recommendations. These were re-submitted to the GDG, to start the Delphi process as described in section 2 (Methodology). The results of the subsequent Delphi rounds can be found in Appendix 6.

5 RECOMMENDATIONS

5.1 Recommendations adapted by GDG from the NICE and HAS guideline

Discussions on the evidence and the recommendations extracted from the NICE and the HAS guidelines led to the formulation of guidelines endorsed by the GDG. The comments provided by the GDG members either by mail or during the face-to-face discussions can be found in the tables in the Appendix. As described in the method section two, and sometimes three, online rounds of votes according to the Delphi method were offered. Only the recommendations that obtained more than 85% consensus were submitted to the stakeholders. Subsequently the stakeholders voted on the recommendations and during the stakeholder meeting all recommendations that did not obtain 85% agreement were discussed. Since no new evidence was presented during the stakeholder meeting, the core of the recommendations did not change but the wording of a number of recommendations was improved. After submitting these changes again to the GDG the recommendations were finalised and are now proposed in Table 18. In other words, for all recommendations presented below, the level of agreement (LOA) by the GDG was always more than 85%. Recommendations with a consensus score lower than 85 % can be found in the Appendix tables but are not considered valid.

Table 18 – Final recommendations for children and young people with autism

Domain 1: Organisation and delivery of care	
Organisation and delivery of care	
1	All staff working with children and young people with autism should have an understanding of autism.
2	In all settings, professionals should take into account the physical environment in which children and young people with autism are supported and cared for and make reasonable and appropriate adjustments. Where it is not possible to adjust or adapt the environment, processes should be adjusted to limit the negative impact of the environment.
3	Children and young people with autism should have access to a key worker approach in order to manage and coordinate treatment, care and support, including the management of transitions, for the child or young person with autism and their family and carers.
4	Children and young people with autism should be offered evidence-based intervention aimed at preparation and coping strategies to facilitate access to community services, including the skills to access public transport, employment and leisure facilities.
5	Children and young people with autism and their family and carers, should have easy access to short breaks, especially at periods of severe stress for the child and/or family.
6	Children and young people with autism, and their family and carers, should be provided with post-diagnosis information about services available and support, for example a family support worker.
7	Treatment and care of children and young people with autism should involve shared decision making and a collaborative approach that takes into account service user preferences.
8	All children and young people with autism should have access to healthcare and social care services, including mental health services. Services should be adapted to the level of care specialisation the child needs. Services should be within a reasonable distance from their homes. Access should take the level of functional impairment into account but should not be restricted based on a child's intellectual ability, autism diagnosis, or any other eligibility criteria.
Stakes and principles of action	
9	A coherent multidisciplinary approach is needed.
10	Define a framework and quality criteria for multi (trans) disciplinary approach in the same or in different institutions.
11	A therapeutic team should establish a framework for an individualized work plan and should identify a coordinator.
12	A framework and quality criteria should be formalised within an institution, in conventions with other professionals, in networks.
13	The framework and quality criteria should be known by all professionals.
14	The personalised educational plan should reflect the framework and quality criteria.
Tools for improving coherent intervention	
15	Develop a personalised program based on evaluation with appropriate tools and on observation in daily life, and in agreement with the patient, the parents and all professionals involved.
16	Assign the task of coordinator to one of the professionals (not necessarily a physician in order to guarantee the coherence and continuity of care.
17	A person who had a comprehensive training (including all the important aspects of ASS) will be responsible for overseeing and/or delegating the coordination task.

18	A file (case record, dossier) is the source document for communication between professionals.
19	The file should contain all relevant information on the person with autism: personalised project, evaluations, treatment and educational plan, specific interventions.
20	Sharing the file necessitates parental consent, in line with the rules of duty of professional confidentiality.
21	In professional communication, it is recommended to use the DSM-5 classification but DSM-IV -TR and ICD-10 are still valid during the transition period.
22	A go-between notebook or electronic tool is recommended to support communication between the professionals and the parents and child but electronic tools should be used for recording not for online communication.
23	Upon transfer between institutions (medical/social) a contact person (referent) should be kept until integration for the child and his family is ensured.
24	Networking, collaboration and regular meetings should be organized between professionals.
25	The Reference Centres for Autism have a specific but not exclusive role in supporting the networking. Referrals should include all relevant collaborators.
26	Institutions, especially hospitals, should provide their staff with a framework or flexible protocol to facilitate contacts when caring for children or adolescents with autism for any medical indication.
27	A medical examination by a medical doctor familiar with autism and chosen by the parents should be offered at the start of the screening and whenever needed.
Sensitive transition periods	
28	Diagnostic and therapeutic teams should collaborate closely. Professionals who intervene only occasionally should consult the team.
29	Participation of representatives of therapeutic teams should be offered to parents early on during the information sessions on the diagnosis.
30	Transition periods e.g. transfer from one type of care/education to another or from childhood to adulthood require particular attention and should be prepared. Continuity of care should be assured.
31	Crisis situations require specific evaluation and intervention. Necessary information should be communicated among professionals, also in case hospitalization is inevitable. Specific education of professionals about crisis situations is necessary.
Education and support for professionals	
32	Continuous education (at least every 2 to 3 years) is needed for all professionals.
33	Therapeutic teams should be accompanied by an external expert (representing a reference centre for autism) for debriefings once per year.
34	Professionals should not work in isolation but share experiences with peers or be supervised.
35	New professionals should be coached.
36	Awareness and support should be offered to professionals to prevent burn-out.

Domain 2: Core features	
Psychosocial interventions	
Overall autistic behaviour	
37	In children and young people with autism, consider a specific social-communication intervention for the core feature of impaired reciprocal social communication and interaction. This intervention should include play-based strategies with parents, carers and teachers to increase joint attention, engagement and reciprocal communication in the child or young person. Strategies should: • be adjusted to the child or young person's developmental level; • aim to increase the parents', carers', teachers' or peers' understanding of, and sensitivity and responsiveness to, the child or young person's patterns of communication and interaction; • include techniques to expand the child or young person's communication, interactive play and social routines. The intervention should be delivered by a trained professional. For preschool children consider parent, carer or teacher mediation. For school-aged children consider peer mediation.
38	There is no evidence on the effect of individual psychoanalysis, therefore no recommendation can be provided.
39	There is no evidence on the effect of treatment in psychoanalytically oriented institutions, therefore no recommendation can be provided.
Pharmacological interventions	
Overall autistic behaviour	
40	Pharmacological interventions involving antipsychotics, anticonvulsants and antidepressants are not recommended to target overall autistic behaviour.
41	Regarding pharmacological intervention for *overall autistic behaviour* there is insufficient evidence on the effect of SNRI's and therefore no recommendation can be provided.
Impaired reciprocal social communication and interaction	
42	Regarding pharmacological intervention for *impaired reciprocal social communication and interaction* there is insufficient evidence on the effect of antioxidants and therefore no recommendation can be provided.
Restricted interests and rigid and repetitive behaviours	
43	A) Regarding pharmacological interventions to target *restricted interests and rigid and repetitive behaviours*, there is insufficient evidence on the effect of antidepressants (especially SSRI's) and therefore no recommendation can be provided. B) Pharmacological interventions involving antioxidants are not recommended to target restricted interests and rigid and repetitive behaviours.
Biomedical interventions	
Overall autistic behaviour	
44	Biomedical interventions involving hormone therapy (secretin), chelation, HBOT and gluten- or casein-free diets are not recommended to target *overall autistic behaviour.*

45	Biomedical interventions involving other drugs such as antibiotics, antifungals, dextrometorphan, famotidine, amantadine, benzodiazepines and antihistamines are not recommended to target *overall autistic behaviour.*
46	Regarding biomedical interventions for *overall autistic behaviour,* there is insufficient evidence on the effect of complementary interventions (such as acupressure, acupuncture, electro-acupuncture and Qigong massage), nutritional interventions (with multivitamins and minerals, L- carnosine or L-carnitine, omega-3 fatty acids) and sensory interventions (neurofeedback and auditory integration training). Therefore no recommendation can be provided for these interventions.
Impaired reciprocal social communication and interaction	
47	Biomedical interventions involving hormone therapy (secretin), chelation, HBOT and gluten- or casein- free diets are not recommended to target *impaired reciprocal social communication and interaction.*
48	Regarding biomedical intervention for *impaired reciprocal social communication and interaction,* there is insufficient evidence on the effect of complementary interventions (electro-acupuncture), nutritional interventions (multivitamins and minerals, L- carnosine or L-carnitine, omega-3 fatty acids) and sensory interventions (neurofeedback). Therefore no recommendation can be provided for these interventions.
Restricted interests and rigid and repetitive behaviours	
49	Biomedical interventions involving hormone therapy (secretin), chelation, HBOT and gluten- or casein- free diets are not recommended to target *restricted interests and rigid and repetitive behaviours.*
50	Regarding biomedical intervention for *restricted interests and rigid and repetitive behaviours,* there is insufficient evidence on the effect of motor intervention (Kata exercise training), nutritional interventions (L- carnosine or L-carnitine) and sensory interventions (neurofeedback). Therefore no recommendation can be provided for these interventions.
Domain 3: Behaviour that challenges	
Anticipating and preventing behaviour that challenges	
51	Assess factors that may increase the risk of behaviour that challenges in routine assessment and care planning in children and young people with autism, including:
	• impairments in communication that may result in difficulty understanding situations or in expressing needs and wishes
	• coexisting physical disorders, such as pain or gastrointestinal disorders
	• coexisting mental health problems such as anxiety or depression and other neurodevelopmental conditions such as ADHD
	• the physical environment, such as lighting and noise levels
	• the social environment, including home, school and leisure activities
	• changes to routines or personal circumstances
	• developmental change, including puberty
	• exploitation or abuse by others
	• inadvertent reinforcement of behaviour that challenges

	• the absence of predictability and structure.
52	Develop a care plan with the child or young person and their families or carers that outlines the steps needed to address the factors that may provoke behaviour that challenges, including:
	• treatment, for example, for coexisting physical, mental health and behavioural problems
	• support, for example, for families or carers
	• necessary adjustments, for example, by increasing structure and minimising unpredictability.
Assessment and initial intervention for behaviour that challenges	
53	If a child or young person's behaviour becomes challenging, reassess factors identified in the care plan and assess for any new factors that could provoke the behaviour.
54	Offer the following to address factors that may trigger or maintain behaviour that challenges:
	• treatment for physical disorders, or coexisting mental health and behavioural problems
	• interventions aimed at changing the environment, such as:
	o providing advice to families and carers
	o making adjustments or adaptations to the physical surroundings
55	If behaviour remains challenging despite attempts to address the underlying possible causes, consult senior colleagues and undertake a multidisciplinary review.
56	At the multidisciplinary review, take into account the following when choosing an intervention for behaviour that challenges:
	• the nature, severity and impact of the behaviour
	• the child or young person's physical and communication needs and capabilities
	• the environment
	• the support and training that families, carers or staff may need to implement the intervention effectively
	• the preferences of the child or young person and the family or carers
	• the child or young person's experience of, and response to, previous interventions.
Functional assessment	
57	In the case of challenging behaviour a functional assessment should first be performed.
58	The functional assessment should include a medical examination in order to exclude physical causes for pain.
59	The functional assessment should identify:
	• triggers for the behaviour,
	• patterns of behaviour,

	• the needs that the child or young person is attempting to meet by performing the behaviour,
	• the consequences of the behaviour.
Psychosocial intervention	
60	In the absence of coexisting mental health or behavioural problems (e.g. anxiety or ADHD) and if no physical disorder or environmental problem has been identified as triggering or maintaining the behaviour that challenges, offer the child or young person a psychosocial intervention as a **first-line** treatment.
61	There is insufficient evidence to recommend any specific type of psychosocial intervention.
62	Psychosocial interventions for behaviour that challenges should include clearly identified target behaviour and attempt to assess and address the underlying cause of the behaviour.
63	Psychosocial interventions for behaviour that challenges should include a focus on outcomes that are linked to quality of life.
64	Psychosocial interventions for behaviour that challenges should include assessment and modification of environmental factors that may contribute to initiating or maintaining the behaviour.
65	Psychosocial interventions for behaviour that challenges should include a clearly defined intervention strategy that takes into account the developmental level and coexisting problems of the child or young person.
66	Psychosocial interventions for behaviour that challenges should include a specified timescale to meet intervention goals in order to promote modification of intervention strategies that do not lead to change within a specified time and to reassess the therapeutic strategy.
67	Psychosocial interventions for behaviour that challenges should include a systematic measure of the target behaviour taken before and after the intervention to ascertain whether the agreed outcomes are being met. Changes may be very small but noticed by caregivers.
68	Psychosocial interventions for behaviour that challenges should be applied consistently in all areas of the child or young person's environment (for example, at home and at school).
69	Psychosocial interventions for behaviour that challenges should include agreement among parents, carers and professionals in all settings about how to implement the intervention.
Crisis intervention	
70	Crisis intervention should aim at providing protection, not punishment**.**
71	The use of isolation chambers should be restricted to exceptional cases where all other approaches have failed and the person and the environment need protection.
72	The use of isolation chambers should respect legal regulations and framework.
73	The use of physical restraint should be restricted to exceptional cases where all other approaches have failed and the person and the environment need protection.
74	It is recommended not to use packing (wrapping in cold, wet towels).
Pharmacological interventions	
75	It is recommended to consider antipsychotic medication 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.

76	Prior to prescribing antipsychotic medication it is recommended to offer a full medical assessment including laboratory and/or functional tests upon indication.
77	Antipsychotic medication should be prescribed and monitored by a child psychiatrist, a neuropediatrician or an experienced pediatrician or neurologist.
78	It is recommended that the prescriber identifies the target behaviour.
79	It is recommended that the prescriber decides on an appropriate measure to monitor effectiveness, including frequency and severity of the behaviour and a measure of global impact.
80	It is recommended that the prescriber reviews the effectiveness and any side effects of the medication after 3–4 weeks and regularly thereafter.
81	It is recommended that the prescriber stops treatment if there is no indication of a clinically important response at 6 weeks.
82	The prescription of antipsychotic medication should start at a low dose and should be maintained at the minimal effective dose.
83	It is recommended not to allow caretakers or parents increase the dose 'as needed'**.**
84	The choice of antipsychotic medication should take into account side effects, acquisition costs, the child or young person's preference (or that of their parent or carer where appropriate) and response to previous treatment with an antipsychotic.
85	When a patient is transferred to primary care clear instructions should be provided regarding all aspects of the prescription but the responsibility is not transferred.
86	The medical expert (child psychiatrist, specialist) should remain in charge of pharmacological treatment and see the patient at least once a year.
87	Pharmacological treatment should be explained to the parents in a comprehensible way, if needed with written information on the therapeutic plan.
88	Based on the available literature, the pharmacological agents that have shown comparable efficacy as treatment for challenging behaviour in children and young persons with autism are haloperidol, risperidone and aripiprazole.
Biomedical interventions	
89	It is recommended to inform parents that currently trials involving massage, multivitamin and mineral supplement, electro-acupuncture, hormone treatment (secretin), medical procedures (HBOT and DMSA), nutritional and sensory interventions have not demonstrated efficacy against challenging behaviour in autism.
90	It is recommended to warn parents against unnecessary spending for alternative treatments that have not shown efficacy.
Domain 4: associated features of autism and coexisting conditions	
Impairments in adaptive behaviour	
91	Based on an evidence based approach, there is insufficient scientific evidence for behavioural intervention, cognitive behavioural intervention, parent training or social-communication intervention for children with autism and impairment in adaptive behaviour. Therefore no recommendation can be provided. However, adaptive behaviour as an outcome (DSM- IV-TR) can be considered as core feature (recommendation 37). Problems with adaptive behaviour are part of what is described as Autism Spectrum Disorder in DSM-5.
92	Based on expert consensus the GDG provided a recommendation to use augmentative communication (such as PECS) for children with autism and impairment in adaptive behaviour.
93	Pharmacological interventions are not recommended to treat isolated impairment in adaptive behaviour in children with autism.

94	Biomedical interventions including complementary interventions (e.g. acupuncture), hormone intervention (e.g. secretin), medical procedures (chelation or HBOT) and nutritional interventions (omega-3 fatty acids, gluten-free or casein-free diet) are not recommended to treat impairment in adaptive behaviour in children with autism.
95	Based on expert consensus it is recommended not to use hormonal therapy (secretin) to improve impairments in adaptive behaviour in children with autism
Speech and language problems	
96	Based on expert consensus speech and language problems in children with autism should be addressed within a personalized project including functional objectives in the field of verbal or non-verbal communication. This program could include augmentative communication, such as PECS and should be initiated early on.
97	There is insufficient evidence to recommend arts-based interventions to address speech and language problems in children with autism.
98	Based on expert consensus the GDG recommended to involve parents when addressing speech and language problems in children with autism.
99	Based on expert consensus speech therapy is recommended in autistic children with identified speech and language problems
100	The indication for speech therapy should be determined independent of the child's IQ and should be integrated in a multidisciplinary approach.
101	The goals of speech therapy should be clearly defined and the effect be evaluated regularly.
102	Pharmacological interventions are not recommended to treat speech and language problems in children with autism.
103	Biomedical interventions, including complementary interventions (acupuncture), hormonal therapies (secretin), medical procedures (chelation or HBOT) and nutritional intervention (including omega-3 fatty acids, multivitamins or L-carnosine) are not recommended to treat speech and language problems in children with autism.
104	Based on expert consensus it is recommended not to use hormonal therapy (secretin) to improve speech and language problems in children with autism.
105	It is recommended not to use the 'hands on' techniques of 'facilitated communication' for speech and language problems in children with autism.
106	It is recommended not to use auditory integration training for speech and language problems in children with autism.
107	It is recommended not to use neurofeedback for speech and language problems in children with autism.
IQ, academic skills and learning	
108	Based on an evidence based approach, there is insufficient scientific evidence to recommend any behavioural intervention to improve IQ, academic skills and learning in children with autism.
109	Based on expert consensus, the implementation of an educational intervention such as LEAP, an alternative program for preschoolers and parents, should be considered and studied to improve IQ, academic skills and learning in children with autism.
110	Based on an evidence based approach, there is insufficient scientific evidence to recommend parent training to improve IQ, academic skills and learning in children with autism. However, expert consensus is to encourage parent involvement.
111	Based on an evidence based approach, there is insufficient scientific evidence to recommend specific social-communication interventions to improve IQ, academic skills and learning in children with autism.
112	Pharmacological interventions are not recommended to improve IQ, academic skills and learning in children with autism.
113	Biomedical interventions, such as acupuncture, hormonal therapy (secretin), multivitamins and auditory integration training are not recommended to improve IQ, academic skills and learning in children with autism.

114	Based on expert consensus it is recommended not to use hormonal therapy (secretin) to improve IQ, academic skills and learning in children with autism.
Sensory sensitivities	
115	There is insufficient evidence to recommend animal-based interventions such as horseback riding to treat sensory sensitivities in children with autism.
116	There is insufficient evidence to recommend educational interventions to treat sensory sensitivities in children with autism.
117	Pharmacological interventions are not recommended to treat sensory sensitivities in children with autism.
118	There is insufficient evidence to recommend biomedical interventions such as massage and auditory integration therapy.
119	Based on expert consensus the use of sensory integration therapy and various massage techniques should be studied to evaluate the effect on sensory sensitivities in children with autism.
120	Based on expert consensus it is recommended not to use hormonal therapy (secretin) to treat sensory sensitivities.
Motor difficulties	
121	There is insufficient evidence to recommend animal-based interventions such as horseback riding to treat motor difficulties in children with autism.
122	There is insufficient evidence to recommend behavioural interventions to treat motor difficulties in children with autism.
123	Based on expert consensus the implementation of an educational intervention such as LEAP, an alternative program for preschoolers and parents, should be considered and studied to improve motor difficulties in children with autism.
124	There is insufficient evidence to recommend parent training to treat motor difficulties in children with autism.
125	There is insufficient evidence to recommend social-communication interventions to treat motor difficulties in children with autism.
126	Based on expert consensus, psychomotor and occupational therapy should be considered in case of comorbid developmental coordination disorder or other well specified motor problems that interfere with daily life, but only after clinical assessment and with regular re-assessments.
127	Pharmacological interventions are not recommended to treat motor difficulties in children with autism.
128	There is insufficient evidence for the use of biomedical interventions, such as hormonal therapy (secretin), nutritional interventions (omega-3 fatty acids, gluten-free or casein-free diet) to treat motor difficulties in children with autism.
129	Based on expert consensus it is recommended not to use hormonal therapy (secretin) to treat motor difficulties in children with autism.
Coexisting mental health problems	
130	It is recommended to consider a cognitive-behavioural intervention to treat anxiety in children with autism who have the required verbal and cognitive ability to engage in CBT.
131	CBT should only be initiated after a thorough assessment of the child and with regular re-assessment performed.
132	It is recommended to adapt CBT to individual needs and the child's environment and to involve the parents in the treatment plan.
133	It is recommended to consult the appropriate NICE recommendations for specific coexisting mental health problems.
134	Complementary interventions, such as omega-3 fatty acids, gluten-free, casein-free diet or chelation are not recommended to treat coexisting mental health problems in children with autism.
Common medical and functional problems	
135	It is recommended to first offer a detailed clinical assessment in children with autism and sleep problems.

136	Based on expert consensus, In the case of persistent sleep problems, it is recommended to consult with a specialist with expertise in the management of autism or paediatric sleep medicine for persistent sleep problems to consider pharmacological treatment (e.g. melatonin).
137	Based on expert consensus feeding problems and eating behaviour deserve special attention in children with autism, and a multidisciplinary assessment should be performed to identify factors that matter.
138	Biomedical interventions, such as multivitamins, omega-3 fatty acids, secretin and immunoglobulins are not recommended to treat common medical and functional problems in children with autism.
Sexuality	
139	Based on expert consensus affective and sexual development deserves special attention in children with autism.
140	Based on expert consensus adapted sexual education should be proposed to adolescents with autism.
Domain 5: improving the impact on the family	
141	Based on an evidence based approach, there is insufficient scientific evidence to recommend any behavioural intervention to improve the impact on the family of children with autism.
142	Based on expert consensus it is recommended to facilitate support for parents and to propose different support modalities.
143	Based on expert consensus it is recommended that special attention be paid to signs of suffering and support seeking expressed by siblings and to propose different modalities to help.
Domain 6: adverse events	
144	It is recommended to balance drugs benefits and risks prior to prescribing psychotropic medication.
145	Parents should receive clear explanations on the expected benefit of the treatment and possible adverse events.
146	It should be verified that the explanation was understood.
147	Parents should be offered the possibility for continuous dialogue with the prescriber.
148	Parents should be warned about the possibility of paradoxical reactions and know an action plan for seeking assistance.

5.1.1 Other considerations

On May 26, 2014 we held a meeting with 31 stakeholders and 4 GDG members to discuss general principles and in particular the (32) recommendations that did not reach 85% consensus amongst the stakeholders. The core of the recommendations elaborated by the GDG could have been altered if missing evidence was presented, however this was not the case. The methods and selection of guidelines were explained since the EBM and consensus process followed by the KCE was neither comprehended nor accepted by a few participants. The discussion led to clarifying and rephrasing 13 recommendations and the GDG members agreed with the process. In addition several definitions of interventions were added to the report.

The discussion furthermore highlighted the following considerations:

- EBM methodology was considered biased, partial and even suspicious by a few participants.
- Psychoanalytical approaches have been used for many years and are deemed unsuitable for EBM evaluation. The users, i.e. representatives of parent organisations, were however uniformely not in favor of these methods.
- Individual positive experiences were reported with a number of non EBM proved methods (danse, horseback riding etc..). These experiences should be considered for future evaluations. However, parents should be protected from unreasonable expectations and costs.
- Intervision was accepted as an opportunity for networking, exchanging information and updating knowledge by some and was rejected as useless and controlling by others.
- Regarding the administration of medications it was pointed out that family physicians have to intervene in case of adverse events or crisis situations. On the other hand home administration of medication can be problematic.
- Individual prescription practices for psychopharmaca vary. There are only a few studies and no clear recommendation for actual prescription of a particular drug.
- A few participants voiced their suspicion towards the pharmaceutical industry in influencing prescriptions and even these KCE recommendations. They therefore stressed their disagreement for pharmacological treatment.
- The reimbursement for speech and language therapy is currently limited to children with normal IQ but it is often not possible to measure the IQ of a child with autism. The INAMI is currently reviewing the reimbursement criteria.
- It was controversial whether IQ could be included as a valid outcome parameter as it should be considered an intrinsic characteristic.
- All agreed that parents should be closely involved in the care of their child, there was a discussion as to whether training or education would be the more appropriate terminology.
- Physical therapy should be considered as a wider range of interventions including psychomotor and occupational therapy.

5.2 Global summary of recommendations

Given the large number of recommendations we summarized the positive and negative recommendations for all interventions and across all domains. These ten positive and five negative global recommendations provide clear guidance based on the reviewed literature and GDG consensus Table 19.

Please note that the organisation and delivery of care is not summarized as it consists of a body of positive recommendations that should be applied in a specific context. A number of these recommendations address the need for a personalized programme and a coordinator who accompanies the child or adolescent and the family.

Table 19 – Summary of recommendations.

Global summary of positive recommendations regarding interventions		
	ref n° (see table 18)	
Psychosocial interventions		
A	37	In children and young people with autism, consider a specific social-communication intervention for the core feature of impaired reciprocal social communication and interaction. This intervention should include play-based strategies with parents, carers and teachers to increase joint attention, engagement and reciprocal communication in the child or young person. Strategies should: • be adjusted to the child or young person's developmental level • aim to increase the parents', carers', teachers' or peers' understanding of, and sensitivity and responsiveness to, the child or young person's patterns of communication and interaction • include techniques to expand the child or young person's communication, interactive play and social routines. The intervention should be delivered by a trained professional. For preschool children consider parent, carer or teacher mediation. For school-aged children consider peer mediation.
B	60	In the absence of coexisting mental health or behavioural problems (e.g. anxiety or ADHD) and if no physical disorder or environmental problem has been identified as triggering or maintaining the behaviour that challenges, offer the child or young person a psychosocial intervention as a first-line treatment.
C	92	Based on expert consensus the GDG provided a recommendation to use augmentative communication techniques such as PECS for children with autism and impairment in adaptive behaviour.
D	96,98,99,100,101	Based on expert consensus speech and language problems in children with autism should be addressed within a personalized project including functional objectives in the field of verbal or non-verbal communication. This program could include PECS, should be initiated early on, include speech and language therapy and involve the parents. The indication for speech therapy should be determined independent of the child's IQ and should be integrated in a multidisciplinary approach.
E	109,123	Based on expert consensus, the implementation of an educational intervention such as LEAP, an alternative program for preschoolers and parents, should be considered and studied to improve academic skills, learning and motor difficulties in children with autism.
F	126	Based on expert consensus, psychomotor and occupational therapy should be considered in case of co morbid developmental coordination disorder, or other well specified motor problems that interfere with daily life, but only after clinical assessment and with regular re-assessments.
G	130	It is recommended to consider a cognitive-behavioural treatment intervention (CBT) to treat anxiety in children with autism who have the required verbal and cognitive ability to engage in CBT.

Pharmacological interventions		
H	75	It is recommended to consider antipsychotic medication 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.
I	88	Based on the available literature, the pharmacological agents that have shown comparable efficacy as treatment for challenging behaviour in children and young persons with autism are haloperidol, risperidone and aripiprazole.
J	136	Based on expert consensus, In the case of persistent sleep problems, it is recommended to consult with a specialist with expertise in the management of autism or paediatric sleep medicine for persistent sleep problems to consider pharmacological treatment (e.g. melatonin).
Global summary of negative recommendations regarding interventions		
K	44,47,49, 89, 94, 95,103, 104, 114,120, 128,129,134,138	Biomedical interventions involving hormone therapy (secretin), immunoglobulins, chelation, HBOT and gluten- or casein-free diets are not recommended to target *overall autistic behaviour.*
L	45	Biomedical interventions involving drugs such as antibiotics, antifungals, dextrometorphan, famotidine, amantadine, benzodiazepines and antihistamines are not recommended to treat ASD.
M	46,48,50,89, 94,103,113,105	There is insufficient evidence on the effect of complementary interventions (such as acupressure, acupuncture, electro-acupuncture, and hands on facilitated communication and Qigong massage), nutritional interventions (with multivitamins and minerals, L- carnosine or L-carnitine, omega-3 fatty acids) and sensory interventions (neurofeedback and auditory integration training) or motor intervention (Kata exercise training). Therefore no recommendation can be provided for these interventions.
N	71,73	The use of isolation chambers and physical restraints should be restricted to exceptional cases where all other approaches have failed and the person and the environment need protection.
O	74	It is recommended not to use packing (wrapping in cold, wet towels).

5.3 Recommendations for further research

The thorough literature review undertaken by NICE and HAS demonstrates that evidence is mostly lacking for the many treatments offered to address various outcomes in children and adolescents with autism and their families. The great majority of recommendations are based on the experience of experts, caregivers and anyone involved with the challenges posed by autism. More randomised controlled trials are needed for all intervention models to improve evidence for identifying a valid intervention for each individual and family. Key environmental factors that interact with the complex genetic architecture of autism also need to be identified.

Based on the currently available but limited evidence the GDG recommends that clinical research involving children and adolescents with autisme focusses on some specific therapies that offer hope for the future. The focus on these interventions is proposed as a series of specific recommendations in Table 20.

Table 20 – Research recommendations made by GDG

GDG: Research recommendations	
149	The GDG recommends to promote community based research and to explore which research designs are best applicable to the population.
150	Given a limited but encouraging amount of evidence, the GDG recommends to focus research interventions on the following domains:
	1. Augmentative communication such as Picture Exchange Communication System (PECS)
	2. Learning Experience and Alternative Program for Preschools and their Parents (LEAP)
	3. Early Start Denver model (ESDM)
	4. TEACCH model
	5. Speech and language therapy
	6. Psychopharmacological therapies for core features, challenging behaviour, associated features and coexisting conditions.

5.3.1 Other considerations

The discussion with the stakeholders led to the following considerations:

- All domains for which no evidence exists should be consideredd for research.

The discussion with the external assessors led to the following considerations:

- Clear definitions are crucial as outcomes for international studies. Currently differences exist between different languages and cultures as to what is understood by similar terminology. Obtaining a broad consensus on internationally standardised definitions for terminology will be the task of scientific organisations.
- Early and very early diagnosis are required to start with early treatment. Diagnostic issues are out of scope for the present report. However, it remains difficult to judge what is best: waiting older age to do a diagnosis and doing a diagnosis that has to be confirmed later. Further, there is a large part of children for whom (very) early diagnosis is impossible. Moreover, the evidence is unclear about the stability of diagnosis in children in preschool years.
- Diagnostic issues are out of scope for the present report. However, research is also required to determine the appropriate diagnostic medical examinations (EEG, MRI, DNA testing, other laboratory tests..) to be used for children and adolescents with autism.
- Some drugs seem to be promising for the treatment of autism in children and adolescents: e.g. dextrometorphan and bumetanide. These drugs should be studied further. However, awaiting further evidence, their prescription should be limited to scientific studies:

5.3.2 Perspectives

The analysis and appraisal of the evidence published up to January 2013 performed by NICE is based on strict EBM criteria. Currently the evidence is insufficient to apply GRADE and to conclude with classical EBM based recommendations.

Autism is a broad spectrum and so is the range of proposed interventions. A frequently heard criticism is that this condition cannot be studied according to EBM criteria. RCT designs are appropriate for the study of pharmacological agents but are more difficult to apply to psychosocial interventions. However, randomized controlled trials have been performed, for example on social communication interventions[30] or and caregiver-mediated intervention.[45] Note that we did not perform a systematic search for publications after the search date of the NICE guideline (January 2013). However, the GDG members provided recent publications supporting amongst others, parent-mediated early intervention[46] or joint attention and

imitation.[47] It is clear that in a few years a larger body of recent evidence should be critically evaluated.

Alternative study models are proposed by several authors who have succeeded in carefully defining and standardizing conditions in order to enforce scientific observation.[48] Any type of intervention can be studied when the appropriate standardization and outcomes are defined. Observational studies in the community are quite feasible. Single case design and case reports enable researchers to also report on psychotherapeutic approaches.[49] However these approaches have important limitations since they are descriptive and should be compared to control cases. In addition the quality and methodology of these designs should be appraised before any conclusions should be drawn. The National Standards Project[19] proposes a Scientific Merit Rating Scale and reports on various psychosocial treatment strategies. Note however, that this document was excluded from our report following appraisal with the AGREE II tool (see 2.5).

The problem of small inclusion numbers can potentially be solved by applying statistical methods such as sequential meta-analysis.[50]

We should keep in mind that there are important contextual differences between regions e.g. the United States and our country. Therefore systematic observation and documentation, the implementation of collaborative registries and outcomes based clinical research in Belgium deserves particular attention.

6 CONSENSUS STATEMENT APPLIED TO THE BELGIAN CONTEXT

6.1 Introduction

This KCE report was mainly based on an evidence based guideline, using a method that has the merit to demonstrate unequivocally which interventions are proven effective for a specific outcome. Based on the currently available evidence, the most effective interventions are behavioural and educational. Recent reviews and opinion papers underline the benefit of early comprehensive and targeted behavioural interventions.[51] The many recommendations proposed by the GDG reflect the emphasis on respect for the individual and tailor-made care. Supportive environments for children and youngsters with autism are characterized by structure, predictability and a coherent approach from caregivers, teachers and family. Transitions need to be prepared and implemented in a coherent and well-organized manner. The American Academy of Child & Adolescent Psychiatry (AACAP) recently published a practice parameter recommending a structured educational approach with explicit teaching, planned, intensive, individualized intervention with an experienced, interdisciplinary team of providers and family involvement. In line with our recommendations, the AACAP recommends careful assessment, personalised care and monitoring of the child progress. Interventions that improve verbal and nonverbal communication, academic skills, social, motor and behavioural capabilities are encouraged. The importance of a parent-education and home component is stressed especially for younger children.[52]

Despite the paucity of RCTs and the need for an, albeit empirical, best practice guideline, the GDG advised to propose the consensus statement applicable to the Belgian context presented below. Whereas all previous recommendations were developed after thorough evaluation of the availability of scientific evidence, the recommendations below were developed based on discussion amongst the GDG. Nevertheless, they went through the same Delphi process (see section Methods) and they were only accepted when more than 85% of GDG members agreed.

6.2 Organization of care and education in Belgium

The organisation of care, support, and education in Belgium provided for children and adolescents with mental health problems has been described previously (KCE report 170 (2011)) and for details on available services and support, the reader is referred to this document.[53]

The responsibilities for mental health care are shared between the federal government and the federated entities. The federal government outsourced all person related issues such as the support of disabled persons and education to the federated entities (communities or regions). The Flemish community established the VAPH (Vlaams Agentschap voor Personen met een Handicap), the Walloon region established the AWIPH (Agence Wallonne pour l'Intégration des Personnes Handicapées) and the German community established the DPB (Dienststelle für Personen mit Behinderung). In Brussels, there are three structures responsible: the COCOF (Commission Communautaire Française) for the French community that established the PHARE (Personne Handicapée Autonomie Recherchée), the VGC (Vlaamse Gemeenschaps Commissie) for the Flemish community that trusted this responsibility to the VAPH and finally the GGC/COCOM (Gemeenschappelijke gemeenschapscommissie/ Commission communautaire commune) that supports the bilingual institutions. The three communities are funded by the federal government and in turn support their three agencies (VAPH, AWIPH, and DPB). Furthermore, the French Community funds the COCOF and their agency (PHARE). The GGC/COCOM receive funds from the Flemish and the French community. The organisations VAPH,AWIPH,DPB,PHARE aim to promote integration, participation and equal opportunities for people with a disability in all areas of social life. Their ultimate goal is to help them to lead a better and more independent life by subsidizing facilities and by offering special services, for example the rehabilitation centres. In the Dutch, French and German-speaking community, the Ministry of education has the overall responsibility for the educational sector, including general administration and funding. In the bilingual Brussels-Capital region, parents have the choice between Dutch-speaking schools (responsibility of Flemish Community) or French-speaking schools (responsibility of French Community).

6.3 Documents and websites related to autism in children and adolescents

In an attempt to capture relevant elements specific to the Belgian context, a search for documents on organisation of care and support for children and adolescents with autism in Belgium, including the regions and communities was conducted. These documents should include evidence-based recommendations and should not yet be included in the literature overview. They could also contain a critical evaluation of the Belgian situation at least partly based on some evidence or scientifically based data. Documents expressing merely an opinion on organisational issues were not included.

Belgian websites were searched on 24 June 2013, the list of these websites can be found in Table 21. The GDG provided additional documentation.

Table 21 – Belgian websites that provide information on autism.

www.autismecentraal.be
www.autismevlaanderen.be
www.bruxelles.irisnet.be/a-propos-de-la-region/ les-institutions-communautaires-a-Bruxelles/cocof
www.kindengezin.be
www.one.be/
www.participate-autism.be
www.susa.be
www.vaph.be/vlafo/view/nl/
www.yapaka.be/

One document corresponding to the criteria was the Advice n°8747 of the Belgian Superior Health Council (2013)[17] and is described in the next paragraph.

6.3.1 Advice of the Belgian National Superior Health Council

This document addresses the question how the quality of life of young children (<6 years) with autism and their family can be improved. It contains a chapter on family issues, screening and diagnosis, intervention and rights of young children with autism and their family. This Advice includes an overview of services available in Belgium for young children (<6 years) with autism and their family. In addition, the report presents the results of two surveys related to the number of organisations that declared to provide care for the target group, and the type of interventions they use. The interested reader is referred to the Advice for further information.[17]

Only the chapter on interventions will be discussed here. The chapter is based on guidelines published in France (HAS 2012) and the Netherlands (Gezondheidsraad 2009), the literature review on the treatment of autism published by KCE in 2008[54] and expert consensus obtained from stakeholders.

The recommendations of the Advice can briefly be summarized as follows:

- Parents should be better informed so that they can improve their involvement in the care of their child. Organisations should mention the scientific framework on which their practices are based, the methods used to individualize the program and how they collaborate with the family. Parents should receive information on available scientific evidence and on their rights.
- Professionals in charge of young children should be trained to recognize early signs and symptoms of autism. A multidisciplinary diagnostic evaluation following specific quality criteria should be performed within three months and parents should be informed promptly regarding necessary adaptations in their attitude towards their child and on available options for care and support.
- Access to home services and services for individual or multidisciplinary rehabilitation should be improved.
- The educational need of each child with autism should be determined and described and access to education in line with these needs should be guaranteed. A formal collaboration between the mainstream and specialized educational system should be established. If possible, children should receive education in the mainstream system, on condition that specific means are provided.
- Children should have access to leisure activities, to give parents some respite. Child care professionals should be trained in order to facilitate integration of children with autism in day care.
- Coordination of care should be improved. Services should develop an action plan to diminish waiting lists and a care coordinator should be assigned to individual cases.
- Evaluation and quality of services should be guaranteed. Professionals should be trained in EBM and GCP. The government should be informed on the current standard of care. Health authorities should criticially evaluate current practices. An expertise centre should be established to integrate national and international research and improve existing practices in collaboration with parent associations.
- Further scientific evaluation of early intervention programs is advised.

6.4 Opinion on priorities to improve the care for children and adolescents with autism in Belgium

The GDG felt that there are many unmet needs in the current care for children and adolescents in Belgium. Recurrent themes were early intervention, the availability for home based support and specialised schools, the sensitive transition to adult care settings. It was stressed that family physician should have the necessary background to address the medical issues adequately and that support necessary for challenging crisis situations should be anticipated. The GDG elaborated recommendations specific for the Belgian context. The recommendations presented in Table 22 do not deter from the complete list of final recommendations but appeared to be the most urgent issues to be addressed in our current Belgian context.

Table 22 – Recommendations specific to Belgium

GDG Recommendations specific to the Belgian context	
151	The GDG recommends to support home based care within a network for all age groups. Home based care also addresses concerns of parents, siblings and their environment.
152	An individual plan should be elaborated for each child or adolescent with autism. This plan or road map should be discussed amongst the care providers, the child's legal representatives and the recipient. Regular assessments should redefine the recipient's participation. Therapies should be updated based on the state of the art in clinical experience and research.
153	Care networks for children and young people with autism should be equally accessible to all.
154	Care networks should integrate adapted residential care as one of the possible treatment options for children and adolescents with autism who present challenging behaviour or are in a crisis situation.
155	Education should be tailored to the needs of the children and young people with autism whether they are included in the mainstream or in the special educational system. It should be accessible to all, independent of their intellectual capacities. This includes also children with higher intellectual capacities than average.
156	Professionals should be provided with adequate training and support.

6.4.1 Other considerations

The discussion with the stakeholders did not lead to any specific considerations regarding these recommendations. All considerations were discussed in Chapter 5.

6.5 Conclusions

The GDG worked diligently in order to demonstrate which interventions are meaningful to improve the lives of children and young people with autism and their families. The problems faced by children and adolescents with autism, caretakers and families are complex. The organizations in six domains as proposed by NICE is helpful in order to evaluate the effect of a particular intervention in a particular domain. We adhered to the strict rules of EBM and found that there is very little evidence, based on RCTs, for any type of intervention. However based on the available evidence it was possible to identity methods that are more promising than others and to make research recommendations. The GDG has discussed extensively to formulate recommendations based on published evidence, on expert consensus provided by NICE and HAS and on their own experiences in the Belgian context.

The research questions addressed whether care should be different for immigrant children. This question could not be answered as there was no information in the guidelines we adapted. The questions was addressed indirectly in the recommendations that state that care should be equally accessible to everyone.

GDG members strongly felt that practical and pragmatic solutions tailored to the individual situation should be offered to children and adolescents with autism and their families. It was stressed that in everyday life the biggest challenges are aggressive behaviour, associated medical conditions and sexuality. The recommendations made by the GDG are comprehensive and address these particular areas. We believe that the GDG recommendations offer a solid base for orienting care, improving existing structures or creating new ones within the available logistic context. In order to ensure a proper implementation of the recommendations a strong educational foundation of professionals is needed. Consequently, this should be a continuous priority for investment.

7 IMPLEMENTATION AND UPDATING OF THE GUIDELINE

7.1 Implementation

7.1.1 Barriers and facilitators for implementation of this guideline

The stakeholders meeting were asked, in preparation of the meeting, to identify potential barriers and facilitators related to the use of this guideline. They are summarized and presented in Table 23.

Table 23 – Facilitators and barriers for implementation of the guideline

Related to	Facilitators	Barriers
The guideline	• Clarity and coherence • Publish on websites • Expert centres should disseminate the guideline • Edit a good practice guide booklet	• Too simplistic • Language • Evidence based approach is seen as too restrictive by some
Caregivers	• Open mind for self-evaluation and growth • Offer training sessions, education • Increase staff	• Lack of introspection • Resistance to change • Convictions related to psycho-analytical approach • Lack of training and education
Organisation of care	• Provide a road map with a list of all available resources • Create a unique website • Implement a unique and uniform electronic medical record that can be accessed by all caregivers • Increase availability for residential care • Fund and structure communication between teams • Implement external consultation teams for networking, consulting, education	• Lack of trained staff • Lack of knowledge and information • Lack of time and money • Lack of availabilities • Waiting lists
Policy	• Funding • Support for evidence based practices	• Lack of funding

7.2 Guideline update

In view of the expected scientific interest in children and adolescents with autism an update of the guideline should be foreseen in 3 years.

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