Gastrointestinal disorders

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Geraldine Leader

Arlene Mannion

National University of Ireland, Galway.

Corresponding author: Geraldine Leader, Ph.D., Irish Centre for Autism and Neurodevelopmental Research, School of Psychology, National University of Ireland, Galway, Ireland. Tel: 00353 91 49 3434, Fax: 00353 91 521355

Gastrointestinal Disorders.

Research into gastrointestinal (GI) symptoms and disorders in autism spectrum disorder (ASD) is a relatively new area of study. This may be because gastrointestinal symptoms can be very difficult to diagnose in individuals with ASD. Diagnosis can be especially difficult for individuals who are non-verbal or who have severe deficits in communicating their needs and wants. If an individual is in pain and cannot communicate this to caregivers, it makes it very difficult to recognize potential gastrointestinal symptoms. Gastrointestinal symptoms in individuals with ASD may present themselves differently than in typically developing individuals. A person with ASD may not reach for their abdomen if in pain. Instead, they may display this pain through challenging behavior.

All too often, comorbid conditions such as gastrointestinal symptoms are seen as being part of ASD, instead of being recognised as a separate comorbid condition. It is very important that we study and understand gastrointestinal symptoms in ASD, as they may be potentially exacerbating symptoms of ASD such as repetitive behavior. Gastrointestinal symptoms have the potential to jeopardize interventions designed to reduce challenging behavior in children and adults with ASD, and interventions designed to teach new skills such as communication skills, academic skills and self-help skills. An individual with ASD who has what appears to be difficulties with toileting or feeding may also have comorbid gastrointestinal symptoms. If intervention just focuses on the presenting issue such as challenging behavior or toilet training, practitioners may find that there are difficulties with teaching certain skills. These difficulties may be due to an individual with ASD experiencing pain and discomfort. It is imperative that we look at the environment for the individual with ASD, but that we also examine the whole body, including gastrointestinal symptoms and disorders.

1.1. Definition

The most common gastrointestinal symptoms reported in individuals with autism spectrum disorder (ASD) are chronic constipation, abdominal pain with or without diarrhea and encopresis as a consequence of constipation (Buie et al. 2010a). Buie et al. (2010a) also commented that other gastrointestinal abnormalities include gastroesophageal reflux disease (GERD), abdominal bloating, disaccharidase deficiencies, inflammation of the gastrointestinal tract and abnormalities of the enteric nervous system. Wang, Tancredi, and Thomas (2011) noted that GI symptoms can include "constipation, diarrhea, abdominal pain, frequent vomiting, gaseousness, abnormal stool pattern, bloody stools, foul-smelling stools, abdominal bloating, feeding issues, food regurgitation, food selectivity, food intolerance, gastroesophageal reflux, encopresis and so on" (p.351).

2. Gastrointestinal Symptoms and ASD Comorbidity

2.1. Prevalence

The reported prevalence of gastrointestinal problems in children with ASD has ranged from 9% to 91% (Coury et al., 2012; Ming, Brimacombe, Chaaban, Ximmerman-Bier, & Wagner, 2008; Black, Kaye, & Jick, 2002; Fombonne & Chakrabarti, 2001; Ibrahim, Voigt, Katusic, Weaver, & Barbaresi, 2009; Mannion & Leader, 2014c; Molloy & Manning-Courtney, 2003; Mouridsen, Rich, & Isager, 2010; Nikolov et al., 2009; Taylor et al., 2002; Valicenti-McDermott, McVicar, Cohen, Wershil, & Shinnar, 2008; Horvath & Perman, 2002; Wang et al., 2011; Parracho, Bingham, Gibson, & McCartney, 2005; Smith, Farnworth, Wright, & Allgar, 2009). Wang et al. (2011) commented on the factors that lead to differing rates of GI symptoms across studies. First, there are differences in the target population being studied. Some participants may have different diagnoses on the autism spectrum. Some studies use control groups, while others do not. Second, there are differences in how

data is gathered, whether it is by medical records, physicians or questionnaire-based research. Finally, there are different definitions used for what are considered gastrointestinal symptoms (Wang et al., 2011). Wang et al. (2011) commented that these definitions can vary on frequency, duration, severity and type of GI symptoms.

2.2. Importance of studying gastrointestinal symptoms

There are many reasons gastrointestinal symptoms in ASD need to be researched. First, given that a high prevalence of GI symptoms have been found in the literature, it is possible that GI symptoms affect a large proportion of those with ASD. Often these symptoms are just seen as part of ASD, rather than being a comorbid condition. Yet GI symptoms are not core symptoms of ASD and should not been dismissed as such. Second, these symptoms may cause pain and discomfort. Individuals that are non-verbal or have little communication skills may not be able to tell parents or caregivers that they are in pain. The communication deficits of ASD can make GI symptoms very difficult for the individual who is in pain and unable to communicate this, as well as to the caregivers who are unsure of what the person is trying to communicate and how best to help this person. Third, it is important to recognise that abdominal pain or discomfort may act as a setting event for challenging behavior (Buie et al., 2010a). This discomfort and in turn, challenging behavior can get in the way of the individual acquiring new academic or self-help skills. Mulloy et al. (2010) commented on these biological motivating operations, whereby an upset stomach may act as a motivating operation affecting social consequences. Mulloy et al. (2010) gave the example that a child with an upset stomach may find academic work more demanding than if they did not have an illness. Therefore they may engage in increasing levels of challenging behavior to escape the demand. It is essential that practitioners are aware of the co-occurrence of GI symptom in some individuals with ASD. By determining that a cause of challenging behavior may be biological rather than environmental, this may mean that appropriate

treatment options can be considered. A practitioner could also then change the learning environment to best support the individual. This may include teaching an individual to identify and communicate the instance of pain. Furthermore, additional environmental supports could be put in place such as having a toilet nearby, decreasing demands or allowing frequent breaks to an individual who may be in pain. Finally, an individual's quality of life can be affected in they present with GI symptoms. Williams, Fuchs, Furuta, Marcon, and Coury (2010) found that children with ASD with GI symptoms had lower quality of life compared to children without GI symptoms. GI complaints are therefore associated with overall decreased health-related quality of life. If interventions seek to improve quality of life in individuals with ASD, it is important that GI symptoms are considered. The effect of treatment of GI symptoms needs to be considered. By treating GI symptoms, an individual's quality of life may be improved.

2.3. Difficulty of diagnosis

GI symptoms are difficult to diagnose in individuals with ASD for several reasons. First, clinical practice guidelines in place for the diagnosis of ASD do not include routine consideration of potential gastrointestinal or other medical conditions (Buie et al., 2010a). GI symptoms need to be routinely screened for. They need to not just be seen as part of ASD or affecting only a limited number of individuals as we know that this is not true. Second, many individuals with ASD are non-verbal or have communication difficulties. Because of this, they may not be able to express pain or discomfort in a typical manner. They may not be able to communicate their symptoms as clearly as those who are typically developing. Those who can verbally communicate may have difficulty describing subjective experiences or symptoms (Buie et al., 2010a). Third, those with ASD may present with GI symptoms in atypical ways. One may assume that if an individual has abdominal or other discomfort that they would touch their abdomen. However, this is not necessarily the case for those with

ASD. Gastrointestinal disorders can present as non-gastrointestinal problems (Buie et al., 2010a). For example, individuals may present with sleep problems or challenging behavior. Where they present with vocal stereotypy or repetitive behavior, it could be incorrectly attributed to being symptoms of ASD. It is important to be aware of atypical presentations of GI symptoms. Fourth, diet may play a role in GI symptoms. Kuddo and Nelson (2003) commented that the insistence on sameness in ASD may lead children to demand stereotyped diets which are lacking in fibres, fluids or other constitutes. Many children with ASD have difficulties with food selectivity and may be rigid in their routines of eating particular types of food. These feeding problems may lead to children exhibiting gastrointestinal symptoms. Finally, if children are on medication, this can have side-effects. Kuddo and Nelson (2003) comment that most medication administered to children with ASD can influence gut function. Children with ASD may be on medication for comorbid conditions such as Attention-deficit/hyperactivity disorder (AD/HD), epilepsy or challenging behavior. Comorbid conditions do not just occur as one additional disorder with ASD. Some individuals may present with a multitude of comorbid symptoms and disorders.

2.4. Measures used to assess gastrointestinal symptoms

While some studies used medical history to assess gastrointestinal symptoms (Molloy & Manning-Courtney, 2003; Nikolov et al., 2009; Maenner et al., 2012), a variety of questionnaires have also been used. As well as past medical history, Nikolov et al. (2009) used the Side Effects Review Form (Research Units on Pediatric Psychopharmacology). The form was designed to establish whether certain problems are present prior to drug exposure and to track changes. Side effects were rated as mild, moderate or severe. A rating of mild was given when the problem was present, but not a source of impairment and there was no need for intervention; a rating of moderate was used if the problem caused some impairment or required intervention to prevent impairment, and a rating of severe was used when the

problem caused impairment and required intervention (Nikolov et al., 2009). In the study by Nikolov et al. (2009), a pre-treatment rating of moderate or severe on the Side Effects Review Form in response to one or more GI questions was classified as the presence of a GI symptom. Hansen et al. (2008) used the CHARGE (Childhood Autism Risks from Genetics and the Environment) gastrointestinal history form, which includes 10 items describing current gastrointestinal symptoms as well as questions relating to food allergies and diet restrictions.

Valicenti-McDermott et al. (2008) developed The Gastrointestinal Questionnaire, derived from the Clinical Diagnostic Questionnaire for Pediatric Functional Gastrointestinal Disorders, as developed by the Committee on Childhood Functional Gastrointestinal Disorders Multinational Working Teams to Develop Criteria for Functional Disorders (Rome II). The Gastrointestinal Questionnaire includes questions on current GI symptoms, as well as lifetime gastrointestinal or feeding problems. Gorrindo et al. (2012) used the Questionnaire on Pediatric Gastrointestinal Symptoms-Rome III Version (QPGS) which is a 71 item parent report instrument that assesses GI symptoms and classifies functional GI disorders (FGID) according to Rome III criteria. It is available online at http://romecriteria.org/. Gorrindo et al. (2012) also included clinical evaluation in their study. The authors found that parent report of any gastrointestinal dysfunction in those with ASD was highly concurrent (92.1%) with a clinical diagnosis of any gastrointestinal dysfunction.

Chandler et al. (2013) constructed a 20 item GI symptom questionnaire. Questions were asked by current (last 3 months) and past (prior to the last 3 months symptoms). The GI symptoms included persistent vomiting; stool consistency; abdominal pain; abdominal pain associated with food, bowel movement or sleep; constipation; subjective difficulties with bowl movements, stool withholding and soiling; diarrhea, weight loss, mouth ulcers and presence of mucus or blood in the stools.

The Gastrointestinal Symptom Inventory (Autism Treatment Network, 2005) is a 35-item questionnaire that was developed by the Autism Treatment Network (ATN). The ATN is the first network of hospitals and physicians dedicated to developing a model of comprehensive medical care for children and adolescents with autism through seventeen participating institutions in the U.S. and Canada. In the inventory, there are additional items should a participant exhibit certain symptomatology, and therefore includes 77 items in total. This tool has not been validated. It was based on previous questionnaires and on clinical symptom assessment for children with autism and identified gastrointestinal disorders. It measures questions about the presence and duration of GI symptoms. The inventory is scored initially dichotomously i.e. whether or not the child has any of the gastrointestinal symptoms. The GI symptoms it measures are abdominal pain, nausea, bloating, diarrhea or other GI symptom. The inventory also allows branching into specific areas of symptomatology: abdominal pain, abnormal bowel movements, reflux, and food insensitivity. These branches will allow determination of rates of these categories as well.

Mazurek et al. (2013b) used the GI Symptom Inventory in their research. It was also used in Williams et al. (2010); Williams, Christofi, Clemmons, Rosenberg, and Fuchs (2012a); Williams, Christofi, Clemmons, Rosenberg and Fuchs (2012b), Mannion, Leader, and Healy (2013), and Mazefsky, Schreiber, Olino, and Minshew (2014). The GI Symptom Inventory is no longer used by the ATN as part of its registry battery. Instead, questions are included about gastrointestinal symptoms in the ATN Parent Baseline Assessment. The following symptoms are assessed: nausea/vomiting, reflux, diarrhea, constipation, stomach/abdominal pain. Mazurek, Kanne, and Wodka (2013a) used the Parent Baseline Assessment in their research.

3. Relationships between Gastrointestinal Symptoms in ASD and other variables

3.1. Regression

Valicenti-McDermott et al. (2008) investigated the relationship between gastrointestinal symptoms and regression. Valicenti-McDermott et al. (2008) found that children with ASD who presented with language regression had more gastrointestinal problems (84%) than those without language regression (61%). The authors also found that abnormal stool patterns were reported more frequently in the group with language regression (42% vs. 12%). Niehus and Lord (2006) found that the medical records of children with ASD and regression indicated significantly more parental reports of bloody stools than those with ASD and no regression. Though non-significant, those with ASD and regression had more chronic diarrhea and stool complaints than those with ASD and no regression or those that were typically developing.

Baird et al. (2008) investigated factors associated with regression in children with ASD. Current gastrointestinal symptoms varied across the three groups in the study; those with no regression, lower level regression and definite language regression. Current gastrointestinal symptoms varied across regression groups, but the rate was higher in the no regression group than the lower or definite regression groups. In terms of past gastrointestinal symptoms, there was no group difference found between those with no regression, lower or definite regression. This is supported by Chandler et al. (2013) who found that there were no differences between ASD children with and without a history of regression for current and past GI symptoms. Molloy and Manning-Courtney (2003) found that 24% of children with ASD had a history of at least one chronic gastrointestinal symptom. It was found that 23.4% of the entire sample had a history of regression. However, in support of previous research, Molloy and Manning-Courtney (2003) found that developmental regression was not significantly associated with gastrointestinal symptoms. Hansen et al. (2008) found no significant differences between the children with ASD with or without

regression in terms of gastrointestinal symptoms. More research is needed on regression, in general, and on the relationship, if any, between GI symptoms and regression. Previous research has indicated that up to one third of children with ASD regress yet little is known about why some children regress and why some do not. More research is needed to better understand regression and the long-term effect of regression on those with ASD.

3.2. Language and Communication

Gorrindo et al. (2012) examined expressive language and social responsiveness as communication variables in their study. They found that children with ASD and GI symptoms showed higher levels of social impairment than those with ASD only. However, social impairment was not associated with impaired language. In the ASD and GI symptoms group, there was no difference in social impairment in those that were verbal and non-verbal. Gorrindo et al. (2012) also investigated the risk factors for constipation as constipation was found to be the most common GI symptom in their study. The authors found that younger, more socially impaired and non-verbal children had increased odds for constipation. Chandler et al. (2013) investigated parental reported GI symptoms in children with ASD, children with special educational needs but no ASD, and typically developing controls. It was found that 46.5% of the ASD group had at least one lifetime GI symptom compared to 29.2% of those with special educational needs, and 21.8% of the typically developing group. The ASD group had significantly increased past vomiting and diarrhea compared to those who were typically developing. They also had more abdominal pain that those with special educational needs. The ASD group had more current constipation and soiling than either the special educational needs group or the typically developing group. In contrast to Gorrindo et al. (2012), Chandler et al. (2013) did not find a difference between verbal ability in children with and without reported pain abdominal pain or constipation. This is supported by

Williams et al. (2012b) who found that rates of GI complaints did not differ between four verbal ability groups; Non-verbal, some words, phrase speech and verbal.

3.3. Autism Severity

Wang et al. (2011) explored the relationship between GI symptoms and autism severity in children with ASD. They also compared children with ASD to their unaffected siblings. Wang et al. (2011) classified autism severity into three groups; full autism, almost autism and not quite autism. Increased autism symptom severity was associated with increased odds of having significantly more GI problems being reported. Specifically, having full autism or almost autism was most highly associated with experiencing GI problems (Wang et al., 2011). However, Molloy and Manning-Courtney (2003) found that frequency of gastrointestinal symptoms did not vary by age, gender, race or severity of autism. In support of this finding, Nikolov et al. (2009) also found that those with gastrointestinal problems were no different from those without gastrointestinal problems in autism symptom severity, demographic characteristics or measures of adaptive functioning. Mazefsky, Schreiber, Olino, and Minshew (2014) found that children with high-functioning ASD who presented with and without gastrointestinal problems did not differ in autism symptom severity. Chandler et al. (2013) found that there was no significant association between autism severity and current and past GI symptoms in the ASD group. Williams et al. (2010) found that presence of GI problems did not differ by gender, ASD subtype, race or IQ. However, Williams et al. (2012b) found that chronic GI symptoms were more likely in children with Asperger's than Autism. Future research needs to be conducted to understand if there is a relationship between autism severity and GI symptoms.

3.4. Challenging behavior

Horvath, Papadimitriou, Rabsztyn, Drachenberg, and Tyson Tildon (1999) commented that unrecognised gastrointestinal symptoms and disorders may contribute to the behavioral problems of non-verbal children with ASD, such as sudden irritability and aggressive behavior. Mazurek et al. (2013a) investigated the relationship between aggression and other variables, including gastrointestinal symptoms in children with ASD. Children with aggression had significantly greater difficulties with GI problems than those without aggression. However, GI problems did not emerge as significant predictors of aggression. Mazefsky et al. (2014) found that children with high-functioning ASD, with and without GI symptoms did not differ in internalizing or externalizing problem behaviors.

Children with GI problems were more likely to present with argumentative, oppositional or destructive behaviors than those without GI problems (Maenner, et al., 2012). Tantrum behaviors were more common in those with GI problems than those without, but the association did not reach statistical significance. No association was found between presence of GI problems and stereotypic/repetitive behaviors or self-injurious behaviors (Maenner et al., 2012).

In contrast, Peters et al. (2014) found a relationship between GI symptoms and rigid-compulsive behavior. The authors found that rigid-compulsive behavior was significantly associated with constipation and diarrhea or soiling. Children with constipation and diarrhea or soiling were more likely to have a parental report of repetitive behavior and compulsive behavior and a parental report of an Obsessive Compulsive Disorder (OCD) diagnosis. Children with constipation and diarrhea or soiling were also more likely to have a clinician report of rituals based on direct observation during the Autism Diagnostic and Observational Schedule (ADOS). Children with constipation only, who did not have diarrhea or soiling were more likely to have a parental report of an OCD diagnosis. Family history of OCD or

anxiety or treatment with atypical antipsychotic medication were associated with constipation and diarrhea or underwear staining.

Chaidez, Hansen, and Hertz-Picciotto (2014) compared GI Symptoms in children with ASD, children with developmental delay and typically developing children. Children with ASD were more likely to have at least one frequent GI symptom compared to children who are typically developing. The authors also investigated the relationship between GI symptoms and behavior problems. Children with ASD and frequent occurrences of constipation, diarrhea, abdominal pain, and gaseousness scored significantly higher on levels of irritability, social withdrawal, stereotypy, and hyperactivity than children with ASD and no frequent GI symptoms. Children with pain on stooling, sensitivity to food, and difficulty swallowing scored higher on irritability, social withdrawal and stereotypy.

3.5. Comorbid Psychopathology

In their review of comorbid psychopathology in ASD, Mannion, Brahm, and Leader (2014) discussed the relationship between comorbid psychopathology and gastrointestinal symptoms. Williams et al. (2010) found that children aged 1 to 5 years with GI symptoms had higher total scores on the Child Behavior Checklist (CBCL) (Achenbach & Roscorla, 2000) and for the emotionally reactive, anxious/depressed, somatic complaints, internalising problems, affective problems, anxiety problems subscales. The authors also found that children aged 6 to 18 years had higher total scores on the Child Behavior Checklist (CBCL) (Achenbach & Roscorla, 2001) and on all subscales. Maenner et al. (2012) found that mood disturbances were more common in children with GI problems than those without but this association did not reach statistical significance. In terms of other comorbid disorders, children with ASD and GI problems were significantly more likely than those without GI problems to have co-occurring cerebral palsy and seizure-like activity (Maenner et al., 2012).

Mazefsky et al. (2014) found that children with high-functioning ASD with gastrointestinal problems had significantly higher levels of affective problems than those without gastrointestinal problems. Future research needs to be conducted on the relationship between GI symptoms and depression in individuals with ASD.

Mannion and Leader (2013a) investigated predictors of GI symptoms in children with ASD. In the study, total number of GI symptoms predicted total scores on the Autism Spectrum Disorder-Comorbid for Children (ASD-CC) (Matson & González, 2007). The ASD-CC is a questionnaire used to assess comorbid psychopathology in those with ASD. Specifically, abdominal pain and constipation also predicted conduct behavior. Diarrhea predicted tantrum behavior. Nausea predicted worry/depressed behavior, avoidant behavior and conduct behavior. The worry/depressed subscale and the avoidant behavior subscale of the ASD-CC form a measure of anxiety (Davis et al. 2011).

Other authors have also investigated the relationship between GI problems and anxiety. Nikolov et al. (2009) found that when compared to children without gastrointestinal problems, those with gastrointestinal problems showed greater symptom severity on measures of irritability, anxiety and social withdrawal. Williams et al. (2012b) found that clinical anxiety is associated with chronic GI symptoms in children with ASD. Chronic GI complaints were greater in children with clinical anxiety compared to those with no anxiety.

Mazurek et al. (2013b) found that children with ASD who presented with each type of gastrointestinal symptom had significantly higher rates of anxiety. The following gastrointestinal symptoms were included: chronic constipation, chronic diarrhea, chronic abdominal pain, chronic bloating and chronic nausea. A relationship was found between the number of gastrointestinal symptoms and anxiety also. Those with more chronic GI problems had higher anxiety scores than those with no chronic GI problems. Those with no chronic

gastrointestinal problems had significantly lower anxiety scores than those with only one gastrointestinal problem, those with 2 problems or those with three or more problems. Anxiety contributed to the prediction of chronic constipation, chronic bloating, chronic nausea and chronic abdominal pain, but not to the prediction of chronic diarrhea.

In typically developing children, Shelby et al. (2013) found that Functional Abdominal Pain (FAP) in childhood was associated with high risk of anxiety disorders in adolescence and young adulthood. During follow-up in adolescence and young adulthood, 51% of those with a childhood history of FAP met criteria for an anxiety disorder during their lifetime and 30% currently met criteria for an anxiety disorder. Lifetime risk of depressive disorder was significantly higher in those with FAP than control participants.

3.6. Sleep Problems

Mannion and Leader (2014d) discussed the relationship between gastrointestinal symptoms and sleep problems in their literature review on sleep problems in ASD. Horvath et al. (1999) commented that unrecognised gastrointestinal symptoms may lead to night time awakenings in non-verbal children with ASD. Maenner et al. (2012) found that children with sleep abnormalities were more likely to have a medically documented history of GI problems, than those without. Williams et al. (2010) found that sleep problems occurred most frequently in those with gastrointestinal problems (50%) than those without (37%). Williams et al. (2012a) found that 24.5% of children with ASD had sleep problems and chronic GI symptoms, while 25.2% had neither sleep nor GI problems. It was found that 42.5% had sleep problems only, while 7.8% had a chronic GI complaint only. Sleep problems occurred in 84% of children with chronic nausea, 82% of children with chronic diarrhea, 81% of children with chronic bloating, 79% of children with chronic constipation and 78% of children with chronic abdominal pain.

Mannion et al. (2013) investigated predictors of sleep problems in children with ASD. The total number of GI symptoms predicted higher rates of sleep problems. Under-eating, avoidant behavior and gastrointestinal symptoms predicted sleep problems. Specifically, abdominal pain predicted sleep anxiety. Under-eating, avoidant behavior and the five GI symptoms (Constipation, Diarrhea, Nausea, Abdominal Pain and Bloating) predicted parasomnias and daytime sleepiness.

This finding of gastrointestinal symptoms predicting sleep problems is supported by Hollway, Aman, and Butter (2013). Hollway et al. (2013) found that gastrointestinal problems including constipation and diarrhea predicted total scores on the Children's Sleep Habits Questionnaire (CSHQ), which was the same measure used by Mannion et al. (2013). Gastrointestinal symptoms predicted sleep anxiety in Hollway et al.'s (2013) research. This is supported by Mannion et al.'s (2013) finding of the relationship between gastrointestinal symptoms and sleep anxiety. The relationship between sleep problems and gastrointestinal symptoms is supported by Williams, Christofi, Clemmons, Rosenberg, and Fuchs (2012a). The authors reported that abdominal pain predicted sleep anxiety.

Mannion and Leader (2013a) found that sleep problems predicted gastrointestinal symptoms. Specifically, sleep disordered breathing and daytime sleepiness predicted both abdominal pain and bloating. Sleep anxiety predicted abdominal pain. It was found that 67.8% of individuals had both sleep problems and gastrointestinal symptoms, while only 8% had neither sleep problems nor gastrointestinal symptoms. Sleep problems occurred in 92.3% of those with nausea and in 91.1% of those with abdominal pain. Sleep problems occurred in 90.9% of those with bloating. Sleep problems occurred in 90% of those with diarrhea, and in 83.7% of those with constipation. It was found that 11.5% had gastrointestinal symptoms only, while 12.6% had sleep problems only.

Kang, Wagner, and Ming (2014) investigated the association between GI dysfunction and other comorbidity. They found that children with ASD with any symptoms of GI disorder exhibited significantly higher rates of sleep disorders. The authors commented that "Sleep could be disrupted by any of the GI symptoms and, therefore, it is not surprising to observe the association between the two" (p.5). The relationship between sleep problems and gastrointestinal symptoms is one that needs to be further explored in future research.

3.7. Sensory Issues

Mazurek et al. (2013b) investigated the relationship between sensory over-responsivity and GI problems. They found that those with chronic GI problems had higher levels of sensory over-responsivity. Increasing numbers of GI problems were associated with higher levels of sensory over-responsivity. Sensory over-responsivity also predicted chronic GI problems. The relationship between sensory problems and GI symptoms needs to be further examined in future research.

3.8. Parental Stress and Psychological Distress

Silva and Schalock (2012) investigated parenting stress and focused on comorbid behavioral and physical symptoms as well as the core symptoms of ASD. The researchers investigated bowel problems, including constipation and diarrhea as a comorbid physical condition. Bowel problems were found to be stressful for 31.8% of parents of children with ASD, compared to 5% of parents of typically developing children and 17.9% of parents of children with other developmental disabilities. Parents of children with ASD who exhibited bowel problems differed significantly from parents of typically developing children in parenting stress levels. However, no significant differences were found between parents of children with ASD and parents of children with other developmental disabilities for bowel

problems. Future research needs to examine the relationship between GI symptoms in ASD and parental stress.

3.9. Adaptive Behavior

Little research has focused on the relationship between GI symptoms and adaptive behavior in individuals with ASD. Nikolov et al. (2009) found that there was no difference between children with ASD with and without GI symptoms on measures of adaptive functioning. Mazefsky et al. (2014) investigated the association between emotional and behavioral problems and gastrointestinal symptoms among children with high-functioning autism. The authors hypothesised that children with GI symptoms would have lower mean adaptive behavior than children without any GI symptoms. However, the study found that participants with and without GI symptoms did not differ in overall adaptive behavior. Future research should further investigate the relationship between GI symptoms and adaptive behavior in individuals with low functioning ASD as well as in individuals with high functioning ASD and Asperger's Syndrome.

3.10. Social Responsiveness and Social Problems

Mazefsky et al. (2014) included social responsiveness as a variable in their study with children with high-functioning ASD. They found that there was no difference between those with and without GI symptoms in terms of social responsiveness. However, the authors found that social problems were significantly associated with the number of GI symptoms. In analysing this relationship, the authors commented that those with and without GI problems did not differ in their mean social problems scores, and that a similar number of participants in the GI and non-GI groups exceeded the borderline clinical level of social problems.

Gorrindo et al. (2012) used the Social Responsiveness Scale (SRS; Constantino & Gruber, 2005) to measure social responsiveness. Gorrindo et al. (2012) found that children with both ASD and gastrointestinal dysfunction showed more severe social impairment compared to children with ASD alone or children with gastrointestinal dysfunction alone. The researchers also found that more socially impaired children with ASD had increased odds of functional constipation. It was found that there was a 5% increase in odds of constipation for each point increase in the SRS T-score.

3.11 Quality of Life

The relationship between gastrointestinal symptoms in individuals with ASD and quality of life is one in which very little research has been conducted in the past. Williams et al. (2010) investigated the relationship between GI symptoms and quality of life in children with ASD. The authors found that children with ASD with GI symptoms had lower quality of life compared to children without GI symptoms. The authors commented on the need for future research to clarify this association.

Physical functioning is often studied as an aspect of quality of life. Previous research has examined the relationship between physical functioning in individuals with ASD. Kuhlthau et al. (2010) compared children with ASD to children with chronic conditions. The authors found that children with ASD did not differ from children with chronic conditions in their physical health. Williams et al. (2010) commented on the need for further investigation on whether treatment of GI disorders improves quality of life in children with ASD. Similarly, Chaidez et al. (2014) commented that "Appropriate treatment of GI symptoms may help alleviate at least some problematic behaviors and improve the quality of life in children with ASD along with their families" (p.1125). Future research needs to further investigate the relationship between GI symptoms and quality of life in individuals with ASD.

3.12 Attention–deficit/hyperactivity disorder (AD/HD)

Mannion and Leader (2014a) discussed the relationship between gastrointestinal symptoms and comorbid Attention-Deficit/Hyperactivity Disorder (AD/HD). McKeown, Hisle-Gorman, Eide, Gorman, and Nylund (2013) investigated the association of constipation and fecal incontinence with AD/HD. Children with AD/HD had an increased prevalence of constipation (4.1% of children with AD/HD versus 1.5% of children without AD/HD) and fecal incontinence (0.9% of children with AD/HD versus 0.15% of children without AD/HD). The rate of constipation and fecal incontinence was the same for children with AD/HD who were prescribed medication, as those not prescribed medication. We know gastrointestinal symptoms are common in children with ASD. We also know that AD/HD and ASD are comorbid conditions. However, we do not yet know about the relationship between AD/HD and gastrointestinal symptoms in individuals with ASD.

3.13. Epilepsy

Mannion and Leader (2014b) discussed gastrointestinal symptoms in their literature review on epilepsy in ASD. Turk et al. (2009) found that those with ASD and epilepsy showed greater incontinence, such as not being clean and dry in day and at night, than those with ASD alone. Gobbi (2005) conducted a review on Coeliac Disease, epilepsy and cerebral calcifications. It is unknown if this association is a coincidence or a genetic condition. Research is needed to determine if there is a relationship between gastrointestinal symptoms and epilepsy, both in typically developing populations and in individuals with ASD.

3.14. Feeding Problems

Feeding Problems has been identified as a common comorbid condition in individuals with ASD (Mannion & Leader, 2013b). Parmeggiani (2014) discussed the relationship

between feeding and GI disorders in ASDs. The author commented on how GI disorders can be causes of feeding problems. These GI disorders include gastroesophageal reflux, food allergies, gastritis, colitis, and celiac disease. Parmeggiani (2014) also commented that "Feeding problems may cause GI disorders, which, in turn, can be responsible for other clinical problems, such as sleep disorders and impaired behavior in ASDs" (p.2041).

Sharp et al. (2013) conducted a literature review and meta-analysis on feeding problems and nutrient intake in children with ASD. The authors commented that future research should determine the long-term health burden associated with atypical patterns of intake on a population level as well as the relationship with other areas of functioning, such as gastrointestinal issues and quality of life. Kral, Eriksen, Souders, and Pinto-Martin (2013) conducted a review for nurses on eating behaviors, diet quality, and gastrointestinal symptoms in children with ASD. The authors concluded that "an assessment of co-occurring medical conditions is a necessary first step in a comprehensive medical evaluation to address concerns about eating behaviors, diet, and limited food variety" (p.555).

Levy et al. (2007) investigated the relationship between dietary intake to gastrointestinal symptoms in children with ASD. The researchers found that GI symptoms are not significantly related to abnormal patterns of dietary intake of carbohydrates, proteins or fats. The researchers also examined stool consistency. No relationship was observed between stool consistency and dietary intake. The authors concluded that future research needs to "describe the relationship between nutritional intake and GI symptoms, determine nutritional risk factors for children with ASD and selective diets, and determine the etiology of GI dysfunction in children with ASD" (p.495).

Ming et al. (2008) found that food intolerance was associated with gastrointestinal dysfunction in children with ASD. Kang et al. (2014) found that children with ASD who

presented with any symptoms of GI disorder exhibited significantly higher rates of food intolerance than children without GI symptoms. The relationship between GI symptoms and feeding problems needs to be further explored in future research.

3.15. Family Medical History and Autoimmune Diseases

Stigler, Sweeten, Posey, and McDougle (2009) conducted a review of autism and immune factors. The review discussed gastrointestinal factors as a possible immune factor. Similarly, Brown and Mehl-Madrona (2011) conducted a review on the possible links between autism, immune system dysfunctions, and gastrointestinal symptoms in a subgroup of children with ASD. Brown and Mehl-Madrona (2011) concluded that "sufficient evidence exists to support the hypothesis that at least a subgroup of children diagnosed with ASD suffers from altered immune function and GI disturbance" (p.472). The authors suggested a number of areas in which research could be conducted within the next 5 years with children with ASD and GI symptoms. First, they recommended identifying autism subgroups so that the diagnosis could eventually have pathophysiological differentiation with specific subdiagnosis criteria. Second, GI symptom criteria to screen for food sensitivities could be created. Third, GI symptom criteria could be used to screen for specific subjects rather than indiscriminately selecting subjects from the greater pool of children with ASD. Fourth, it should be determined if this GI symptom-prone group has higher rates of food sensitivities, food allergies, lactose intolerance, celiac disease and/or other GI enzyme deficiencies or autoimmunities. Fifth, the effectiveness of dietary therapy, including an elimination diet, should be determined in alleviating GI and/or behavioral symptoms. Sixth, the prevalence of GI symptoms in all autoimmune conditions should be determined and not just autism. Finally, the effectiveness of a dietary therapy in reducing GI symptoms should be determined in all autoimmune conditions.

Mouridsen, Rich, Isager, and Nedergaard (2007) examined autoimmune disease in the parents of children diagnosed with infantile autism and a matched control group of parents during an observation period of 27 years. It was found that 10.8% of mothers of children diagnosed with infantile autism had an autoimmune disease compared to 9.1% of mothers in the control group. The researchers found that 8.6% of fathers of children diagnosed with infantile autism had an autoimmune disease compared to 4.6%. Type 1 Diabetes was found in significantly more fathers of children with infantile autism compared to controls. Ulcerative colitis was found in significantly more mothers of children with infantile autism. It was found that 2.7% of mothers of children with infantile autism had a diagnosis of ulcerative colitis, compared to 0.3% of controls.

Valicenti-McDermott et al. (2006) examined the association of gastrointestinal symptoms with a family history of autoimmune disease. Family history of autoimmune disease was reported in 38% of the ASD group and in 34% of control participants. The researchers found that there was no association between family history of autoimmune disease and GI symptoms in children with ASD. A family history of cognitive or psychiatric problems was not associated with an increased risk of gastrointestinal symptoms.

Valicenti-McDermott et al. (2008) found an association between language regression, a family history of autoimmune disease, and gastrointestinal symptoms. Children with language regression were more likely to exhibit an abnormal stool pattern, had an increased family family history of celiac disease or inflammatory bowel disease and of rheumatoid arthritis. Of all of the children with a family history of autoimmune disease, an abnormal stool pattern was reported more frequently in those with language regression than those without language regression. An abnormal stool pattern was found in 78% of those with a family history of autoimmune disease and language regression and, compared to 15% of those with a family history of autoimmune disease, but without language regression. Peters

et al. (2014) commented that obtaining a family history of GI symptoms "could be useful in establishing a genetic or familial component to bowel symptoms" (p.1431).

4. Gastrointestinal Symptoms throughout the lifespan

Ibrahim, Voigt, Katusic, Weaver, and Barbaresi (2009) conducted a long-term population-based retrospective study of the incidence of gastrointestinal symptoms in children with ASD, compared to matched controls. The participants were followed from their date of birth to their last follow-up before the age of 21 years old. Significant differences were found for the incidence of constipation before the age of 20 years old, in those with ASD (33.9%) compared to 17.6% of controls. There was a significant difference between feeding issues in those with and without ASD, with there being a higher incidence of feeding problems in those with ASD. No significant association was found for those with ASD and overall incidence of gastrointestinal symptoms, diarrhea, gastroesophageal reflux/vomiting, or abdominal bloating/discomfort/irritability.

Mouridsen, Rich, and Isager (2010) conducted a longitudinal study of gastrointestinal diseases in individuals diagnosed with autism as children. The research was conducted using medical records. The participants were observed over an average of a 30 year time period. The mean age at the end of the observation period was 42.7 years, with participants ranging from age 27 and 57 years of age. It was found that 30.5% of those with infantile autism had received a diagnosis of a disease of the digestive tract, while 30.7% of those in the control group received a diagnosis of a disease of the digestive tract. Therefore individuals with infantile autism were found to be no more likely to be diagnosed with a gastrointestinal disease.

Kral et al. (2013) commented on the need for longitudinal studies conducted over an extended period of time to assess children's dietary intake and GI and bone health. Future

longitudinal studies are needed to examine if gastrointestinal symptoms change over time. If so, do they improve or do they get worse as children and adolescents with ASD grow into adulthood?

5. Mouse Model Studies

Hsiao et al. (2013) conducted research using the maternal immune activation (MIA) mouse model. The offspring of these mice display autism-like symptoms including communicative, social and stereotyped impairments. The offspring of immune-activated mothers were found to exhibit GI symptoms of human ASD. The researchers found that adult offspring of immune-activated mothers exhibited increased gut permeability and abnormal intestinal cytokine profiles. The researchers targeted the gut microbiota by administering *Bacteroides fragilis* to the mice. *Bacteroides Fragilis* was found to relate to specific microbiota changes in the MIA offspring. The *Bacteroides Fragilis* treated offspring exbited improved communicative, repetitive, anxiety-like, and sensori-motor behavior. However, deficits in sociability and social preference remained. The authors concluded that microbiome-mediated therapies may be an effective treatment for neurodevelopmental disorders.

Desbonnet, Clarke, Shanahan, Dinan, and Cryan (2014) studied the contributions of microbiota to social behavior in mice. They examined the effects of germ-free (GF) rearing conditions through early life and adolescence on social behavior in adulthood. They found that germ-free mice spent a decreased proportion of time engaging in social investigation, and spent a greater proportion of time engaged in repetitive self-grooming behavior during social interaction. The behaviors were normalised following germ-free bacterial colonisation. This demonstrated the role of microbiota in social behaviors. The authors concluded that

microbiota are important for normal social behaviors, including social motivation and preference for social novelty.

Mouse model studies are an effective way of better understanding the biological mechanisms of gastrointestinal symptoms. As well as examining the autism-like symptoms in mice, researchers can examine how these symptoms affect the entire body, including the gut. Levels of bacteria can be researched in the gut. If treating the gut with certain types of bacteria proves effective in animal models, this gives hope of probiotic treatment for GI symptoms in ASD. Some mouse model studies look at treating ASD and treating the behavioral manifestations of ASD in mice. However, research also needs to focus on how the GI symptoms can be treated in the first place. Furthermore, the effect treating GI symptoms has on the behavioral symptoms then needs to be further understood. We need to first understand the basic animal models of research before focusing on how the basic research can be applied to individuals with ASD.

6. Genetic and Environmental Risk Factors

Campbell et al. (2009) found that there was a genetic risk based on the association of *MET* in families with co-occurring ASD and gastrointestinal conditions. MET is a pleiotropic receptor that functions in both brain development and gastrointestinal repair. A *MET* gene variant was associated with both ASD and gastrointestinal conditions. The authors suggested that disrupted *MET* signalling may contribute to increased risk for ASD that includes familial gastrointestinal dysfunction. The researchers also suggested that future research could focus on families with co-occurring ASD and gastrointestinal symptoms versus ASD alone.

Hsiao (2014) conducted a review of gastrointestinal issues in ASD, and discussed the potential gastrointestinal manifestations of genetic and environmental risk factors for ASD.

The author discussed *MET,* and also discussed that *SLC6A4 i*s another susceptibility gene that may be linked to gastrointestinal dysfunction. SLC6A4 encodes the integral membrane transporter for the neurotransmitter, serotonin (SERT). The author noted that the endocrine cells of the GI tract are known to produce over 90% of the body's serotonin. Hsiao (2014) discussed how maternal autoreactive antibody production may be a risk factor for ASD with GI abnormalities. Hsiao (2014) discussed possible environmental risk factors for comorbid ASD and GI abnormalities. Maternal immune activation is one possible risk factor. The author discussed how research has been conducted on mice, but research on humans with ASD is still needed.

We need to better understand the genetics of ASD as well as the genetic risk factors of comorbid conditions such as GI symptoms. It is promising that research is being conducted into the genetics of GI symptoms. We can therefore better understand why some individuals present with GI symptoms and others do not. We need to learn more about familial risk factors, including family medical history as well as genetic risk factors of GI symptoms in families of individuals with ASD. More research is needed to better understand how environmental risk factors play a role in ASD, as well as how they interact with GI symptoms. Mouse model studies are very useful for understanding possible environmental risk factors such as the maternal immune activation. However, this basic research needs to be expanded and transferred to humans for applied research in the future.

7. Neuroimaging Research

Breece et al. (2013) compared the frequencies of dendritic cells in children with ASD and typically developing controls. The authors commented on the role of dendritic cells in innate immunity. It was found that myeloid dendritic cells frequencies are increased in children with ASD. The researchers collected information on parental report of the

gastrointestinal symptoms of constipation and diarrhea to determine if there were associations with dendritic cell frequencies. Myeloid dendritic cells were associated with the severity of gastrointestinal symptoms. Increased frequency of mDC2 was positively associated with increased frequency of symptoms of constipation.

Neuroimaging technologies are a state of the art way of better understanding the brain. Neuroimaging studies structural differences in the brain. More research is needed on how the brain structure and anatomy is different in individuals with ASD. By understanding structural neurological research, we can understand the effect that differences in the brain have on the entire human body including the gastrointestinal tract. We need to better understand the gut-brain connection in ASD in order to conduct important research. By understanding this connection, we can also understand how treatment will be most effective.

8. Celiac Disease

Buie (2013) conducted a review on the relationship of autism and gluten. Buie (2013) commented that most people who have GI symptoms do not have celiac disease but have a different reaction to gluten. The author also commented that there are several non-gastrointestinal manifestations of celiac disease including cerebellar ataxia, peripheral neuropathy, epilepsy, dementia, and depression. Lau et al. (2013) assessed immune reactivity to gluten in children with ASD in order to evaluate the potential link between autism and celiac disease. The researchers found that a subset of children displayed increased immune reactivity to gluten in a manner unrelated to that of celiac disease. Children with GI symptoms were found to have significantly higher levels of IgG antibody to gliadin when compared to those without GI symptoms. However, no association was observed between the elevated anti-gliadin antibody level and the presence of markers of celiac disease. The authors concluded that the majority of individuals with ASD with elevated antibody to

gliadin do not have celiac disease but this subset of individuals may have "non-celiac gluten sensitivity" (p. 66155). The authors also commented that the increased anti-gliadin antibody response may involve immunological and/or intestinal permeability abnormalities in children with ASD.

9. Special Diets

Perrin et al. (2012) investigated complementary and alternative medicine (CAM) use in children with ASD. Parents of children with ASD were asked if their children use any of the following treatments: acupuncture, chelation, chiropractic, or hyperbaric oxygen therapy; dietary supplements (vitamin supplements, probiotics, antifungal agents, digestive enzymes, glutathione, sulfation, amino acids, or essential fatty acids); and special diets(classified as gluten free, casein free, Feingold, no processed sugars, no salicylates, or other). Special diets usage versus no CAM usage was investigated in the study also. Parents reported higher rates of CAM usage in general and for special diets when they also reported GI problems. The authors commented that families seek to address problematic behaviors or symptoms using CAM and that parents whose children have GI symptoms may try both dietary changes and other CAM treatments to improve their child's nutrition and symptoms.

Whitehouse (2013) reviewed CAM for autism spectrum disorders and included a discussion of the gluten-free, casein-free (GFCF) diet. Whitehouse (2013) concluded that "Currently, there is a lack of evidence to support the use of GFCF diets as an effective intervention for children with ASD" (p.439). Pennesi and Klein (2012) investigated the effectiveness of the gluten-free, casein-free (GFCF) diet in children with ASD. The authors found the diet to be effective in improving ASD behaviors, physiological behaviors and social behaviors for children with GI symptoms (specifically, constipation and diarrhea) compared to children with no GI symptoms. The authors suggested that children predisposed to GI abnormalities might particularly benefit more from a GFCF dietary intervention.

However, the authors also commented that the findings reported may be highly sensitive to parental perceptions and that the high effectiveness ratings may be explained by a placebo effect. In terms of future research, the authors stated that the priority of future research should be to define the immunological and GI diagnoses and symptoms that best predict those individuals who will be most responsive to the gluten-free, casein-free diet.

Mulloy et al., (2010) conducted a systematic review on gluten-free and casein-free diets in the treatment of autism spectrum disorder. The authors concluded that the published studies they located do not support the use of GFCF diets in the treatment of ASD. The authors commented on negative consequences for the use of the GFCF diet, such as use of treatment resources, stigmatization and reduced cortical bone thickness. The authors recommended that should a child with ASD experience behavioral changes seemingly associated with change in diet, practitioners should consider testing the child for allergies and food intolerances and eliminate identified allergens or irritants from their environment.

10. Cognitive Behavior Therapy

van der Veek, Derkx, Benninga, Boer, and de Hann (2013) conducted a randomised controlled trial of Cognitive Behavior Therapy (CBT) for Pediatric Functional Abdominal Pain in typically developing children. Six sessions of CBT were compared to six visits to a pediatrician for Intensive Medical Care (IMC). Abdominal pain was measured was reported on questionnaires and diaries. Other outcomes were measured including gastrointestinal complaints, functional disability, other somatic complaints, anxiety, depression, and quality of life. It was found that both CBT and IMC resulted in a significant decrease in abdominal pain. CBT was found to be equally as effective as IMC. Both treatments were also equally effective at reducing gastrointestinal complaints, functional disability and other somatic complaints and increasing quality of life. CBT was found to be more effective than IMC for decreasing anxiety and depression symptoms at 6-month follow-up, but there was no

difference between CBT and IMC at 12 month follow-up. The researchers commented that future research should focus on determining the working mechanisms of CBT. As this research was conducted with typically developing children, it may be a fruitful line of research to determine if the effectiveness of CBT for abdominal pain can be transferred to children with high functioning ASD who present with gastrointestinal pain and symptoms. Future research should also examine the use of CBT for abdominal pain in high functioning, adolescents and adults with ASD.

11. Meta-Analysis of Gastrointestinal Symptoms in Autism Spectrum Disorder

McElhanon, McCracken, Karpen, and Sharp (2014) conducted a meta-analysis of gastrointestinal symptoms in ASD. The authors analysed all studies with a non-ASD comparison group. It was found that GI status was assessed by caregiver report in 73% of the studies, while medical chart review was used in 27% of studies. It was found that the odds of GI symptoms in children with ASD were four times more prevalent than in children without ASD. There was an increase of three times more diarrhea and constipation in children with ASD. There was a two-fold increase of abdominal pain in children with ASD. The authors commented on the need for future research to examine "factors such as immune abnormalities, mucosal barrier dysfunction, gastrointestinal mobility, feeding and toileting concerns, and the gut microbiome" (p.881).

12. Recommendations for treatment

Buie et al. (2010b) commented that children with ASD can benefit from the adaptation of general pediatric guidelines for diagnosing GI symptoms. The authors provided a review of guidelines to diagnose and treat GI symptoms using current general pediatric guidelines, until specific guidelines are designed for those with ASD. Information on differential diagnosis, evaluation and treatment considerations are provided for chronic

abdominal pain, constipation, chronic diarrhea and gastroesophageal reflux disease (GERD) in children with ASD.

Furuta et al. (2012) developed an algorithm to help health care providers identify, evaluate and manage constipation in children with ASD. The consensus among the authors is that 1) subtle or atypical symptoms might indicate the presence of constipation; 2) screening, identification and treatment through a deliberate approach for underlying causes of constipation is appropriate; 3) diagnostic-therapeutic intervention can be provided when constipation is documented and 4) careful follow-up after any intervention be performed to evaluate effectiveness and tolerance of the therapy (Furuta et al., 2012). According to the algorithm any child with atypical behaviors should be evaluated for constipation. Examples of these behaviors include self-injurious behavior, posturing, grimacing, holding the abdomen, squeezing the legs together or walking around with a narrow gait to hold the stool in (Furuta et al., 2012).

Buie et al. (2010a) commented that integrating behavioral and biomedical roles can be advantageous. Firstly, functional behavioral assessments can be used in order to interpret the function of challenging behavior. Second, it is important to be aware of pain and discomfort can function as a setting event for challenging behavior. Third, functional communication skills may be taught. Buie et al. (2010a) commented that it would be useful for diagnosis to teach a child to identify the location and type of pain they are experiencing. Finally, the individual could be taught skills for coping with a task demand appropriately during moments of pain or discomfort (Buie et al., 2010a).

13. Future research

Coury et al. (2012) developed a research agenda for gastrointestinal conditions. They defined four priority areas for research: epidemiology of GI conditions in ASD; underlying

pathology; treatment and outcome; and nutrition. There is a need for rigorously designed prevalence studies in order to identify risk factors including clinical and behavioral indicators of GI problems; identify atypical presentations of GI disorders in ASD and identify subpopulations within ASD that have GI symptoms (Coury et al., 2012).

As evidenced by the lack of papers on adults with ASD discussed in this chapter, there is a real need for more research to be conducted with adults with ASD to investigate the relationship between GI problems and ASD in adults. Edwards, Watkins, Lotfizadeh, and Poling (2012) found that in intervention research on ASD, only 1.7% of participants were 20 years or more. In ASD research, in general, there is a need for adult research and this is especially so in relation to gastrointestinal symptoms.

Longitudinal studies are needed to determine if GI symptoms change over time. We need to understand if GI symptoms continue on to adolescence, adulthood and older adulthood. Do these symptoms get better? Do they get worse? Do symptoms remain constant over time? These are questions that we not know the answer to as of yet. Future research needs to investigate these questions.

Research is needed on the relationship between GI symptoms and other comorbid conditions in ASD, such as sleep problems, anxiety, and depression. The relationship between gastrointestinal symptoms and outcome variables such as quality of life, behavior problems, social functioning, and adaptive behavior needs to be better understood. We need to understand what effect GI symptoms have on an individual's level of functioning. We need to better understood treatment options for these GI symptoms in animal models, as well as in humans with ASD. Furthermore, the effects of treating these GI symptoms have on an individual's quality of life, behavior problems, social functioning and adaptive behavior needs to be determined.

The animal model research gives us an underlying understanding of the biological mechanisms that interact with the gastrointestinal symptoms. This research is in the early stages but a greater understanding of the biological mechanisms will allow us to investigate and design effective treatment models in the future. Future treatment may include the use of dietary interventions, such as probiotics. While special diets or nutritional therapy may be found to be a possible treatment option in the future, it is important that dietary intervention is not just seen as a treatment for all individuals with ASD. Instead we need to better understand what symptoms can best predict the individuals who will be most responsive to special diets such as the gluten-free, casein-free diet.

We now know that gastrointestinal symptoms and disorders are a prevalent comorbid condition in ASD. However, they are difficult to diagnose due to the communication deficits in ASD. It may be difficult to determine if individuals are in pain if they cannot communicate this verbally, or instead communicate it through challenging behavior. We know that gastrointestinal symptoms may present in atypical ways, such as through aggression, repetitive behavior or sleep disturbances. We need to better understand how to diagnose these GI symptoms that present atypically. Gastrointestinal symptoms can exacerbate the core symptoms of ASD, and can cause a variety of other behaviors that are not the core symptoms of ASD. Gastrointestinal symptoms need to be screened for by medical practitioners, so that treatment can be provided.

Researchers need to understand that gastrointestinal symptoms may be an exacerbating variable in ASD research, whereby gastrointestinal symptoms are affecting an individual with ASD and their behavior. Often GI symptoms are not considered or controlled for in ASD research. Practitioners need to be aware of how GI symptoms may interfere with an individual's learning environment. A key skill that practitioners need to focus on teaching is to identify and communicate pain to parents, caregivers or teachers. In

conclusion, an awareness and understanding of GI symptoms is essential for practitioners and researchers alike.

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