The Medicine Cabinet: gastrointestinal disorders and autism

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It has long been recognised that there may be a link between gastrointestinal (GI) disorders such as reflux and autistic spectrum disorders (ASD) as well as other developmental disabilities. These disorders can include functional diarrhoea, functional constipation and gastrointestinal reflux disease. In one study comparing ASD subjects with unaffected siblings found significantly more GI symptoms (42% to 12%). Another study has found increased severity of autism increased the odds of having GI problems.[2]

In a 1999 study looking specifically at gastrointestinal symptomology in autistic disorder or pervasive developmental disorder found nearly 70% patients had reflux oesophagitis and 88% had symptoms including night time awakening with irritability, signs of abdominal discomfort.[1] This study further showed on histology there was chronic inflammation of oesophagus, stomach and duodenum – high prevalence of reflux oesophagitis, hyperplasia of duodenal cells as well as intestinal carbohydrate digestive enzyme deficiencies. Children with developmental delay are three times more likely than children with typical development to experience frequent sensitivity to foods, pain on defecating, diarrhoea, constipation as well as difficulty swallowing and vomiting.[2] This study also concluded that children with ASD had not only the highest reports of food dislikes but also highest odds of reporting GI symptoms not explained by other factors.

Although some individuals with ASD may respond to dietary intervention such as removal of milk for symptoms of lactose intolerance, these need to be assessed empirically as there has been reported a high degree of placebo effect (See previous article MHCAIDD Volume 9 Issue 2, 2018). There is not the support for the use of casein-free diet or gluten-free or combination for individuals with ASD.[4] There is a need for standardised definitions of adverse reactions to both food and medications. The term food allergy is sometimes applied where the reaction is non toxic but immunologically generated.

Gastro-oesophageal disorders are sometimes communicated especially in the non verbal developmentally delayed by challenging behaviours including agitation and aggression as well as sleep disturbance. So understanding the reason behind the challenging behaviour and treating can reduce the need for psychotropic medication.

Medication used to treat gastrointestinal disorders

Neutralising agents

These include preparation such as aluminium hydroxide gel and magnesium hydroxide gel (brand names such as Mylanta® and Maalox®) have largely been discontinued as they were used primarily for the neutralisation of acid in heartburn and gastritis. Mylanta® is now available in tablet form. For best results the tablets should be taken apart from other medication (at least 2 hours). There are also several drug interactions with these preparations so use should always be discussed with doctor and/or pharmacist. These preparations also sometimes contained simethicone which was added as it reduces the production of gas.

Anticholinergic agents

These are related to belladonna (atropine) and hyoscine preparations and by themselves can be helpful for abdominal discomfort as well as peptic ulcers, diarrhoea as well as nausea and vomiting but there is an additive effect with antipsychotic medications such as risperidone, olanzapine and quetiapine together with some antidepressants such as amitriptyline and mirtazapine as they also have anticholinergic effects. Additive anticholinergic effects include dryness of mouth leading to increased risk of dental caries, constipation, urinary retention and incontinence, agitation and disorientation.

Proton pump inhibitors

This group of medications has been available since 1980s but their use has become more widespread and availability increased with some being able to purchase over the counter. They work by blocking the gastric acid secretion of the parietal cells of the stomach

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suppressing both the stimulated and basal acid secretion when taken before a meal. These medications include pantoprazole, omeprazole, esomeprazole and lansoprazole. They are primarily used to treat peptic ulcer disease, help in eradication of *Helicobacter pylori* infections, treatment and prevention of gastroduodenal ulcers caused by other medications including non-steroidal anti-inflammatories (NSAIDs such as ibuprofen), and gastrointestinal reflux disease (GERD). These medications are commonly prescribed on PBS and in 2018/9 esomperazole was number 8 in the list of top 10 drugs by defined daily dose prescribed on PBS/RPBS.

H2 antagonists

The other class of medications used for GERD is the H2 antagonists such as cimetidine and ranitidine. These work by inhibiting the gastric acid secretion by blocking the histamine 2 receptors on the basolateral plasma membrane of the parietal cells mainly during the night. Not quite as effective for post meal reflux but effective for gastroduodenal ulcers. H2 antagonist’s effect quickly rises after first dose but a tolerance can develop by gradually weakened acid suppression with repeated administration over 2 weeks. In recent times there has been some issues with the manufacture of ranitidine, finding that it has been contaminated with N-nitrosodimethylamine (NDMA) and thus supply has not been able to be guaranteed. Cimetidine use has also decreased due to potential for drug drug interactions due to its ability to inhibit one of the drug metabolising enzymes CYP2C9 and thus affect the drug levels of several medications.

Some gastrointestinal conditions

Gastrointestinal reflux

Gastrointestinal reflux in very young may be associated with vomiting and regurgitation but improves by 12 months of age. Signs associated with gastro oesophageal reflux disease (GORD) include failure to thrive, oesophagitis, stricture, refusing to feed, recurrent pneumonia, anaemia, dental erosions, apnoea and life threatening events and these can be hard to describe

and should be fully investigated not just as GORD but also other conditions maybe contributing[7].

Acid suppression
The stomach is only organ that secretes acid (pH 2). Such gastric secretion is important for the sterilisation of bacteria in ingested foods but also for digestion and absorption of nutritional factors such as proteins, iron, calcium and vitamin B12. These can lead to deficiencies.

Helicobacter infections
Helicobacter pylori is a bacterial infection causing gastritis and peptic ulceration is prevalent in up to 30% of adult Australians and primarily acquisition occurs during childhood[5]. Apart from the gastritis symptoms, there is also a degree of functional dyspepsia which when treated with H pylori medication eases symptoms. It is diagnosed by a breath test or via scope. Successful eradication treatment includes two different antibiotics and a PPI (first line is esomeprazole) over a 7 day course.

According to Australian Therapeutic Guidelines Gastroenterology, empirical treatment should be avoided in children, and the 'test-and-treat' strategy for upper gastrointestinal tract symptoms used for adults is not appropriate. Children should only be tested for *H. pylori* in the rare situation where their symptoms are strongly suggestive of organic disease. Upper gastrointestinal endoscopy is recommended to confirm *H. pylori* infection in children.[7]

Constipation
This can be overlooked as well as managed by the general practitioner and can be medication related as well as other factors. These can include poor food including low fibre content or oral intake especially in those with swallowing difficulties. Poor mobility and severe intellectual disability also increase the incidence of constipation. Constipation may be expressed as intermittent pain and then in some circumstances lead to constipating medications being prescribed to fix a pain problem but also contributing to underlying constipation problem.

Constipation in children had three principles of management.[6]

- Adequately soften stools to eliminate fear of painful evacuation
- Empty rectum if impacted and keep it empty
- Encourage good toileting behaviour

Mild constipation is often treated with increased dietary fibre and toilet training and any use of laxatives continued until after training has occurred or regular bowel movements.

Chronic constipation will need laxatives used include macrogol 3350 (brand names include Movicol or Osmolax) powder which is dissolved in water or other fluids as per instructions and the consumed. Other preparations include lactulose as well as sorbitol. Liquid paraffin 50% (Parachoc®) can also be used but contains 50% chocolate flavouring. Daily dosing if preferable and needs to continue until stools are the correct consistency – wet cement or porridge.[6]

After 2-3 months treatment and not inducing regular stooling then stimulant laxatives can be started, these include either bisacodyl tablets or enemas, senna preparations or sodium picosulfate (Coloxyl Drops®). Colicky pain is often an adverse effect of these preparations.

For severe faecal impaction, adolescents can have up to 8 sachets of macrogol 3350 daily for 3 days under medical supervision. If this unsuccessful then admission to hospital maybe needed. Followed by the regimen for chronic constipation.

Long term effects of proton pump inhibitors
While most of these epidemiological studies have been in the older population there has been some interesting findings which has lead the PBAC (Pharmaceutical Benefits Advisory Council) to change the benefits available for the PPIs on the PBS (Pharmaceutical Benefits Scheme) in May 2019.
In recent years it has become apparent that there is long term/chronic effects of proton pump inhibitor (PPI) use, these include hypocalcaemia, hypomagnesaemia, *Clostridium difficile* infections, changes in gut microbiome as well as small intestine bacterial overgrowth and pneumonia. The long term loss of calcium and magnesium can cause cardiac and bone density problems leading to fractures and osteoporosis. More epidemiological studies are needed.
Infections such as community acquired pneumonia and *C. difficile* are possibly due to increase in the gastric acid pH due to chronic use of PPIs leading to inability to suppress the opportunistic enteric bacteria thus allowing colonisation.

"Poor mobility and severe intellectual disability also increase the incidence of constipation..."

PBS changes

These included changes in the classification of doses from highest, high and low to high, standard and low. Restrictions on highest dose esomeprazole has increased to needing a telephone authority. Standard doses of PPIs all now require telephone authority prescriptions and high dose treatment for GORD, have symptoms which are inadequately controlled using standard dose PPI. Standard dose treatment for GORD is streamlined authority and be long term maintenance in patients not adequately controlled using low dose PPI. These restrictions will be reviewed in 2 years.

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Further Reading:

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This article includes some non-pharmalogical treatment options.