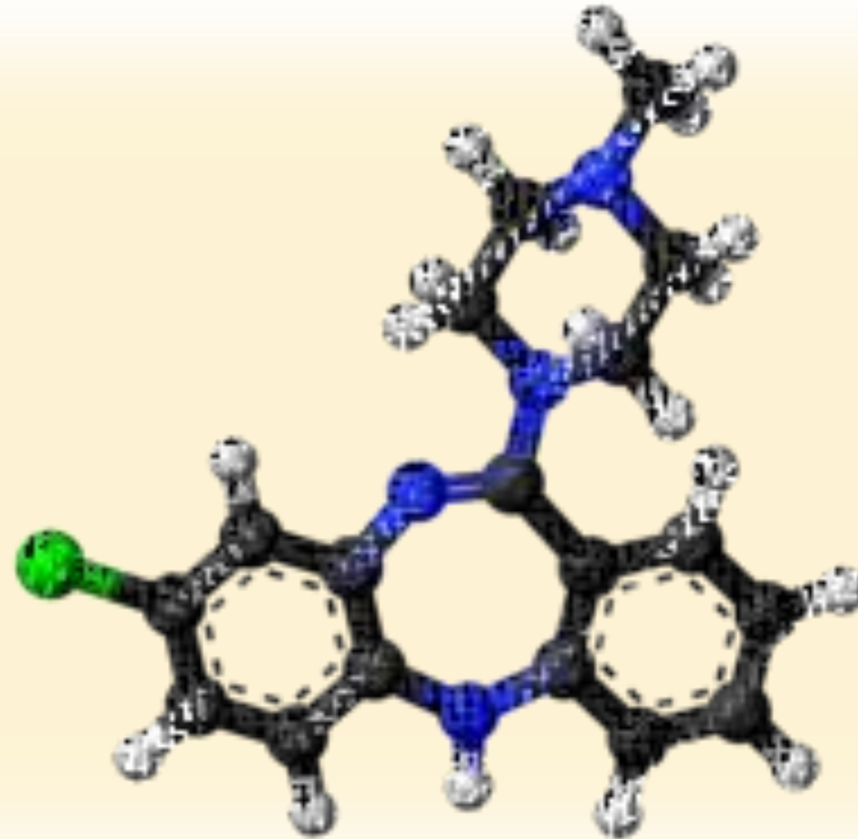
Clozapine-induced Gastrointestinal Hypomotility (CIGH)



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What is Clozapine?

- Chemically a dibenzodiazepine – Atypical antipsychotic (first atypical)
- Treatment-resistant schizophrenia / Psychosis in Parkinson's Disease
- Complex pharmacology – D1-D4, 5-HT, H, M, A
- Initiation and continuation only by specialist – special monitoring
- Denzapine®, Clozaril®, Zaponex®

(PubChem; BNF)

Clozapine's journey through history

- 1956-1959 clozapine is identified and produced
- 1974, withdrawal of clozapine due to agranulocytosis
- 1989, re-introduction of clozapine and MHRA/FDA approval (Clozaril® brand)
- 2022, Treatment-resistant schizophrenia / Psychosis in Parkinson's Disease (BNF)

(Hippius, 1999)

Clozapine's adverse effects

- Dyscrasias (neutropenia/leucopoenia)
- Weight gain
- Glucose tolerance – Diabetes Mellitus
- Drowsiness, Dizziness
- EEG changes – Decrease in seizure threshold
- Tachycardia and postural hypotension (with/without syncope)
- Myocarditis, cardiomyopathy
- Hypersalivation
- Aspiration pneumonia

- Constipation
- Nausea/vomiting

Gastrointestinal Hypomotility?

- Intestinal obstruction/paralytic ileus/faecal impaction
- Megacolon, intestinal infarction/ischaemia, diarrhoea, abdominal discomfort/heartburn/dyspepsia, colitis

(SmPC)

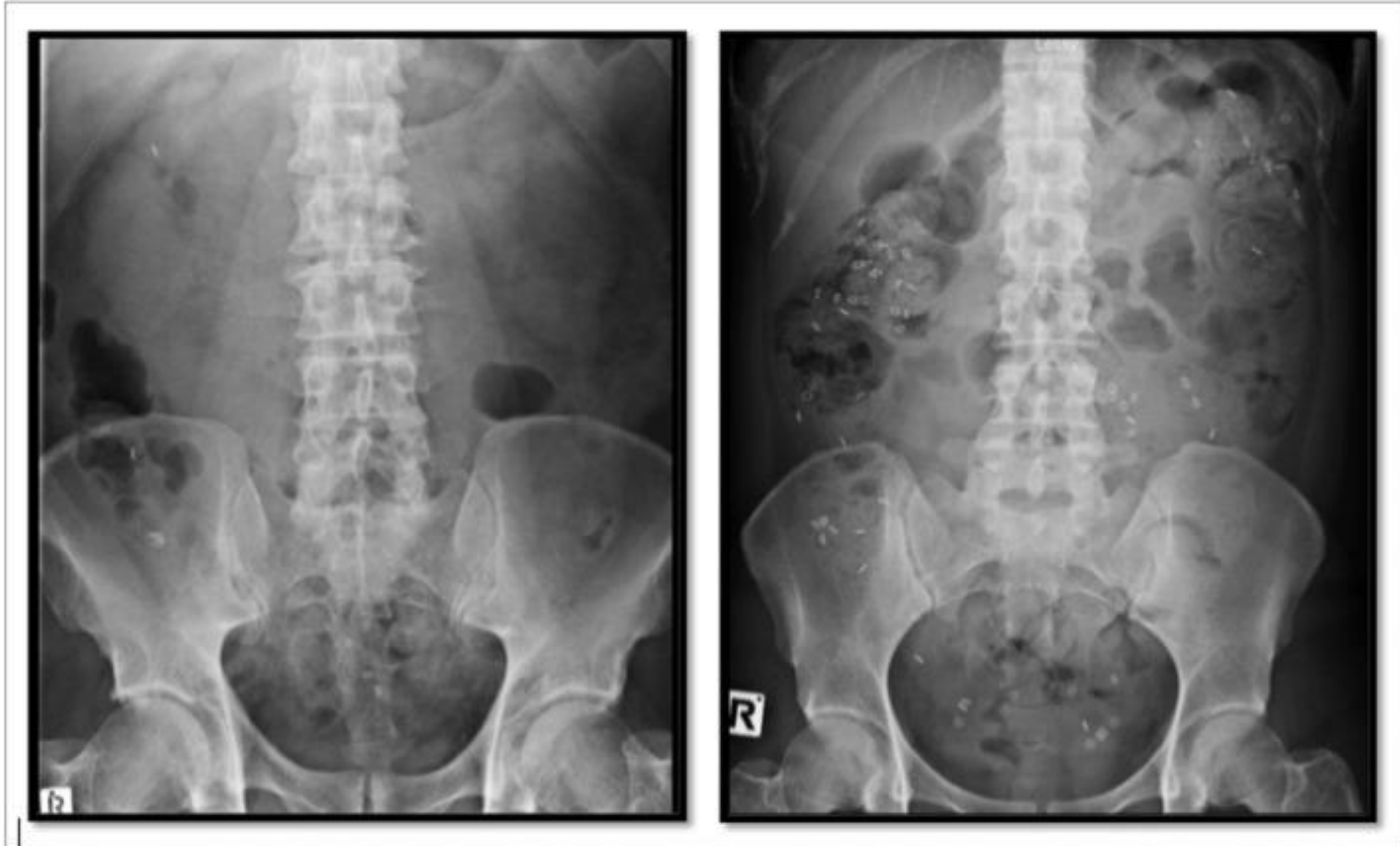
CIGH – ‘slow gut’

Gastrointestinal Hypomotility refers to the compromised contractile forces of the gastrointestinal tract, which can be either inherited or acquired

- Delayed transit through the gastrointestinal tract
- May occur anywhere from the oesophagus to the rectum
- Material takes 4 times longer to pass through the colon
- Occurs in up to 80% of clozapine patients regardless of demographic factors or treatment duration
- CIGH severity is correlated with clozapine plasma levels.

(Bielefeldt, Tuteja & Nusrat, 2016; Every-Palmer et al., 2016)

CIGH – ‘slow gut’



(Every-Palmer et al., 2016)

CIGH symptomatology

- Constipation
- Dyspepsia
- Dysphagia
- Abdominal pain/cramps
- Distended abdomen or bloating
- Fever
- Nausea
- Overflow diarrhoea
- Faeces-like smelling breath
- Faecal vomiting

(Every-Palmer et al., 2008)

ClGH serious manifestations

- Severe constipation
- Toxic megacolon
- Dysphagia
- Intestinal obstruction
- Faecal impaction
- Ischaemia
- Perforated bowel
- Aspiration
- Gastroparesis
- Paralytic ileus

(Cohen, 2017;
Every-Palmer & Ellis 2017)

MHRA 2017

- August 2017, a Coroner investigating a death raised concerns to the MHRA that healthcare professionals might have a lack of awareness about the risk of pseudo-obstruction or paralytic ileus and their fast onset

- Impaired intestinal peristalsis

- 370 Yellow Card reports of gastrointestinal obstruction associated with clozapine between 3 August 1993 and 11 September 2017. In this time period, there have also been 135 reports of faecaloma and 86 of paralytic ileus

MHRA 2017 – Message for prescribers

Pay the attention required for patients at risk of constipation, including those:

- receiving medications known to cause constipation (especially those with anticholinergic properties such as some antipsychotics, antidepressants and antiparkinsonian treatments)
- with a history of colonic disease or a history of lower abdominal surgery
- aged 60 years and older

Clozapine is contraindicated in patients with paralytic ileus!

It is vital that constipation is recognised early and actively treated!

Constipation

- Fewer than 3 bowel movements per week
- Hard, dry, small or lumpy stools and may be abnormally small or large (n. 1-2 in the Bristol Stool Scale)
- Painful or difficult to pass stools

(Longstreth et al., 2006)

- Problematic defacation because of infrequent and/or hard stools, difficulty passing stools (often involving straining), or the sensation of incomplete emptying or anorectal blockage

in practice

- Passage of stools less frequently than the person's normal pattern

(NICE)

Diagnosis of Constipation

Adults

- Bowel movements less than three times a week
- Daily bowel movements but associated symptoms such as excessive straining
- Lower abdominal pain or discomfort, distension, or bloating
- Passage of stools less frequently than the person's normal pattern.

Elderly

- Confusion or delirium, functional decline
- Nausea or loss of appetite
- Overflow diarrhoea
- Urinary retention

Faecal loading/impaction

- Hard, lumpy stools, which may be large and infrequent, or small and relatively frequent
- Use of manual methods to extract faeces
- Overflow faecal incontinence, or loose stool

(NICE)

The pharmacology behind CIGH

Anticholinergic action

- M3 receptor in the gut peripheral innervation
- Inhibition of the GI smooth muscle contraction
- Delayed intestinal transit

Antiserotoninergic action

- 5-HT3 antagonism in the gut wall
- Affecting the gut-brain axis
- Discouraging peristaltic reflex and intraluminal secretions
- Reduced motility

Antiserotoninergic action - Nociception

- Inhibition of visceral nociception
- Distention
- Distorted perception of bowel function
- Lack of pain

(Handley et al., 2022; Shirazi et al., 2016)

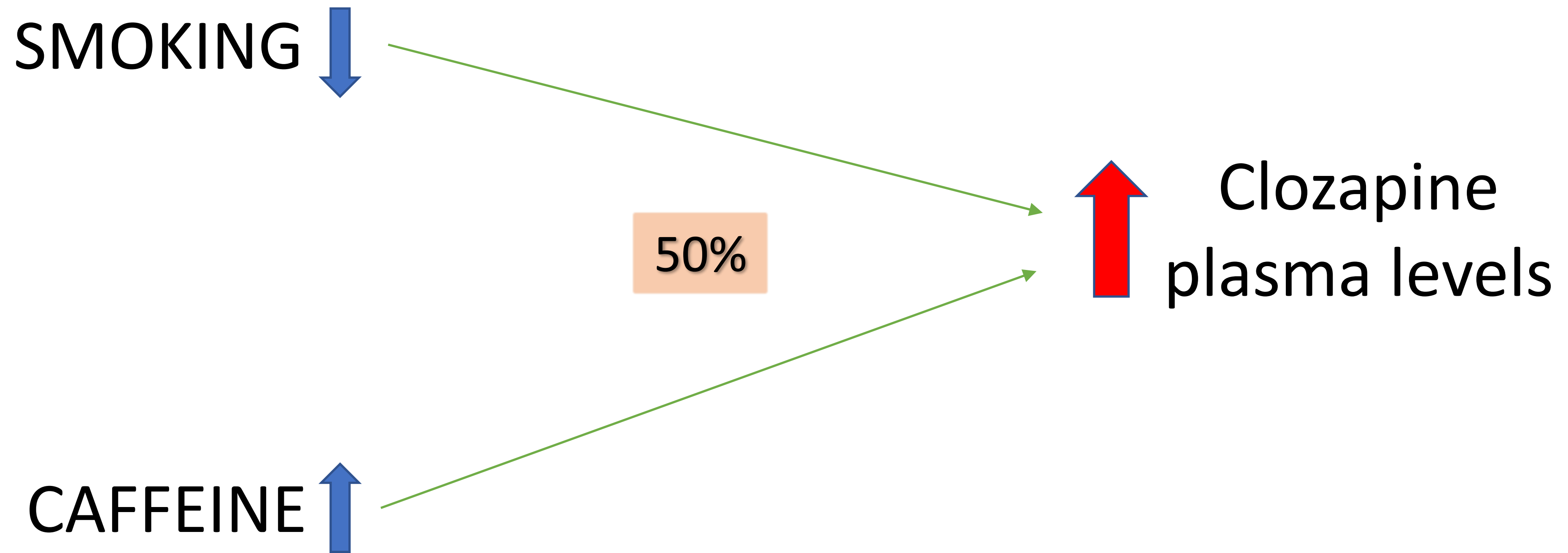
Potentially detrimental factors

- Other medications which could contribute to constipation (anticholinergics, opioids etc.)
- High clozapine plasma levels (high clozapine dose, smoking, and caffeine)
- Poor diet (at least 18-30g of fibre per day)
- Poor fluid intake (at least 1.5-2.0L per day)
- Lack of physical activity (at least 150mins per week)

Male sex	Hypothyroidism
Increasing age	Diabetes
Diaphoresis	Obesity
Hypercalcaemia	Parkinson's Disease
Gastrointestinal disease	Multiple Sclerosis
Poor bowel habit	

(Taylor et al., 2021;
HPFT, Clozapine Policy)

Potentially detrimental factors



(Taylor et al., 2021)

Some stats

- CIGH occurs in up to 80% of clozapine patients
- Constipation will manifest in up to 60% of clozapine treated patients

For every 1000 clozapine-treated patients

- 300-600 will suffer constipation
- At least 4 will develop serious gastrointestinal complications (i.e., bowel obstruction)
- At least 1 will die

- CIGH may occur at any time, although patients are more vulnerable during the first 4 months of clozapine treatment.

- THREE times more clozapine-treated patients die due to the consequences of CIGH and constipation than agranulocytosis. Yet, mandatory monitoring covers only for the latter

(Emery-Palmer et al., 2016; Emery-Palmer & Ellis, 2017)

Some Intellectual Disabilities (ID) stats

The Learning Disability Mortality Review (LeDeR) found the following:

- 23% of deaths identified constipation as a long-term health problem for the LD population
- 33% of the LD population studied were on prescribed laxatives

The Public Health Education (PHE) Guidance for constipation states:

- 59.8% of people with profound intellectual and multiple disabilities have been reported with constipation as a health issue, and 65.0% had been prescribed laxatives in the previous year
- In one year, 18.8% of people with Down syndrome were prescribed laxatives

Causes

General population

- Inadequate diet and fluid intake
- Reduced mobility and lack of exercise
- Side effects of certain medications
- Anxiety or depression

ID population

- Poor diet
- Further reduced physical mobility
- Iatrogenic

- Cerebral Palsy
- Down Syndrome
- Hypothyroidism
- Diabetes

Environmental contributors in ID

- Inappropriate toileting facilities
- Ignoring the urge to pass stools can cause constipation (potty trained when young?)
- Lack of privacy or time to use them can cause constipation
- Disruption in someone's routine or changes to their care or environment

(PHE, 2016)

Warning signs and symptoms

Moderate to severe abdominal pain lasting over an hour or any abdominal pain lasting over an hour and:

- Absent or high pitched bowel sounds
- Abdominal dilation
- Temperature/fever
- Blood or mucus in faeces
- Weight loss
- Overflow diarrhoea
- Vomiting

Immediate attention by a gastroenterologist and/or Emergency Department

(HPFT, Clozapine Policy)

Pharmacological approach and laxatives

Type	Mechanism of action	Examples	Place in CIGH and clozapine constipation
Stimulant laxatives	Increase gastrointestinal peristalsis, hence motility	• Sennosides • Sodium picosulfate • Bisacodyl	1st line in combination with an osmotic laxative or stool softener
Stool softeners	Encourage water permeation into the bowel	• Sodium Docusate	In combination with a stimulant laxative when treating constipation
Osmotic laxatives	Hypertonic increase in stool water	• Polyethylene Glycol (PEG) aka macrogol • Lactulose • Milk of magnesia • Sorbitol	In combination with a stimulant laxative when treating constipation
Prokinetic agents	Increase gastrointestinal peristalsis, hence motility	• Prucalopride • Lubiprostone	When conventional laxatives fail
Cholinergic medications	May counteract clozapine's anticholinergic effect	• Betanechol	Consider in refractory constipation, after consulting gastroenterologist
Bulk-forming laxatives	Increase stool bulk when taken with water	• Methylcellulose • Psyllium • Calcium Polycarbophil • Bran	Preventive measure only. May worsen the condition and should be avoided in CIGH

Review all medications that may impact on the constipation and (de)prescribe accordingly and when clinically appropriate to optimise treatment and healthcare outcomes

(Emery-Palmer et al., 2008; NICE, CKS 2021; Poetter & Steward, 2013; Thomas et al., 2018)

HPFT pharmacological treatment algorithm

1st Choice:

Stimulant laxative and Stool softener combination (e.g., sennosides 7.5mg-15mg OD and sodium docusate 100mg three times daily up to 500mg a day)

2nd Choice:

Osmotic laxatives (e.g., macrogol 3350 twice daily; lactulose 10-30mLs twice daily both up to their maximum licensed doses)
These may be used as monotherapy or in addition to the stimulant & stool softener combination

Remember: If diarrhoea develops, rule out overflow diarrhoea prior to reducing the regular laxatives!

(HPFT, Clozapine Policy)

Patient – Clinician communication issues and transfer of care

- Even with severe CIGH manifestation some patients will not experience symptoms (and hence they will not complain of them)
- Frequently, patients DO NOT report CIGH or constipation

- Transfer of care issues and awareness of any clinical teams involved
- Patients may not mention they are on clozapine

Increased fatality risk of this serious clozapine's side-effect

Health Literacy

- Consultation 50% lost information 50% remaining information is misinterpreted
- Jargon (are you constipated? VS How many times per week do you visit the toilet?; Fresh blood? VS Red blood?; Read leaflet? VS Explain the leaflet in a nutshell simply?)
- Teach-back technique (did you understand that? VS Can you explain what are you agreeing to, please show me how do you use the inhaler, can you explain to me your disease?
- Chunk and Check information
- Pictures and Diagrams (Stool Scales!)
- Simple Language
- Ask patients if help is needed with filling forms

(NHS Scotland)

Health Literacy for people with Intellectual Disabilities

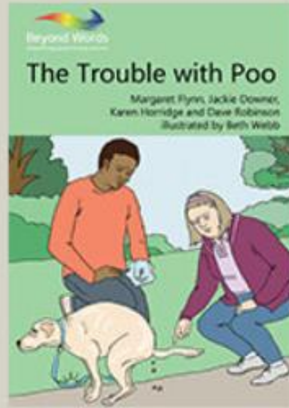
- Curative education and nursing research suggests that people with intellectual disabilities have major problems in the field of language (reduced ability to communicate is characterized by short and incomplete sentences and altered semantics)

- Training to nurses or caregivers to be competent in providing understandable health-related information in a corresponding manner.

- Proactively seek feedback from people with intellectual disabilities and their representatives regarding the communication behaviour of health professionals towards them

- In the intellectual disability population audio or video information may significantly improve the understanding and the confidence in following the health recommendations

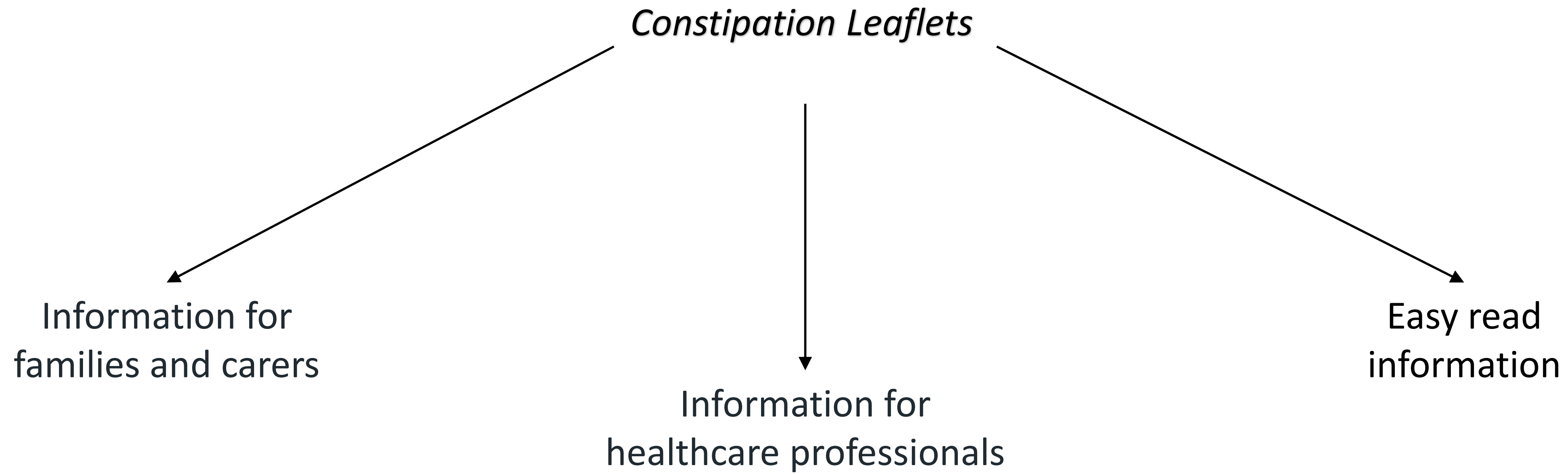
*(*Geukes, Bröder, & Latteck, 2019; RSPH)



a look inside

(Beyond Words)

Constipation and people with a learning disability



(NHS England)

BRISTOL STOOL CHART

1 **SEVERE CONSTIPATION**
Separate hard lumps

2 **MILD CONSTIPATION**
Lumpy and sausage like

3 **NORMAL**
A sausage shape with cracks in the surface

4 **NORMAL**
Like a smooth, soft sausage or snake

5 **LACKING FIBRE**
Soft blobs with clear-cut edges

6 **MILD DIARRHEA**
Mushy consistency with ragged edges

7 **SEVERE DIARRHEA**
Liquid consistency with no solid pieces

(Lewis & Heaton, 1997; Illustration taken from HPFT CIGH e-learning)

Take-home messages

- CIGH and constipation constitute serious adverse events
- Remember the statistics and the risk
- Learn the patient’s responsible clinical teams and liaise with them
- Remember smoking, remember caffeine!
- Encourage core principles of well-being
- Patients may not experience symptoms
- Patients do not always report/complain
- Health Literacy
- Assertive use of laxatives
- Adapt treatment and communication to the needs of the individual

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Questions?