Medicines Adverse Reactions Committee

Meeting date	10/06/2021	Agenda item	3.2.2
Title	**Misuse of stimulant laxatives**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice

Active ingredient	**Product name**	**Sponsor**
Bisacodyl	Bisacodyl Laxative (Pharmacy Health) tablet	PSM Healthcare Limited trading as API Consumer Brands
	Dulcolax tablet	Sanofi-Aventis New Zealand Limited
	Dulcolax Suppository	Sanofi-Aventis New Zealand Limited
	*Lax-Suppositories Bisacodyl	AFT Pharmaceuticals Limited
	*Lax-Tab tablet	AFT Pharmaceuticals Limited
Docusate sodium	*Coloxyl tablet	Pharmacy Retailing (New Zealand) Limited trading as Healthcare Logistics
Docusate sodium + sennosides	Coloxyl with Senna tablet	Pharmacy Retailing (New Zealand) Limited trading as Healthcare Logistics
	*Laxsol tablet	Pharmacy Retailing (New Zealand) Limited trading as Healthcare Logistics
Glycerol	*Glycerol Suppositories	PSM Healthcare Limited trading as API Consumer Brands
Sennosides	*Senokot tablet	Reckitt Benckiser (New Zealand) Limited
Sodium picosulfate	Dulcolax SP Drops oral solution	Sanofi-Aventis New Zealand Limited

PHARMAC funding	***Pharmaceutical Schedule** Lax-Tab tablets, Lax-Suppositories Bisacodyl, Coloxyl tablets and Glycerol Suppositories are fully-funded only on a prescription. Senokot tablets are part-funded.
Previous MARC meetings	Misuse of stimulant laxatives has not been discussed previously.
International action	Following a national safety review published in August 2020, the MHRA in the UK has introduced pack size restrictions, revised recommended ages for use and new safety warnings (see section 3.1).
Prescriber Update	No articles.
Classification	See section 2.5.
Usage data	See section 2.4.
Advice sought	**The Committee is asked to advise whether:** • the evidence of the misuse of stimulant laxatives in New Zealand warrants taking further action. If further action is recommended, options could include: • applying to the MCC to reclassify stimulant laxatives • updating the Label Statements Database to include warnings for stimulant laxatives • communicating to healthcare professionals (eg, an article in *Prescriber Update*).

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1 PURPOSE

In August 2020, the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK published their benefit-risk review of over-the-counter (OTC) stimulant laxatives (orally and rectally administered) [1]. Following this review, the MHRA introduced [2]:

- pack size restrictions
- revised recommended ages for use
- new safety warnings.

The purpose of this paper is to review the information on the misuse of stimulant laxatives in New Zealand.

2 BACKGROUND

2.1 Stimulant laxatives

Laxatives are used to treat constipation in adults and children.

The New Zealand Formulary divides laxatives into five main groups: bulk-forming laxatives, stimulant laxatives, faecal softeners, osmotic laxatives and bowel cleansing preparations [3].

Stimulant laxatives increase intestinal motility, helping the muscles move stools along the gut [1]. They take 6 to 12 hours to work [1].

Stimulant laxatives often cause abdominal cramp [3]. They should be avoided in intestinal obstruction [3]. Excessive use of stimulant laxatives can cause diarrhoea and related effects such as hypokalaemia [3]. However, prolonged use may be justifiable in some circumstances [3].

Treatment with a laxative is only recommended if lifestyle measures, such as eating plenty of fibre, drinking enough fluid and exercising regularly do not work well [4].

Children often need laxatives for months to years, rather than weeks [5].

2.2 Constipation

Constipation is common [1].

Constipation may be described as defaecation that is unsatisfactory due to infrequent stools, difficulty passing stools or a sensation of complete evacuation [6].

Constipation is a symptom not a disease and its exact cause is not fully understood [1]. It may result from underlying conditions such as [7]:

- irritable bowel syndrome
- dehydration
- diabetes
- neurological conditions (eg, Parkinson's, multiple sclerosis)
- electrolyte disorders such as hypercalcaemia or hypokalaemia
- depression and other psychiatric disorders
- coeliac disease
- hypothyroidism
- gastrointestinal obstruction (eg, due to tumours)
- damage to pelvic floor muscles (eg, after childbirth)
- anatomical or physiological causes.

2.2.1 Managing constipation in adults

bpac^{nz} recommends a systematic approach to managing constipation, as follows [6]:

1. identify constipation and the predominant symptoms

2. conduct a physical examination and exclude red flags
3. treat any reversible causes
4. recommend lifestyle changes
5. initiate laxatives and monitor the response.

Stimulant laxatives are recommended in combination with an osmotic laxative for patients with soft stools that remain difficult to pass [6]. Prophylactic stimulant laxatives (eg, docusate with senna or bisacodyl) are recommended to prevent opioid-induced constipation [6].

The main adverse effects of stimulant laxatives summarised by bpac^{nz} are cramping, bloating, nausea and electrolyte disturbances [6]. There are some concerns about long-term use causing atonic colon due to smooth muscle or myenteric plexus damage, however these appear to be rare [6].

2.2.2 Managing constipation in children

Health Navigator recommends preventing and easing constipation in children initially by [8]:

1. increasing the fibre content of the child's diet by giving them more fruit (either fresh or dried) and vegetables
2. limit foods that have little or no fibre, such as ice cream, cheese, meat and processed foods
3. increasing the amount of water the child drinks by giving them water at each meal time and extra water when it is hot
4. encouraging a regular toileting routine such as sitting on the toilet for five minutes, once or twice a day
5. encouraging daily exercise and physical activity which helps stimulate normal bowel function
6. (for children over 12 months of age) give one glass of undiluted apple juice or kiwifruit juice

If the above does not work, medicines such as laxatives may be needed [8]. Parents or caregivers are advised to talk to a doctor or pharmacist for advice on a suitable laxative for a child [8].

Despite the widespread use of laxatives to manage constipation in children, there is a lack of evidence to support this practice [8].

Comments:

There is also a bpac^{nz} Best Practice Article on constipation, which includes a summary of laxative misuse and eating disorders which states [9]:

'Misuse of laxatives can occur in people with eating disorders such as anorexia and bulimia but also in normal or overweight persons. Laxative misuse in the UK has been reported at 2% in secondary school students and 13% in college students. All healthcare providers need to be aware of the possibility of misuse, especially pharmacists, as many laxatives can be purchased easily without prescription.'

It is important to note that the Best Practice Journal article is over 13 years old and may be out of date.

The overall advice is patients should talk to their doctor or pharmacist if they think they need a laxative.

2.3 Misuse

Misuse is difficult to define. Prescription medicine misuse is generally described as 'using a medicine in a manner or dose other than prescribed' [10].

Laxatives have been used for health purposes for over 2,000 years, and for much of that time abuse or misuse of laxatives has occurred [11].

Individuals who abuse or misuse laxatives can generally be categorised into one of the following four groups [11].

1. Individuals suffering from an eating disorder such as anorexia or bulimia nervosa. The prevalence of laxative abuse has been reported to range from approximately 10% to 60% of individuals in this group

(studies investigating the prevalence of laxative abuse are complicated – almost all investigations rely on self-report and may have used different criteria to define laxative abuse or misuse).
2. Individuals who are generally middle aged or older who begin using laxatives when constipated but continue to overuse them. This pattern may be promulgated on certain beliefs that daily bowel movements are necessary for good health.
3. Individuals engaged in certain types of athletic training, including sports with set weight limits.
4. Surreptitious laxative abusers who use the drugs to cause factitious diarrhoea and may have a factitious disorder.

The most frequently abused or misused group of laxatives are stimulant laxatives [11].

Comments:

This section was taken from an article published in 2010 so some of the information provided may be out of date.

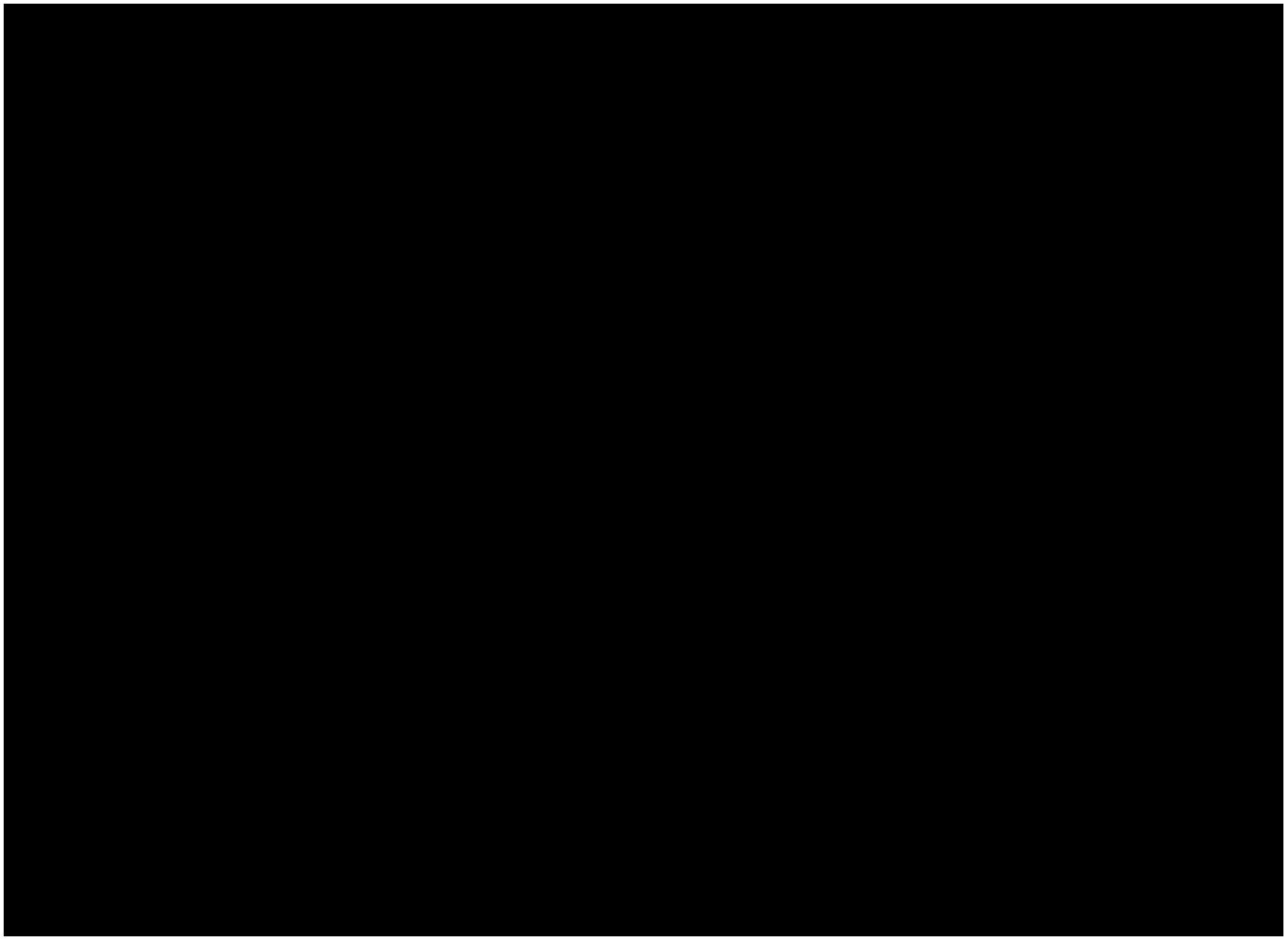
The Pharmaceutical Society of New Zealand commented via email that there is potential for misuse of stimulant laxatives here in New Zealand. All pharmacists cover some aspects of this in their training.

[redacted]

Misuse of stimulant laxatives is discussed further in section 3.2.

2.4 Usage

Table 1 shows the sales data provided by the sponsors from the last five years.



[redacted]

Comments:

The sponsors were asked to provide annual sales data for the last five years. Any data missing from the table was not provided by the sponsor.

[redacted]

2.5 Classification

Table 2 below shows the current classification of stimulant laxatives.

Table 2: Classification of stimulant laxatives

Active ingredient	Classification
Bisacodyl	Pharmacy-only
Docusate sodium	Not listed in the First Schedule to the Medicines Regulations 1984
Glycerol	Not listed in the First Schedule to the Medicines Regulations 1984
Sennosides	Pharmacy-only
Sodium picosulfate	Restricted; in oral preparations for bowel cleansing prior to diagnostic, medical or surgical procedures
	Pharmacy-only; in oral laxative preparations

Source: Medsafe. 2021. *Classification Database* 28 April 2021. URL: www.medsafe.govt.nz/profs/class/classintro.asp (accessed 10 May 2021).

Comments:

Medicines not listed in the First Schedule to the Medicines Regulations 1984 and amendments are deemed to be unclassified and are referred to as general sales medicines. These medicines may be sold from any outlet (eg, a supermarket).

2.6 New Zealand data sheets and labels

The following tables present the product information in the New Zealand data sheets and / or consumer medicine information (CMI) regarding indication, dose, warnings and precautions, and undesirable effects. Where a data sheet or CMI was not available, the information is taken from the product label or leaflet provided by the sponsor (see Annex 1 for the labels and Annex 2 for the leaflet).

2.6.1 Bisacodyl

Table 3: Product information for Bisacodyl Laxative

Product name	Bisacodyl Laxative (Pharmacy Health)
Dosage form	5 mg enteric coated tablet
Pack size	50 and 200
Approval date	15 February 2018
Indication(s)	Bisacodyl Laxative is mainly used for the treatment of constipation. Under medical supervision, Bisacodyl Laxative can be used for the evacuation of the bowel before a radiological examination or as an enema alternative.
Dose	Bisacodyl Laxative tablets should be taken as needed to relieve constipation. It is recommended to start with the lowest dose. The dose may be adjusted up to the maximum recommended dose to produce regular stools. The maximum daily dose should not be exceeded. Adults and children over 10 years: one or two tablets at night. Children 4 to 10 years: one tablet at night. Bisacodyl Laxative tablets are not recommended in children under 4 years of age.
Warnings and precautions	Do not take antacids within one hour of taking Bisacodyl Laxative. Prolonged use of a laxative is undesirable and may lead to dependence.
Undesirable effects	All medicines carry some risks and all possible risks may not be known at this stage despite thorough testing. Your doctor or pharmacist has weighed the risks of using Bisacodyl Laxative tablets against the benefits they expect it will have for you. Ask for the advice of your doctor or pharmacist if you have any concerns about the effects of using this medicine. The following side effects of Bisacodyl Laxative tablets may occur: • colitis • abdominal discomfort • abdominal cramps • abdominal pain • nausea • vomiting • diarrhoea • anorectal discomfort • blood in the stools • dehydration • dizziness • fainting. Abdominal pain and diarrhoea are the most commonly reported side effects. These side effects are usually mild and short lived. Tell your doctor immediately or go to casualty at your nearest hospital if you notice any of the following: • rash, itching or hives on the skin, • swelling of the face, lips, tongue or other parts of the body, • shortness of breath, wheezing or trouble breathing. These are the symptoms of life threatening allergic (anaphylactic) reactions. These are serious side effects. You may need urgent medical attention or hospitalisation. Serious side effects are rare. Other side effects not listed above may also occur in some patients. Tell your doctor if you notice anything else that is making you feel unwell. Do not be alarmed by this list of possible side effects. You may not experience any of them.

Sources:

1. Medsafe. 2019. *Medicines Product/Application Search*. URL: www.medsafe.govt.nz/regulatory/dbsearch.asp (accessed 11 May 2021).
2. PSM Healthcare Limited trading as API Consumer Brands. 2017. *Bisacodyl Laxative (Pharmacy Health) New Zealand Consumer Medicine Information* July 2017. URL: www.medsafe.govt.nz/Consumers/CMI/b/BisacodylLaxativePharmacyHealth.pdf (accessed 11 May 2021).
3. Annex 1 (labels 1a and 1b).

Table 4: Product information for Dulcolax

Product name	Dulcolax
Dosage form	5 mg enteric coated tablet
Pack size	30 and 100
Approval date	31 December 1969
Indication(s)	For the use in cases of constipation. In preparation for diagnostic procedures, in pre- and postoperative treatment and in conditions which require defecation, the use of DULCOLAX must be under medical supervision.
Dose	Adults and children over 10 years: 1 to 2 coated tablets at night. Children 4 to 10 years: One coated tablet at night. Children under 4 years: Not recommended.
Warnings and precautions	As with all laxatives, DULCOLAX should not be taken on a continuous daily basis for extended periods without investigating the cause of constipation. Prolonged excessive use may lead to fluid and electrolyte imbalance and hypokalaemia. Intestinal loss of fluids can promote dehydration. Symptoms may include thirst and oliguria. In patients suffering from fluid loss where dehydration may be harmful (e.g. renal insufficiency, elderly patients) DULCOLAX should be discontinued and only be restarted under medical supervision. Stimulant laxatives including DULCOLAX do not help with weight loss. Patients may experience haematochezia (blood in stool) that is generally mild and self-limiting. Dizziness and/or syncope have been reported in patients who have taken DULCOLAX. The details available for these cases suggest that the events would be consistent with defecation syncope (or syncope attributable to straining at stool), or with a vasovagal response to abdominal pain related to the constipation and not necessarily to the administration of DULCOLAX itself. The use of suppositories may lead to painful sensations and local irritation, especially in patients with anal fissures and ulcerative proctitis. One coated tablet contains 33.2 mg lactose, resulting in 66.4 mg lactose per maximum recommended daily dose for treatment of constipation in adults and children over 10 years of age. For radiographic examination this will result in 132.8 mg per maximum recommended daily dose in adults. Patients with rare hereditary conditions of galactose intolerance (eg, galactosaemia) should not take this medicine. One coated tablet contains 23.4 mg sucrose (saccharose), resulting in 46.8 mg sucrose (saccharose) per maximum recommended daily dose for treatment of constipation in adults and children over 10 years of age. For radiographic examination this will result in 93.6 mg per maximum recommended daily dose in adults. Patients with the rare hereditary condition of fructose intolerance should not take this medicine. Prolonged use of laxatives is undesirable and may lead to dependence.
Undesirable effects	The most commonly reported adverse reactions during treatment are abdominal pain and diarrhoea. **Immune system disorders** Anaphylactic reactions, angioedema, hypersensitivity. **Metabolism and nutrition disorders** Dehydration. **Nervous system disorders** Dizziness, syncope. Dizziness and syncope occurring after taking bisacodyl appear to be consistent with a vasovagal response (eg, to abdominal spasm, defecation). **Gastrointestinal disorders** Abdominal cramps, abdominal pain, diarrhoea, vomiting, nausea, haematochezia (blood in stool), abdominal discomfort, anorectal discomfort, colitis including ischaemic colitis.

Sources:

1. Medsafe. 2019. *Medicines Product/Application Search*. URL: www.medsafe.govt.nz/regulatory/dbsearch.asp (accessed 11 May 2021).

2. Sanofi Aventis New Zealand Limited. 2021. *Dulcolax New Zealand Data Sheet* 11 March 2021. URL: www.medsafe.govt.nz/profs/Datasheet/d/dulcolaxtabsupp.pdf (accessed 12 May 2021).
3. Sanofi Aventis New Zealand Limited. 2021. *Dulcolax New Zealand Consumer Medicine Information* 11 March 2021. URL: www.medsafe.govt.nz/profs/Datasheet/d/dulcolaxtabsupp.pdf (accessed 12 May 2021).
4. Annex 1 (labels 2a and 2b).

Table 5: Product information for Dulcolax Suppository

Product name	Dulcolax Suppository
Dosage form	10 mg suppository
Pack size	6
Approval date	31 December 1969
Indication(s)	For the use in cases of constipation. In preparation for diagnostic procedures, in pre- and postoperative treatment and in conditions which require defecation, the use of DULCOLAX must be under medical supervision.
Dose	Adults and children over 10 years: One suppository (10mg). Do not coat the suppository in any lubricant such as paraffin oil or paraffin jelly. By warming the suppository in the hand before it is removed from the foil wrapper, sufficient lubrication will be produced. Insert into the rectum the pointed end first. Suppositories are usually effective in about 20 minutes (range 10 to 30 minutes). It is recommended to start with the lowest dose. The dose may be adjusted up to the maximum recommended dose to produce regular stools. The maximum daily dose should not be exceeded. Children aged 10 years or younger with chronic or persistent constipation should only be treated under the guidance of a physician.
Warnings and precautions	As with all laxatives, DULCOLAX should not be taken on a continuous daily basis for extended periods without investigating the cause of constipation. Prolonged excessive use may lead to fluid and electrolyte imbalance and hypokalaemia. Intestinal loss of fluids can promote dehydration. Symptoms may include thirst and oliguria. In patients suffering from fluid loss where dehydration may be harmful (e.g. renal insufficiency, elderly patients) DULCOLAX should be discontinued and only be restarted under medical supervision. Stimulant laxatives including DULCOLAX do not help with weight loss (see Section 5.1 Pharmacodynamic properties). Patients may experience haematochezia (blood in stool) that is generally mild and self-limiting. Dizziness and/or syncope have been reported in patients who have taken DULCOLAX. The details available for these cases suggest that the events would be consistent with defecation syncope (or syncope attributable to straining at stool), or with a vasovagal response to abdominal pain related to the constipation and not necessarily to the administration of DULCOLAX itself. The use of suppositories may lead to painful sensations and local irritation, especially in patients with anal fissures and ulcerative proctitis. One coated tablet contains 33.2 mg lactose, resulting in 66.4 mg lactose per maximum recommended daily dose for treatment of constipation in adults and children over 10 years of age. For radiographic examination this will result in 132.8 mg per maximum recommended daily dose in adults. Patients with rare hereditary conditions of galactose intolerance (eg, galactosaemia) should not take this medicine. One coated tablet contains 23.4 mg sucrose (saccharose), resulting in 46.8 mg sucrose (saccharose) per maximum recommended daily dose for treatment of constipation in adults and children over 10 years of age. For radiographic examination this will result in 93.6 mg per maximum recommended daily dose in adults. Patients with the rare hereditary condition of fructose intolerance should not take this medicine. Prolonged use of laxatives is undesirable and may lead to dependence.
Undesirable effects	The most commonly reported adverse reactions during treatment are abdominal pain and diarrhoea. **Immune system disorders** Anaphylactic reactions, angioedema, hypersensitivity.

	Metabolism and nutrition disorders Dehydration. **Nervous system disorders** Dizziness, syncope. Dizziness and syncope occurring after taking bisacodyl appear to be consistent with a vasovagal response (e.g., to abdominal spasm, defecation). **Gastrointestinal disorders** Abdominal cramps, abdominal pain, diarrhoea, vomiting, nausea, haematochezia (blood in stool), abdominal discomfort, anorectal discomfort, colitis including ischaemic colitis.

Sources:
1. Medsafe. 2019. *Medicines Product/Application Search*. URL: www.medsafe.govt.nz/regulatory/dbsearch.asp (accessed 11 May 2021).
2. Sanofi Aventis New Zealand Limited. 2021. *Dulcolax New Zealand Data Sheet* 11 March 2021. URL: www.medsafe.govt.nz/profs/Datasheet/d/dulcolaxtabsupp.pdf (accessed 12 May 2021).
3. Sanofi Aventis New Zealand Limited. 2021. *Dulcolax New Zealand Consumer Medicine Information* 11 March 2021. URL: www.medsafe.govt.nz/profs/Datasheet/d/dulcolaxtabsupp.pdf (accessed 12 May 2021).
4. Annex 1 (label 3).

Table 6: Product information for Lax-Suppositories Bisacodyl

Product name	Lax-Suppositories Bisacodyl
Dosage form	5 mg and 10 mg suppository
Pack size	10
Approval date	5 February 2015
Indication(s)	LAX-SUPPOSITORIES is mainly used for the treatment of constipation. Under medical supervision, LAX-SUPPOSITORIES can be used for the evacuation of the bowel before a radiological examination or as an enema alternative.
Dose	**Lax-Suppositories 5 mg:** Adults and children over 10 years: One or two suppositories inserted into the rectum. Children 4-10 years: One suppository inserted into the rectum. Use only on medical advice. Children under 4 years: Use only on medical advice. **Lax-Suppositories 10 mg:** Adults and children over 10 years: One suppository inserted into the rectum. Use of Lax-Suppositories 10 mg in children under 10 years should only be under medical advice.
Warnings and precautions	Do not use LAX-SUPPOSITORIES if you are allergic to bisacodyl or any of the other ingredients in LAX-SUPPOSITORIES. Before using LAX-SUPPOSITORIES, you must tell your doctor or pharmacist if you have, or have had any medical conditions including: • an anal fissure (painful tear in the lining of the anus) • ulcerative proctitis (inflammation of the rectum [back passage]). Suppositories may cause pain and local irritation, especially if you have an anal fissure (painful tear in the lining of the anus) or ulcerative proctitis (inflammation of the rectum). If you are uncertain as to whether you have, or have had any of these conditions, you should raise any concerns with your doctor or pharmacist. Before using LAX-SUPPOSITORIES, you must tell your doctor or pharmacist if you are taking any other medicines obtained with or without a doctor's prescription. In particular, you should tell your doctor or pharmacist if you are taking: • diuretics (medicines that increase urine volume) • corticosteroids • medicines which stimulate the heart e.g. digoxin.

	It is important to discuss this with your doctor or pharmacist because LAX-SUPPOSITORIES may not work as well in the presence of some other medicines or side effects may be increased. Prolonged use of a laxative is undesirable and may lead to dependence.
Undesirable effects	All medicines carry some risks and all possible risks may not be known at this stage despite thorough testing. Your doctor or pharmacist has weighed the risks of using LAX-SUPPOSITORIES against the benefits they expect it will have for you. Ask for the advice of your doctor or pharmacist if you have any concerns about the effects of using this medicine. The following side effects of LAX-SUPPOSITORIES may occur: • colitis • abdominal discomfort • abdominal cramps • abdominal pain • nausea • vomiting • diarrhoea • anorectal discomfort • blood in the stools • dehydration • dizziness • fainting. Abdominal pain and diarrhoea are the most commonly reported side effects. These side effects are usually mild and short lived. Tell your doctor immediately or go to casualty at your nearest hospital if you notice any of the following: • rash, itching or hives on the skin • swelling of the face, lips, tongue or other parts of the body • shortness of breath, wheezing or trouble breathing. These are the symptoms of life-threatening allergic (anaphylactic) reactions. These are serious side effects. You may need urgent medical attention or hospitalisation. Serious side effects are rare. Other side effects not listed above may also occur in some patients. Tell your doctor if you notice anything else that is making you feel unwell. Do not be alarmed by this list of possible side effects. You may not experience any of them.

Sources:
1. Medsafe. 2019. *Medicines Product/Application Search*. URL: www.medsafe.govt.nz/regulatory/dbsearch.asp (accessed 11 May 2021).
2. Annex 1 (labels 4a and 4b).
3. Annex 2 (AFT Pharmaceuticals Limited. 2015. *Lax-Suppositories Patient Information Leaflet* 20 January 2015. Auckland: AFT Pharmaceuticals Limited).

Table 7: Product information for Lax-Tab

Product name	Lax-Tab
Dosage form	5 mg enteric coated tablet
Pack size	50 and 200
Approval date	12 September 2002
Indication(s)	Provides relief of constipation
Dose	Adults and children over 10 years: One or two tablets at night if needed. Children 6-10 years: One tablet at night if needed.
Warnings and precautions	Not recommended for use in children under 6 years. Patients requiring laxatives should drink plenty of water and increase the fibre in their diet. Prolonged use of laxatives is undesirable and may lead to dependence. If symptoms persist seek medical advice. Do not take Lax-Tab within 2 hours of taking antacids. Tablets contain lactose and sucrose.

Undesirable effects	Not listed in the information provided.

Sources:
1. Medsafe. 2019. *Medicines Product/Application Search*. URL: www.medsafe.govt.nz/regulatory/dbsearch.asp (accessed 11 May 2021).
2. Annex 1 (labels 5a and 5b).

2.6.2 Docusate sodium

Table 8: Product information for Coloxyl

Product name	Coloxyl
Dosage form	50 mg and 100 mg tablet
Pack size	100
Approval date	31 December 1969
Indication(s)	Relief of constipation
Dose	Adults and children over 12 years: Take 2 or 3 tablets twice daily.
Warnings and precautions	Not recommended for use in children under 12 years. Drink plenty of water. Increase fibre in your diet except in cases of medication-induced constipation. Do not take with other medicines or liquid paraffin, unless advised by a doctor. If symptoms persist, seek advice from a health care practitioner. Prolonged use is not recommended and may lead to dependence. Contains benzoates and gluten.
Undesirable effects	Not listed in the information provided.

Sources:
1. Medsafe. 2019. *Medicines Product/Application Search*. URL: www.medsafe.govt.nz/regulatory/dbsearch.asp (accessed 11 May 2021).
2. Annex 1 (labels 6a and 6b).

2.6.3 Docusate sodium + sennosides

Table 9: Product information for Coloxyl with Senna

Product name	Coloxyl with senna
Dosage form	50 mg with 8 mg sennosides film coated tablet
Pack size	30 and 90
Approval date	18 March 1988
Indication(s)	Relief of constipation
Dose	Adults and children over 12 years. Take 1 or two tablets at night. Increase up to 4 tablets if necessary.
Warnings and precautions	Not recommended for use in children under 12 years. Drink plenty of water. Do not use when abdominal pain, nausea or vomiting are present, or if you develop diarrhoea. Do not take with other medicines or liquid paraffin, unless advised by a doctor. If you are pregnant or breastfeeding, seek the advice of a healthcare professional before taking this product. Increase fibre in your diet except in cases of medication-induced constipation. If symptoms persist, seek advice from a health care practitioner. Prolonged use is not recommended and may lead to dependence or serious bowel problems.
Undesirable effects	Not listed in the information provided.

Sources:

1. Medsafe. 2019. *Medicines Product/Application Search*. URL: www.medsafe.govt.nz/regulatory/dbsearch.asp (accessed 11 May 2021).
2. Annex 1 (labels 7a and 7b).

Table 10: Product information for Laxsol

Product name	Laxsol
Dosage form	50 mg with 8 mg sennosides film coated tablet
Pack size	200
Approval date	7 February 2002
Indication(s)	Treatment of constipation.
Dose	Adult dosage: Take 1 or 2 tablets at night. Increase up to 4 tablets if required.
Warnings and precautions	Drink plenty of water and increase fibre in diet. Prolonged use of any laxative is undesirable and may lead to dependence. Consult your doctor if constipation persists.
Undesirable effects	Not listed in the information provided.

Sources:
1. Medsafe. 2019. *Medicines Product/Application Search*. URL: www.medsafe.govt.nz/regulatory/dbsearch.asp (accessed 11 May 2021).
2. Annex 1 (label 8).

2.6.4 Glycerol

Table 11: Product information for Glycerol Suppositories

Product name	Glycerol Suppositories
Dosage form	3.6 g suppository
Pack size	20
Approval date	9 June 2011
Indication(s)	Relief of acute and temporary constipation in adults.
Dose	Take the recommended dose as directed by your doctor or pharmacist.
Warnings and precautions	Do not use Glycerol Suppositories if you have an allergy to any medicine containing glycerol (or glycerine), gelatin, methyl hydroxybenzoate. Do not use Glycerol Suppositories without medical advice if you believe you have an intestinal obstruction or rectal bleeding. Do not use Glycerol Suppositories without medical advice if you are pregnant, or plan to become pregnant, or are breast-feeding. Prolonged use of Glycerol Suppositories is not recommended. If your symptoms persist, consult your doctor.
Undesirable effects	Not listed in the information provided.

Sources:
1. Medsafe. 2019. *Medicines Product/Application Search*. URL: www.medsafe.govt.nz/regulatory/dbsearch.asp (accessed 11 May 2021).
2. Annex 1 (label 9).

2.6.5 Sennosides

Table 12: Product information for Senokot

Product name	Senokot
Dosage form	7.5 mg tablet
Pack size	100
Approval date	9 July 1963
Indication(s)	Relief from occasional or non-persistent constipation.
Dose	Adults and children over 12 years: Take 2-4 tablets daily. Do not exceed 4 tablets daily except on doctor's advice. Doses of more than 4 tablets are best divided and taken morning and night, or as prescribed by your doctor. Drink plenty of water and increase fibre in your diet.
Warnings and precautions	If symptoms persist seek advice from your healthcare professional. For short term use only. Do not use for longer than a week unless advised by your healthcare professional. Prolonged use may cause serious bowel problems. Keep out of reach of children. Not recommended for use by children under 12 years of age. Do not use if abdominal pain, nausea or vomiting are present or if you develop diarrhoea. Unless a doctor has told you to, do not use if you are pregnant or breastfeeding. Contains lactose.
Undesirable effects	Not listed in the information provided.

Sources:
1. Medsafe. 2019. *Medicines Product/Application Search*. URL: www.medsafe.govt.nz/regulatory/dbsearch.asp (accessed 11 May 2021).
2. Annex 1 (label 10).

2.6.6 Sodium picosulfate

Table 13: Product information for Dulcolax SP Drops

Product name	Dulcolax SP Drops
Dosage form	7.5 mg/mL oral solution
Pack size	30 mL
Approval date	24 August 2017
Indication(s)	To treat constipation.
Dose	Adults and children over 10 years: Initially 10 drops (5 mg) at night. Increase up to 20 drops (10 mg) only if required. Children 4 to 10 years: Initially 5 drops (2.5 mg) at night. Increase up to 10 drops (5 mg) only. The maximum recommended dose should not be exceeded. If your doctor or pharmacist has changed the recommended dose, you should ask for further information from your doctor or pharmacist.
Warnings and precautions	Sodium picosulfate, the active ingredient in Dulcolax SP Drops, is ineffective in altering the digestion or absorption of calories in the small intestine and therefore does not assist with weight loss. Do not take Dulcolax SP Drops if you are allergic to: • any medicine containing sodium picosulfate • any of the ingredients listed at the end of this leaflet.

	Do not take Dulcolax SP Drops if you have, or have had, any of the following conditions: • acute abdominal conditions including appendicitis • acute inflammatory bowel disease • severe abdominal pain associated with nausea and vomiting • blockage in the bowel (ileus) • a blockage in the intestine • severe dehydration • symptoms of water and electrolyte disturbances such as fatigue, weakness, muscle cramps, thirst, dizziness and fainting • symptoms of water fructose intolerance (as this medicine contains sorbitol).
Undesirable effects	All medicines can have side effects. Sometimes they are serious, most of the time they are not. You may need medical attention if you get some of the side effects. Do not be alarmed by the following list of side effects. You may not experience any of them. Ask your doctor or pharmacist to answer any questions you may have. Side effects of Dulcolax SP Drops include: • abdominal discomfort • abdominal cramps • abdominal pain • diarrhoea • vomiting • nausea • dizziness • fainting. Dulcolax SP Drops may also cause allergic (hypersensitivity) reactions such as: • swelling of the face, lips, mouth, tongue or throat which may cause difficulty in swallowing or breathing • skin rashes including hives, blisters, red patches and itching. If these occur, seek medical attention immediately. Tell your doctor or pharmacist if you notice anything that is making you feel unwell. Other side effects not listed above may also occur in some people.

Sources:

1. Medsafe. 2019. *Medicines Product/Application Search*. URL: www.medsafe.govt.nz/regulatory/dbsearch.asp (accessed 11 May 2021).
2. Sanofi-aventis New Zealand Limited. 2017. *Dulcolax SP Drops Consumer Medicine Information* 24 August 2017. URL: www.medsafe.govt.nz/Consumers/CMI/d/dulcolaxspdrops.pdf (accessed 14 May 2021).
3. Annex 1 (label 11).

Comments:

The sponsors were asked to provide current label and packaging (which include any warning statements). The information regarding dose (including use in children), warnings and precautions, and undesirable effects is variable.

This variability can be explained by the following:

- only restricted and prescription medicines are required under the Medicines Act 1981 to have a data sheet, therefore this is not a current requirement for stimulant laxatives
- the Label Statements Database does not have any requirements for warning and advisory statements for stimulant laxatives (this database lists the warning and advisory statements that are required on medicine and related product labels under regulations 13(1)(i) and 14(1)(f) of the Medicines Regulations 1984) [12]
- stimulant laxatives approved a long time ago would not have gone through the same approval process as those approved more recently (for products approved in the 1960s it is unlikely assessment was part of the approval process).

Misuse is not mentioned. Most refer to the fact prolonged use is not recommended. Some mention that stimulant laxatives do not aid weight loss.

There is also a product specifically for children: Coloxyl Infant drops [13]. The active ingredient is poloxamer (a stool softener) which is why the product is not included in this report. Coloxyl Infant drops do contain glycerol as an excipient.

3 SCIENTIFIC INFORMATION

3.1 Benefit-risk review by the MHRA

The following section summarises the MHRA's benefit-risk review OTC stimulant laxatives [1]. Information on the management of constipation and usage in the UK has not been included.

3.1.1 Background

OTC stimulant laxatives had been under close review in the UK for some time. Previous recommendations included the addition of warnings that laxatives do not aid weight loss and that taking them for a long time may be harmful. However, these warnings were not consistently added to all stimulant laxatives.

More recently, the MHRA conducted a comprehensive review to assess the benefits and risks of stimulant laxatives (both orally and rectally administered formulations) and their continued OTC availability. In light of evidence of misuse/abuse and overuse, and current clinical advice on the treatment of constipation, the review considered:

- overuse in people with eating disorders
- long-term use in the elderly
- use in children.

The review looked at evidence from numerous sources, including professional and patient bodies, clinicians working in eating disorder clinics, a submission from the Proprietary Association of Great Britain (PAGB) on behalf of member companies, submissions from marketing authorisation holders (MAHs), and the scientific literature. The review also considered the legal status, product information and pack sizes of these products.

3.1.2 Efficacy

Bisacodyl

The MHRA found that double-blind, placebo-controlled efficacy studies and active-controlled studies have demonstrated that bisacodyl is effective for the treatment of constipation. No relevant placebo-controlled efficacy studies on oral bisacodyl in children and adolescents were identified. One uncontrolled trial carried out by one MAH in a small number of children with a wide spread of ages indicated that there may be efficacy in the OTC setting.

Comments:

Two studies were referenced in this section:

1. In 2011 a randomised, double-blind, placebo-controlled, parallel-group study was conducted in 27 centres in the UK [14]. After a 2-week baseline period without study medication, patients were randomly assigned, in a 2:1 ratio, to groups that were given 10 mg bisacodyl (n = 247) or placebo (n = 121), once daily, for four weeks. Patients used an electronic diary each day to record information relating to their constipation. The study concluded that oral bisacodyl is an effective and well-tolerated treatment for patients with chronic constipation. It improves bowel function, constipation-related symptoms, and disease-related quality of life.
2. In 2006 a phase IV, multi-centre, double-blind, randomised, placebo-controlled, parallel group design study was conducted in patients attending out-patient general practice clinics [15]. Eight general practices in Germany participated in the trial. Patients were randomised to receive either 10 mg bisacodyl, as two 5 mg sugar-coated tablets (Dulcolax), or matching placebo tablets, to be taken orally,

once daily. The study concluded that bisacodyl is effective and safe in improving stool frequency and consistency in acute treatment of idiopathic constipation.

Senna and sennosides (as calcium salts)

The Committee on Herbal Medicinal Products (HMPC) Assessment Report on senna leaf and fruit includes a comprehensive review of efficacy. The report concludes that there is no well-designed, non-experimental descriptive study to investigate the use of senna leaf or fruit as a single preparation for the short-term relief of occasional constipation. However, there are well-designed clinical studies for combination products containing senna used for the short-term relief of occasional constipation and for products containing high doses of senna for bowel cleansing. Despite the shortcomings of studies reported, they showed that senna containing combination products had a clear laxative effect. The European Union herbal monograph for senna leaf and pods states that these products should not be used in children under 12 years of age.

Sodium picosulfate

Several old studies of poor quality were identified which indicate the efficacy of sodium picosulfate for the treatment of constipation in both adults and children and suggest that it is similarly effective to bisacodyl and senna.

Several published reviews have compared the efficacy of different types of laxatives.

In 2010, a review surveyed 51 systematic reviews, randomised controlled trials (RCTs) or observational studies and concluded:

- macrogols improve symptoms of constipation without serious adverse effects – lactitol and lactulose may be equally effective in improving frequency of bowel movements
- the bulk-forming laxative ispaghula husk seems more effective than lactulose at improving the overall symptoms of constipation
- prucalopride and lubiprostone efficacy has been shown in RCTs but there are relatively frequent adverse events
- the effectiveness of senna, bisacodyl, cascara, docusate and glycerol/glycerine suppositories could not be established
- no evidence examining the efficacy of faecal softeners was found but the authors state that these are "generally considered beneficial".

A 2016 guideline for the management of chronic constipation of adults within the community considers that the strongest evidence is for the use of macrogols solution and psyllium (ispaghula). They also noted that there is no research evidence to support use of stimulant laxatives, lubricants or stool softeners.

In 2005, a systematic review of the efficacy and safety of traditional medical therapies for chronic constipation in order to make evidence-based recommendations showed:

- good evidence (grade A) was found to support the use of macrogol
- moderate evidence (grade B) to support the use of ispaghula husk, and lactulose
- a lack of good quality data regarding many commonly used agents including senna and bisacodyl (as well as milk of magnesia and stool softeners).

Comments:

Two reviews were referenced in this section:

1. In 2010, the authors conducted a systematic review and aimed to answer the following clinical questions [16]: What are the effects of non-drug interventions, bulk-forming laxatives, faecal softeners, stimulant laxatives, osmotic laxatives, prostaglandin derivatives, and 5-HT4 agonists in adults with idiopathic chronic constipation? They presented information relating to the effectiveness and safety of the following interventions: arachis oil, biofeedback, bisacodyl, cascara, docusate, exercise, glycerol/glycerine suppositories, high-fibre diet, increasing fluids, ispaghula husk, lactitol, lactulose,

lubiprostone, macrogols (polyethylene glycols), magnesium salts, methylcellulose, paraffin, phosphate enemas, seed oils, senna, sodium citrate enemas, prucalopride, and sterculia.

2. In 2005 the authors searched the English literature for drug trials evaluating treatment of constipation by using MEDLINE and PUBMED databases from 1966 to 2003 [17]. Only studies that were randomised, conducted on adult subjects, and published as full manuscripts were included.

Summary
Stimulant laxatives are well established medicines which have been available for many years. Due to their age, it is not expected that there would be data available from high-quality, modern trials to assess their efficacy. The data which are available, together with their widespread use, suggest that they are effective and well-tolerated when used appropriately. There are reasonable supporting data for other types of laxatives such as lactulose, macrogol and ispaghula husk which can be used to treat constipation in the OTC setting.

3.1.3 Safety

Bisacodyl

Bisacodyl has been widely used for many years and the safety profile of both the tablet and suppository formulation in short-term use were found to be favourable. Up to 31 December 2019, the MHRA had received 149 reports containing 449 suspected adverse drug reactions for bisacodyl; two of these reported fatalities. Gastrointestinal side effects such as abdominal cramp, diarrhoea and vomiting were the most frequent reactions reported.

Senna and sennosides (as calcium salts)

Clinical trials involving senna found that most side effects reported were hypersensitivity reactions or gastrointestinal in nature. Up to 31 December 2019, the MHRA had received 424 reports containing 923 suspected adverse drug reactions for senna products; 12 of these reported fatalities. The majority of the reports relate to products which include other active ingredients in combination with senna and allergic adverse reactions relating to the skin were the most frequently reported.

Sodium picosulfate

The adverse events seen in clinical studies involving sodium picosulfate were also mainly gastrointestinal and non-serious, such as stomach pain, diarrhoea, nausea and vomiting. These were found to be more manageable when the dosage was reduced. Up to 31 December 2019, the MHRA had received 279 reports containing 809 suspected adverse drug reactions for sodium picosulfate; 19 of these reported fatalities. Reports were most frequently concerning gastrointestinal side effects. In many of the fatal cases, the patients were taking other medications.

3.1.4 Misuse/abuse

MAHs were requested to provide details of cases of misuse/abuse received in association with stimulant laxatives. These were identified for all three of stimulant laxatives reviewed, although the reports are often incomplete, and it is noted that many cases may not be reported. The cases were often found to occur within the context of eating disorders. The highest number of reports of misuse received related to bisacodyl tablets. MAHs identified 167 relevant reports – 84 of which were serious and five fatal. These included a report of a young patient with bulimia who had increased their intake of bisacodyl over two years up to 100 tablets daily and experienced non-serious abdominal pain and decreased therapeutic response. There was also a Coroner's report) of a patient who had overdosed on 80 bisacodyl tablets and was admitted to A&E and subsequently deteriorated and died of multi-organ failure. The patient had a medical history of anorexia nervosa and long-term laxative abuse.

MAHs for senna received 49 reports (53 events) of misuse, abuse or intentional overdose, seven of which were serious. One of these was a case of a patient with a 23-year history of using maximum strength senna tablets. This included a period where they were taking 90 pills a day and having daily accidents from bowel urgency.

Following treatment for the addiction the patient continued to take 10 laxatives a day in order to control their bowels and suffered from several conditions including irritable bowel syndrome, low blood pressure and osteoporosis.

For sodium picosulfate, MAHs identified a total of 12 cases (containing 34 events) associated with eating disorders. In half of these, drug abuse was reported. Several cases did not provide sufficient information, however those which did were indicative of long-term misuse. There were fewer cases of abuse/misuse reported in association with sodium picosulfate than with bisacodyl or senna.

3.1.5 Discussion

Stimulant laxatives have been available as OTC products in the UK for many years. Constipation and its management have changed considerably since the time of first licensing. The widespread use of these products suggests that they are effective, and the rate of adverse event reports is relatively low. The Commission on Human Medicines (CHM) – the UK government's independent expert advisors on medicinal products – noted that these products are generally used responsibly. However, the serious nature of the cases of misuse and abuse in patients with eating disorders is concerning, particularly within the context of the large General Sales List (GSL) pack sizes which have been readily available to patients, including children and adolescents.

In their review, CHM noted that the product information for stimulant laxatives was inconsistent between products and that the large GSL pack sizes are not consistent with their use for short term constipation. They noted current clinical guidance recommends that stimulant laxatives should not be used first line in either adults or children and that they should not be used long-term without medical advice. They also advised that children under the age of 12 years who are experiencing constipation should receive medical advice and noted that macrogol is the recommended first-line treatment. CHM therefore recommended that GSL pack sizes should be reduced, there should be appropriate warnings against overuse and advising that these products do not help with weight loss consistently for all products, and age recommendations should be introduced.

In addition to patients who may deliberately overuse or misuse stimulant laxatives, elderly people may inappropriately overuse them due to misconceptions about constipation. Long-term overuse could mask more serious underlying conditions. Constipation is more common in the elderly and may be caused by a number of different factors. CHM advised that pharmacists are well placed to advise older people who may be taking several medications and/or have underlying medical conditions on the best way to treat their constipation, and on whether they need to seek further medical advice. Smaller GSL pack sizes would provide a large enough supply to treat short-term constipation but if a larger pack size is needed then a pharmacist can provide support and advice.

Several of the efficacy studies which were considered during the review noted the need to understand the underlying cause of constipation, so that the best treatment can be given. CHM advised that pharmacists are well placed to provide guidance to all patients, and to parents and caregivers, on the most appropriate treatment options for constipation. Educational materials have been produced in collaboration with the Royal Pharmaceutical Society to support pharmacists.

3.1.6 Expert advice

The CHM advised the following new risk minimisation measures for over-the-counter stimulant laxatives.

1. Removal of GSL availability for children so that they are only licensed for use in adults.
2. Restricting pharmacy-only availability so they are only licensed for use in patients aged 12 years and above.
3. Harmonising GSL and pharmacy-only indications across the products and in accordance with current clinical practice and removing indications that are not appropriate for the self-care setting.
4. Restriction of GSL pack sizes to two short treatment courses (ie, packs of 20 standard strength bisacodyl or senna tablets, 10 tablets of maximum strength senna and 100 mL bottles of senna syrup or sodium picosulfate solution). Any larger pack sizes would only be available through pharmacies.

5. Seeking to restrict the number of packs that can be bought in a single purchase through voluntary best practice.
6. Harmonisation of safety warnings and improving patient information.
7. Educational materials for pharmacists.

Comments:
The MHRA's benefit-risk review considered bisacodyl, senna and sennosides, and sodium picosulfate.
This report also includes docusate sodium and glycerol.

3.2 Published literature

The literature presented in this section is from the last 10 years.

3.2.1 Patel and Esposti (2010)

Title: A case of superior mesenteric artery syndrome secondary to surreptitious laxative abuse [18]

The authors present a case of a young woman who developed Superior Mesenteric Artery (SMA) syndrome after extensive weight loss from surreptitious laxative abuse.

A 29-year-old female with no significant past medical history was referred to hospital in the US for evaluation of a one year history of abdominal pain, diarrhoea and new onset weight loss.

Upon presentation, the patient appeared ill and extremely cachectic with a BMI of 14. The patient underwent MR enterography upon admission which demonstrated a new proximal small bowel obstruction with a dilated stomach. Additionally, a laxative abuse screen was sent upon admission. A CT scan of the abdomen and pelvis was obtained to further evaluate the proximal small bowel and stomach. This too demonstrated the dilated small bowel and stomach with an approximate measurement of the angle between the SMA and aorta to be less than 10 degrees. This was consistent with a diagnosis of SMA syndrome.

The patient underwent laparoscopic duodenaljejunal bypass to alleviate the obstruction. One day after discharge, the patient's laxative abuse screen reported to be positive for bisacodyl in both her urine and faeces. She continued to deny any current or previous laxative use.

3.2.2 McManus, et al (2014)

Title: Accidental, but initially suspicious injury [19]

The authors present a case of a 2-year-old boy who was referred to a paediatric burns centre in Australia by his GP. The boy had significant blistering consistent with a superficial partial thickness burn that had developed over the perineum, buttocks and posterior scrotum with sparing of the natal cleft and anus.

There was initial concern that the injury may have been inflicted, as the pattern was similar to that seen in a deliberate hot liquid immersion. However, following investigation it was concluded that the burns had been caused by senna-containing laxatives.

3.2.3 Atukorale and Jayatunga (2015)

Title: Fictitious illness due to chronic laxative poisoning [20]

Fictitious illness is a form of child abuse where a perpetrator makes a child appear sick by either fabricating symptoms or actually causing harm to the child in order to gain attention.

The authors reported the case of a girl who presented with chronic diarrhoea and severe failure to thrive, as a result of chronic laxative poisoning, by her mother. Positive urine toxicology for bisacodyl was confirmed on two occasions.

3.2.4 Forney, et al (2016)

Title: The medical complications associated with purging [21]

The authors identified over 100 scholarly articles describing medical complications associated with purging. Most of the articles involved case studies or small, uncontrolled samples. Given the limited evidence base, the authors conducted a qualitative (rather than systematic) review to identify medical complications that have been attributed to purging behaviours.

The review found that self-induced vomiting, laxative abuse and diuretic abuse are associated with a number of health complications, ranging from issues affecting the teeth (eg, dental erosion), the heart (eg, cardiac arrest), the gastrointestinal system (eg, rectal prolapse), and the kidneys (eg, renal failure).

The authors commented that stimulant laxatives are typically fast-acting and are particularly prone to abuse. A severe long-term problem associated with stimulant laxative use is the so-called 'cathartic colon', wherein the colon's motility is impaired and can no longer function normally. However, the existence of this condition is controversial, the majority of reports date back to the 1960s.

3.2.5 Kelly and White (2016)

Title: Community pharmacists' perspectives on non-prescription supply of laxatives when abuse is suspected: A qualitative study [22]

Aim

To explore community pharmacists' perspectives on managing the non-prescription supply of laxatives when abuse is suspected.

Methods

A qualitative approach was adopted on the basis of being well-suited to exploring participants' perspectives. In-depth digitally-recorded telephone interviews were conducted with 15 community pharmacists from pharmacies within Staffordshire in England. Participants were recruited by sending an invitation letter to pharmacies, followed by telephone contact. The interview guide was developed from the existing literature and from the objectives of the study. Key topics included experiences of laxative abuse, policies, and perspectives on control of laxative sales. Interviews were transcribed verbatim and analysed using framework analysis.

Results

All participants, except one, reported having experience of suspecting a customer of abusing laxatives. Participants usually reported characteristics of suspected abusers in clusters, from which two distinct customer caricatures emerged: the young, underweight, typically female customer, making regular laxative purchases for likely intentional abuse and the older, typically elderly customer making regular purchases apparently unaware of laxative overuse.

Participants reported that younger customers tended to react more defensively than elderly customers when questioned about their intended purchase. Some participants attributed such defensive responses to the GSL status of laxatives. Participants also reported that the GSL status of laxatives hindered effective management of suspected abuse by laxatives being widely available from non-pharmacy outlets where there is typically no restriction of sales or provision of medicines-related advice.

Differences noted by participants about laxatives compared to other abusable non-prescription medicines included customers tending not to become aggressive when sales were challenged (compared to medicines such as co-codamol) and larger pack sizes of laxatives making abuse more difficult to identify. When asked about control of prescription sales of laxatives, most participants said that they thought more control should be introduced, with reclassification to a pharmacy-only medicine or restriction of large packs to pharmacy-only status being commonly reported approaches.

Discussion

Whilst limited to one country, the findings suggest that policy-makers should consider legal reclassification or pack size restrictions.

3.2.6 Kita and Wakakuri (2016)

Title: Clubbing in an anorexia nervosa patient [23]

The authors present a case of a 32-year-old female in Japan who was being evaluated for cellulitis of the lower legs. She was hospitalised in a psychiatric ward for the treatment of anorexia nervosa.

The patient was severely emaciated (body mass index, 11.2) with clubbing of all fingers and toes. She had noticed this condition several years previously. Although the cellulitis was completely treated with antibiotics, the clubbing of the fingers and toes remained unchanged. Imaging studies and laboratory data showed no organic diseases that may have caused clubbing other than severe hypokalemia (2.5 mEq/L). The patient had a more than 15-year history of senna laxative misuse (three times the recommended dose).

In malnourished patients with anorexia nervosa, clubbing seems to be associated with long-term laxative abuse. However, the pathophysiological basis for this remains to be explained.

3.2.7 Dickison, et al (2019)

Title: Don't point the finger: Laxative abuse induced nail clubbing [24]

The authors present a case of a 36-year-old female in Australia with a history of laxative abuse and an eating disorder.

The patient was reviewed by a nephrologist for renal impairment, electrolyte disturbances and a history of multiple renal calculi. She also had a history of gastroesophageal reflux disease, depression and anxiety. In the years prior she had been consuming between 15 and 100 senna, or docusate sodium (Coloxyl) and senna tablets. On examination, her BMI was 16.8 kg/m2 and she had significant finger clubbing, which she had initially noted 10 years prior. The rest of her examination was normal.

Finger clubbing has been associated with cardiac, pulmonary, neoplastic and gastrointestinal diseases or infections, which were not present in this case. The link between clubbing and laxative abuse has been reported several times in the literature, all cases being young females. The nature of this association is unknown however it has been postulated to be related to diarrhoea or malnutrition.

3.2.8 Fleurentin, et al (2019)

Title: Senna laxative-induced dermatitis in children: a dermatitis mimicking child abuse [25]

The authors state that senna is not usually prescribed to children who still wear nappies because it can cause senna-laxative induced dermatitis.

Two cases of such dermatitis associated with an abscess are presented.

A three-year-old boy (Patient 1) was admitted following severe nappy rash discovered by his parents while changing diapers. The child achieved daytime continence, but he still wore nappies at night. He presented a well-demarcated erythema on the buttocks, associated with large skin erosions and coalescing flaccid blisters sparing the gluteal fold. These lesions were induced by profuse diarrhoea. An abusive scald burn was initially suspected. The biological results were normal. No microorganism was detected in stools or skin swabs. Rectosigmoidoscopy did not reveal any lesions of the rectal mucosa. After extensive and precise questioning, the authors discovered an accidental intake of senna tea the day before admission, reported by the father. The consumed dose was unknown.

A 14-month-old boy (Patient 2) was admitted regarding a recent nappy. Neither daytime nor night-time continence were achieved. At examination, he presented with well-demarcated erythema on the buttocks with large skin erosions and blisters. Necrotizing lesions were noted on the left buttock. The skin lesions presented linear demarcation closely aligned with the diaper edge, sparing the gluteal fold. The presence of an ecchymosis-like mark on the sacral area (actually a misinterpreted mongoloid spot) lead to the suspicion of child abuse with scald burns by intentional immersion. The biological results were normal. After specific questioning, the family reported daily intake of senna infusion according to a naturopath's prescription eight days before, in order to treat the child's constipation.

The authors comment that in the US, senna laxatives are very common and accidental intake by children is not uncommon.

3.2.9 Keenan and Hodgman (2019)

Title: A Case of senna-induced skin burns [26]

The authors present the case of a three-year-old male who was admitted to the burn service in the US with extensive second degree burns to his buttocks. His mother reported he had consumed several of his 12-year-old brother's chocolate laxatives the day prior and had experienced five loose stools before bedtime. She discovered the next morning the child had been in a soiled diaper overnight. When cleaning him she noted blistering and sloughing of skin on his buttocks. This prompted an Emergency Department visit for further evaluation and management of his injury. Extensive sloughing and peeling of skin consistent with a second degree burn was noted and the burn service consulted.

The burn service did not feel the injury was consistent with mother's story. Paediatric and child protective services were consulted for an evaluation. Toxicology was also consulted. Based on the mother's history and the appearance of the injury the toxicology service was able to corroborate the mother's history and expedite the child's discharge home with mother.

Senna laxatives are not recommended for children under two years of age in the US without a doctor's approval. Skin burns are not listed as a warning on these products. Although it seems that this type of injury could also occur in the debilitated elderly patient with incontinence, the authors were unaware of any reports of this.

Senna-induced skin burns in children appears similar to scald injuries associated with neglect and abuse.

3.2.10 Melvin and Hickey (2019)

Title: Laxative-induced contact dermatitis [27]

The authors present the case of a five-year-old female in the US with Charcot-Marie-Tooth neuropathy and a history of constipation.

The patient was taken to an emergency department with a new blistering buttocks rash, which was initially concerning for non-accidental burn. Upon further investigation, it was found that Ex-Lax had been given to the patient for constipation. This had resulted in a bowel movement, which led to an irritant dermatitis.

The patient was eventually diagnosed with senna-induced erosive diaper dermatitis.

3.2.11 Genta and Alexander (2020)

Title: Laxatives Soften More Than Just Stools: Osteomalacia Caused by Laxative Abuse in a Young Woman [28]

The authors present the case of a 37-year-old woman with no significant medical history who had fatigue, morning stiffness and lumbar spine, hip and bilateral leg pain for eight months. The patient was taking 20 tablets of ibuprofen (200 mg) daily without relief. She experienced difficulty walking, climbing stairs and lifting objects. Medication history included 16 bisacodyl (Dulcolax) 5 mg tablets daily since age 14 years for weight control.

A diagnosis of laxative-induced vitamin D deficiency induced osteomalacia was made.

The authors suggest the patient’s lower-extremity weakness and associated waddling gait may have resulted from defective calcium transport due to vitamin D deficiency or, alternatively, from the pain due to her pelvic fractures. They acknowledged there was no evidence to support either hypothesis.

3.2.12 Goldman and Cody (2020)

Title: Severe edema after cessation of laxative abuse and use of a loop diuretic: Case report [29]

The authors present the case of a patient with anorexia nervosa with binge-purge subtype who was taking ~100 stimulant laxatives per day. Upon discontinuation of stimulant laxatives, she experienced severe peripheral oedema with rapid gain of 11.6 kg over 1 week.

The authors describe the unique features of this case include the:

- high quantity of stimulant laxatives consumed per day
- amount of weight gained due to oedema
- three month duration of oedema after laxative cessation.

This case report details the time course of development of oedema after abrupt laxative cessation. It also details the dosing and duration of furosemide used for diuresis in order to provide a precedent to inform future care. This case calls into question the best treatment approach for patients with severe oedema after laxative cessation who do not meet criteria for Pseudo Bartter syndrome.

Comments:

The majority of articles in the literature are case reports of misuse of stimulant laxatives. None of them were conducted in New Zealand. There are no literature reviews or meta-analysis. Misuse of stimulant laxatives seemed a common area of research in the 1980s and 1990s.

The Eating Disorders Association of New Zealand were contacted for comment via email. Laxative abuse is an issue for many people with eating disorders. The Association could not share any specific stories in New Zealand due to confidentiality issues, however they provided the following link which would mirror the experience of others:

www.eatingdisorderhope.com/blog/hannah-struggle-laxatives-inspiration

[redacted]

3.3 CARM data

There are no cases in the Centre for Adverse Reaction Monitoring (CARM) database indicating abuse, misuse, overuse, or intentional overdose with stimulant laxatives.

Comments:

No cases in the CARM database does not necessarily mean there is no issue with stimulant laxatives in New Zealand, it means there were no reports received by CARM.

3.4 Data from the National Poisons Centre

The National Poisons Centre (NPC) has advised Medsafe that 255 calls relating to the use products containing stimulant laxatives were received between 1 January 2017 to 31 December 2020 (see Annex 3 for the full report).

Table 14 below shows the number of calls to the NPC of stimulant laxatives exposures from 2017 to 2020.

Table 14: Contacts to the National Poisons Centre relating to stimulant laxative exposures (2017-2020)

Year	Records with stimulant laxatives	All human exposure records
2017	51	21,066
2018	50	21,313
2019	70	22,925
2020	84	24,123
Total	255	89,427

Source: National Poisons Centre. 2021. *Contacts to the National Poisons Centre relating to stimulant laxatives* 4 May 2021. Dunedin: National Poisons Centre.

Table 15 below shows the type of exposure.

Table 15: Contacts to the National Poisons Centre relating to the type of stimulant laxatives exposures

Stimulant laxative	Child Exploratory	Intentional	Therapeutic error	Unintentional	Unknown	Total	Substance % of all records
Bisacodyl	14	1	5	5	0	25	10%
Castor oil (capsules)	22	5	13	2	0	42	16%
Docusate sodium	18	1	17	2	0	38	15%
Docusate sodium + sennosides	72	7	39	14	2	134	53%
Sennosides	0	2	3	2	0	7	3%
Sodium picosulfate	0	1	3	0	0	4	2%
Other*	3	0	2	0	0	5	2%
Total	129	17	82	25	2	255	100%
Reason % of all records	51%	7%	32%	10%	1%	100%	

*Glycerol suppository, frangula, unknown stimulant laxative.

Source: National Poisons Centre. 2021. *Contacts to the National Poisons Centre relating to stimulant laxatives* 4 May 2021. Dunedin: National Poisons Centre.

A manual review of these records by the NPC found three cases of possible abuse of docusate sodium + sennosides, one of bisacodyl and one of senna-containing laxative tea.

Comments:

The number of exposures reported by the NPC are small. The largest number of exposures are due to either child exploratory cases or therapeutic error. There are more stimulant laxatives included in the NPC report that are not included in this report (eg, bowel cleansing preparations).

The limitations of the data from the NPC are:

- contacting NPC is voluntary, and therefore data presented here only capture an unknown proportion of all exposures that occur
- multiple records may represent the same patient, leading to slightly over-counting the number of unique cases.

4 DISCUSSION AND CONCLUSIONS

In August 2020, the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK published their benefit-risk review of over-the-counter stimulant (OTC) laxatives [1]. Following this review, for OTC stimulant laxatives (orally and rectally administered), the MHRA introduced [2]:

- pack size restrictions (eg, restriction of general sale pack sizes to two short treatment courses)
- revised recommended ages for use (eg, restricting pharmacy-only availability for use in patients aged 12 years of age and above)
- new safety warnings.

This paper reviewed the information on the misuse of stimulant laxatives in New Zealand.

Stimulant laxatives have been available OTC in New Zealand for many years. The widespread use of these products suggests that consumers consider them to be effective. Although there are no cases in the CARM database and the number of exposures reported by the NPC are small, there is a potential for misuse of stimulant laxatives in New Zealand as there is internationally.

A review of the published literature over the past 10 years presents case reports in adults and children of the damaging effects that misuse of stimulant laxative can have.

Constipation is a symptom not a disease and may be the result of underlying conditions. The concern is that these products are available to patients OTC, and in packs as large as 200 tablets, yet no health care professional consultation is required before purchase. In New Zealand there are no restrictions on the age of the purchaser or the pack size. There are no mandatory warning or advisory statements required on the product labels.

Should the Committee consider that the evidence supports action to manage these risks, the classification of stimulant laxatives could be referred to the Medicine Classification Committee (MCC) for consideration. The MCC makes recommendations regarding the classification of medicines as prescription, restricted or pharmacy-only medicines [30]. It also considers any matter concerning the classification of medicines and access to medicines by health care professionals and the public [30].

Medsafe could make an application to the MCC proposing that stimulant laxatives should be:

1. available for general sale (ie, docusate sodium and glycerol) for use only in adults (ie, 18 years of age and older)
2. classified as pharmacy-only medicines (ie, bisacodyl, sennosides and sodium picosulfate) for use only in patients aged 12 years of age and above
3. otherwise classified as restricted medicines.

Pack size restrictions could also be included in the proposed classification statements to reflect that these medicines should only be used for short-term, occasional constipation.

It is difficult to recommend updates to the data sheets for stimulant laxatives. Only restricted and prescription medicines are required under the Medicines Act 1981 to have a data sheet therefore this is not a current requirement for stimulant laxatives.

The Label Statements Database does not have any requirements for warning and advisory statements for stimulant laxatives. In the absence of data sheet updates, the Label Statements Database could be updated to include statements for stimulant laxatives. For example:

1. does not help with weight loss
2. prolonged or excessive use can be harmful
3. consult a healthcare professional before using in children under 12 years of age.

5 ADVICE SOUGHT

The Committee is asked to advise whether the evidence of the misuse of stimulant laxatives in New Zealand warrants taking further action.

If further action is recommended, options could include:

- applying to the MCC to reclassify stimulant laxatives
- updating the Label Statements Database to include warnings for stimulant laxatives
- communicating to healthcare professionals (eg, an article in *Prescriber Update*).

6 ANNEXES

1. Labels provided by the sponsors [**Confidential**].

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3. National Poisons Centre. 2021. *Contacts to the National Poisons Centre relating to stimulant laxatives* 4 May 2021. Dunedin: National Poisons Centre [**Confidential**].

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