CHAPTER 1 INTRODUCTION

1.1 BACKGROUND

Laxative products in South Africa account for an extremely large portion of the over-the-counter medicine sales. There are over 100 related products sold through pharmacies, health stores, supermarkets, cafés and convenience stores.

In the 1970's there were more than 700 different laxative and purgative preparations for sale in the United States. These accounted for one percent of all medical prescriptions.[1] In South Africa, there are currently in excess of 80 products on the retail market with laxative properties.

Normal defaecation empties only the descending colon, whereas powerful purgatives empty the entire colon. Thus after use of a laxative or purgative, a few days may elapse while material collects in the colon before natural defaecation may occur again. During these few days, the patient may believe he is again constipated and take more drug, so that a cycle is built up which is difficult to break. This is common in patients who have the mistaken belief that daily defaecation is necessary to maintain health.
Disturbances to normal daily routine may disrupt an established pattern of defaecation e.g. in travel, children going to a new school or long distance driving.
Certain drugs are well documented as producing constipation e.g. morphine and its congeners, aluminium salts, atropine and other anticholinergics, ganglion blockers, sympathomimetics, phenothiazines and tricyclic antidepressants.

Laxatives are agents which promote bowel evacuation. They may be misused and overused. In excess, they may cause diarrhoea, dehydration, hypokalaemia, atonic bowel and weight loss. Their use may be appropriate in certain situations e.g.
▪ if there is no response to dietary and lifestyle advice after approximately one month;
▪ if faecal impaction is present;

- if constipation or painful defaecation is associated with illness, post-surgery or during pregnancy;
- in elderly patients with poor diet;
- in drug-induced constipation;
- if a patient has a pre-existing condition in which bowel strain is undesirable e.g. coronary heart disease;
- if required pre-operatively.

Use of traditional remedies is significant within the indigenous population of Southern Africa. Anecdotal evidence suggests modern laxatives are frequently incorporated and misused within this population. This has led to a number of fatalities, particularly within the paediatric population.[2] The media often promote the use of laxatives and advertising encourages the public "to be more regular" or to "cleanse the blood of toxins".[3]

In general, the lowest dose of laxative should be used which should then be reduced once symptoms resolve. Long-term use of laxatives may be required in certain medical conditions e.g. in the use of opioids in palliative care, in progressive neurological conditions e.g. Parkinson's Disease, Multiple Sclerosis, due to old age or illness, and occasionally in children to prevent relapse of constipation.[4]

In South Africa, laxatives are classified as Schedule 0 drugs in terms of the Medicines and Related Substances Act (Act 101 of 1965). The act states that any Schedule 0 substance may be sold in an open shop and their sale is thus not controlled. They are available to the public over-the-counter in pharmacies, as well as at supermarkets, café's and convenience stores.

Laxative abuse has been defined as diarrhoea caused by self-medication or by a patient simulating diarrhoea by drugs which increases amount of fluid in the stool.[5] The condition is far more prevalent in females than in males. In western civilization, it is predominant in the 18 to 40 year age group in patients with bulimia nervosa, but also in the 40 to 60 year age group without bulimia.[5]

Well-known causes of abuse include:-

- Ingestion of any laxative agent unnecessarily
- Psychological factors:- Bulimia Nervosa
  Secondary gain of attention
  Hysterical behavior
  Multiple personality disorders
  Inappropriate perception of "normal bowel habits"
  Chronic constipation.[6]

Research indicates laxative abuse in females is often associated with dissatisfaction in body shape or size[7]. The abuse of laxatives increases the incidence of intestinal and renal diseases. The loss of the protective intestinal mucous exposes the bowel to infection. Chronic abusers lose muscle tone in the bowel, causing retention of large amounts of faecal material. Electrolyte imbalances like hypokalaemia can occur which may lead to severe cardiac arrhythmias and cardiac arrest. Other signs and symptoms include irritable bowel syndrome, sluggish bowel functioning, malabsorption of fat, protein and calcium, rectal bleeding, tumours of the colon and laxative dependence.[8]

1.2 CONSTIPATION

Constipation is defined as the difficult or infrequent passage of faeces. It can refer to stool hardness, difficulty in defecation, a feeling of incomplete evacuation or infrequent defecation. Normal bowel function can be affected by dietary, cultural and individual physiological factors. The frequency can range from three times per day to once in three days or less frequently in certain individuals[9]. Symptoms of headache, fatigue and loss of appetite often accompany faecal impaction.[10,11]

Constipation has been described in terms of both the character and frequency of stool. Normal bowel frequency ranges between three bowel movements per day to one

movement every three days. Yet a well formed, normal stool only once a week does not require therapy. A constipated stool is scyballous i.e. overdessicated, hard, dry and difficult to pass.[12]

Many symptoms are incorrectly associated with or attributed to constipation, such as headache, malaise, bad taste in the mouth and coated tongue, but there is no scientific basis that any of these is caused by constipation. This concept has unfortunately created a tremendous market for laxatives.[12] The media often promote the use of laxatives and advertising encourages the population to be more "regular", or to "cleanse the blood of toxins".[2] As far back as 1919, it was claimed that symptoms of headache, fatigue and loss of appetite that accompanied faecal impaction were due to mechanical distension of the colon rather than by production or absorption of toxins. [10,11]

The commonest causes of constipation are:

- Decreased stool weight or bulk, usually from lack of dietary fibre.
- Decreased propulsive activity, usually from medication e g. opiates, certain antacids, drugs with anticholinergic properties (e.g. antipsychotics, antidepressants, antiparkinsonian drugs), opiates, sympathomimetics, clonidine, diuretics, NSAIDS, calcium channel blockers, antacids, iron supplements, laxatives, etc, but occasionally from intrinsic muscle disease.
- Suppression of normal defacatory rectal stimulus by voluntarily contracting the external anal sphincter due to inconvenience or painful anal disease e.g. thrombosed haemmorhoids, anal fissure.
- Depression- decreased bowel function.
- Decreased physical activity.
- Hypothyroidism.[12]

Chronic constipation is more common than acute and often more difficult to remedy, commonly falling into two categories:-

The older patient with a well-established habit of laxative use; and the younger patient, often female, who is constipated due to her lifestyle, and often is headed towards laxative

dependence. In chronic constipation, common functional causes are those which hamper normal bowel movement. This can be due to the storage, transporting and evacuating mechanisms of the colon being deranged. Examples include systemic disorders (e.g. infection, hypothyroidism, hypercalcaemia, uraemia, or porphyria), but are more commonly by local neurogenic disorders (e.g. irritable bowel syndrome, inactive colon and megacolon). Certain other neurological disorders are important extraintestinal causes (e.g. Parkinson's disease, cerebral thrombosis, tumour and spinal cord injuries).[9] Laxative abuse due to chronic constipation is rare and almost always associated with psychosomatic-psychiatric disorders.[13]

Acute constipation represents a definite change in bowel movement for that particular individual. This could include causes due to mechanical bowel obstruction, adynamic ileus, post-traumatic causes or following general anaethesia. This is also seen in the bedridden patient, particularly in the elderly, or due to drug adverse effects.[9]

1.2.1 PSYCHOGENIC CONSTIPATION

Many patients incorrectly believe that daily defecation is normal. They complain of constipation due to a change in frequency of bowel movements, or due to appearance or consistency of stools.[9]

As a result, laxatives by mouth, suppositories or enemas are abused. This can result in irritable bowel syndrome, which can be accompanied by cathartic colon and melanosis coli. This condition is commonly found in obsessive-compulsive patients in whom their anxiety is controlled by their perfectionistic behavior and their need to rid their bodies of unclean wastes.[9]

Ignoring or postponing the urge to defecate may blunt colonic and rectal response and could lead to prolonged stool retention.

Psychiatric patients have been known to suffer from constipation. It has been noted that a number of these patients improve with the onset of psychotherapy.[14] This could in part be attributed to their medication especially the older generation antipsychotics where tolerance to the adverse effects have been noted.

1.3 LAXATIVES

Laxatives are divided into four main groups according to their mechanisms of action. The recommended dosage depends on the individual patient and is usually defined as the dosage that regularly produces a comfortable formed stool. In patients with simple constipation, advice on diet as well as on regularity of bowel habit is important so that a regular pattern may be established without use of purgatives.

1.3.1 Bulk-forming Agents

These are hydrophilic compounds taken orally, which act by absorbing water, swelling, and increasing stool bulk, which in turn stimulates rectal reflexes and promotes defecation. These laxatives are administered orally and take a few days to exert their full effect. They are used to establish a normal bowel habit in patients with chronic constipation, as well as in patients with simple constipation, constipation associated with diverticular disease, irritable bowel syndrome or pregnancy.[7] These products have been recommended to be the agent of choice to be considered for chronic use[9].

Site of Action:- Small and Large intestine.

Onset of Action:- 12-72 hours.[15]

Examples:-

- Bran
- Ispaghula Husk & Psyllium Preparations e.g. Fybogel®, Agiobulk®, Agiolax®*
- Methylcellulose e.g. Kolantyl®*
- Sterculia e.g. Normacol®, Alvercol®* (* in combination)

These products can cause intestinal obstruction in patients with intestinal disease and should therefore be avoided in these cases e.g. intestinal adhesions, stenosis, ulceration, scleroderma or autonomic neuropathy.
Flatulence is a common side-effect.
Sterculia has been known to cause hypersensitivity reactions.

1.3.2 Faecal Softeners and Lubricants

These include the vegetable and mineral oils which lubricate and soften the stool and are taken orally or rectally. These agents are generally used when intestinal pathology prevents the use of the bulk-forming agents. They are also commonly used in patients with anal fissures or haemorrhoids, to prevent the pain of defaecation. They are also of value when rapid effects are required.
Site of Action:- Small and Large Intestine.
Onset of Action:- 6-8 hours[15]
Examples:-

- Arachis Oil
- Dioctyl sodium sulphosuccinate
- Glycerine
- Liquid Paraffin e.g. Agarol®* (recently discontinued)

Liquid paraffin is no longer recommended due to causing malabsorption of fat-soluble vitamins, as well as faecal leakage causing pruritis ani.

1.3.3 Gastro-intestinal Stimulants

These drugs act on the bowel, stimulating peristalsis and reducing the net reabsorption of water and electrolytes. These drugs are taken orally when rapid bowel evacuation is required e.g. prior to radiological examination of the bowel or colonic surgery, and are also used in the short-term after treatment of faecal impaction following severe constipation.
Site of Action:- Colon.
Onset of Action:- Bisacodyl
suppositories: 15 minutes to 1 hour.
Oral formulations: 6- 10 hours.[15]

Examples:-

- Frangula e.g. Normacol Plus®
- Senna e.g. Senokot®, Soflax®, Depuran®, Brooklax Chocolate®, Black Draught, Black Forest®, X-Prep®.
- Danthron
- Bisacodyl e.g. Dulcolax®, Perilax®, Puritone®, Brooklax pills®, Freshen®
- Castor Oil.
- Phenolphthalein e.g. Laxa®, SB Strong Laxative®, Supertabs®, Surge®.

The anthraquinones (Frangula, Senna and Danthron) and bisacodyl have an onset of action of six to eight hours after oral administration, but bisacodyl per rectum has a faster action.

Castor oil acts on the small intestine and acts in its metabolized form, ricinoleic acid, within one to three hours.

Repeated abuse of these drugs leads loss of fluids and electrolytes, especially hypokalaemia which can lead to severe cardiac arrhythmias and cardiac arrest.[15] This in turn leads to colonic atony, leading to constipation and further abuse.

Certain phenylmethane derivatives are no longer recommended because of adverse effects e.g. oxyphenisatin is hepatotoxic, phenolphthalein has been associated with hypersensitivity reactions, possibility of carcinogenicity and dermatological problems.[14] Products containing phenolphthalein were banned in February 2002 with provision for phasing these products in April 2002. Final cancellation and withdrawal of these products from the market with immediate effect was published in the Government Gazette on 4 August 2006.

1.3.4 Osmotic Laxatives

Osmotic laxatives are taken orally or rectally and act by decreasing water reabsorption in the bowel.

Site of Action:-

Saline agents:- Small and Large Intestine.

Hyperosmotic agents:- Colon.

Onset of Action:- 0.5- 3 hours.[15]

Examples:-

- Magnesium salts e.g. Be-lax tablets®*.
- Sodium salts e.g. Microlax Microenema®, Klean-prep®*
- Lactulose e.g. Duphalac®, Lacson®, Laxette®. (* in combination)

Magnesium and sodium salts are generally used as purgatives due to the fact that they retain large amounts of water in both the small intestine and large bowel. This increases peristalsis throughout the bowel. These are often reserved for rectal use due to their severe and rapid effects and are most commonly used for diagnostic bowel procedures[9]. Lactulose is a disaccharide of galactose and fructose, which is hydrolysed by colonic bacteria into its component monosaccharides which are then fermented into acetic and lactic acids which lowers colonic pH and thereby increases peristalsis. This may be used orally or rectally. Lactulose normally takes a few days to act if administered orally. It has been reported to cause abdominal discomfort and flatulence.[16]

1.3.5 Other Laxative Products

Laxatives have long been used by the black members of the South African population as a regular cleansing treatment and include use in infants and children, adults and well as the elderly and the sick.[13] It has for many years been believed that "cleansing one's system" can treat numerous conditions ranging from constipation, bile (inyongo), hypertension (i-high blood), gonorrhoea (i-drop) and many, many more.

There are two main groups of patent laxative products currently on the market in South Africa; the first group (1.3.5.1) includes the formulations based on established laxatives containing the appropriated package inserts stating pharmacological action, indications, side-effects, special precautions and contra-indications.

The second group (1.3.5.2) is more informally packaged for marketing directly to the consumer often making medical "claims" as to the product's efficacy to enhance customer appeal. These products generally do not supply a package insert, nor do they list their actual ingredients, often just stating "herbal remedy". These products are more specifically marketed for the African members of the community, often with an African name, directions and indications in one of the African languages, most commonly Zulu.

An assessment of a few products on sale in South Africa showed the following:

1.3.5.1 Established Patent Laxatives

~ Super-Tabs® – Yellow phenolphthalein- produced by Pharmacare- states on package insert: *"for relief of occasional constipation; do not exceed stated dose. If you have noticed a change in bowel habits for over a week or have rectal bleeding or failure to have a bowel movement after use of a laxative, this may indicate a serious condition- discontinue use and consult a doctor"*.

~ Freshen® Tablets - Bisacodyl- manufactured by Adcock Ingram- states on package *"for relief of occasional constipation"*. The package insert also states: *"not to be used:-*
- in the presence of abdominal pain, nausea and vomiting,
- for more than 1 week without consulting your doctor,
- if bowel habits have changed for 2 weeks or more, consult your doctor
- in rectal bleeding,
- in constipation even after having used a laxative."

~ Brooklax Laxative Pills® - Bisacodyl- produced by Group Labs- has all the necessary warnings on the package insert as well as dosage regimen on the box.

~ Black Draught Tablets® – Senna Leaf Extract- produced by Nativa Pharm- states on package insert:-
"Not to be used for more than 10 days without consulting doctor or healthcare practitioner";
"Not to be use in pregnancy or lactation or if hypersensitive to ingredients."

~ SB Strong-Lax® – Yellow phenolphthalein- produced by Universal Pharmaceuticals- States on package insert: *"relief on constipation in adults and children over 15 years; not to be used in undiagnosed abdominal pain, nausea and vomiting, in intestinal obstruction. Consult doctor should prolonged use of laxatives become necessary".*

1.3.5.2 Informal Patent Laxatives

A few of the products from this group showed:
~ "Stametta"® – (product containing aloe in combination with vitamins, minerals, herbal extracts) – manufactured by Bodicare- for *"nervous disorders, skin eruptions, boost of sexual performance, improves quality of blood, high blood pressure, blood circulation, helps chest pains, helps lungs, liver, kidneys, etc, fights colds and flu, gout, erratic heart functions, lower back pain, persistent tiredness, regulates female organs, treats easy bruising, clears out bile, bleeding gums, stomach gas, body odours, body sores, tension headaches, constipation, gout, stomach pain, painful female periods, muscle cramps, strengthens bones and muscles, strengthens body and blood immune system against viruses and infections".* It does state *"not for pregnant women and children under 14 years".*

~ "Ishlambeza Mixture"® (Magnesium Sulphate) – *"A product for pregnant women"* (with a diagram of a pregnant woman) – used as a tonic for the unborn baby.

~ "Ingwe Izifizonke Muti"® (aloe powder combination) – *"Treats all medical conditions"* e.g. bile (inyongo), kidney problems, gonorrhoea, halitosis, flatulence, arthritic pains, etc.

~ "Real Herbs Real Good"®- "African herbs for All diseases" (no specific ingredients stated). –manufactured by Bodicare; Treats 30 medical conditions in 2 African Languages; Directions state *"Quarter cup every night before sleep after meals. Drink on a regular basis".* It does state *"not for pregnant women and children under 14 years".*

~ "Ingwe Special Muti"®- (no ingredients stated)- supplied by Guideline Trading – *"African roots for all diseases"* eg. Cough, arthritis, boosts and replaces blood, gonorrhoea, (total of 30 diseases stated in 2 African Languages)– directions state *"Drink your medicine on a regular basis".* This product has 30 indications printed on the bottle in two different African languages and consists of a 500ml liquid as well as a sachet of green/brown powder. The powder is to be added to the bottle once half the bottle has been consumed.

There are presently a vast number of products of this type on the market which advertise as above with graphics showing the human body, but no ingredients stated on the package or package inserts included.

The former group of drugs is far more acceptable than the latter. Legislation should enforce highly visible warnings on the package and not only in the fine-print which many patients often neglect to read.

1.4 LAXATIVE MISUSE

Laxative misuse has been defined as:-

- Frequent use of laxatives over an extended period of time;
- Use of laxatives for the purpose of weight loss.

Laxative Abuse Syndrome is relatively common due to misconceptions about normal bowel patterns and the effects of laxatives. Availability of laxatives in chocolate, chewing gum and various other forms conveys to the public that these products are devoid of adverse effects.

In more recent times, it has become common to use these products for the purpose of weight loss and not only for the treatment of constipation. In cases of indiscriminate use of these strong laxatives and cathartics, serious illness may result. Long term users of these products may present with contradictory findings of weight loss and diarrhoea, as well as vomiting, abdominal pain, lassitude, weakness, thirst, oedema, bone pain (due to osteomalacia), fluid and electrolyte imbalances, (including acid-base imbalance and hypokalaemia), protein-losing gastroenteropathy, hypoalbuminaemia and colitis-resembling syndromes. Eating disorders have reached epidemic proportions- all segments of society are affected: men and women, young and old, rich and poor, all minorities, all socio-economic levels.[17]

In patients using laxatives for weight-loss, which appears to be on the increase, treatment has proven to be difficult.[18] Many laxative abusers deny laxative use or misuse making diagnosis of this difficult. In the United States, middle-aged women tend to be the most common abusers of laxatives.[19] Patients suffering from laxative abuse should be addressed by psychiatric evaluation, dietary modification with reliance on bulk-forming laxatives, and guidelines for the withdrawal of stimulant laxatives.[19]

Studies of individuals attending inpatient substance abuse treatment centers suggest that 15% of women and 1% of men had eating disorders- primarily bulimia nervosa.[21]

About 1-3% of young women in the general population have bulimia nervosa and a further 1-3% have mild variants of this disorder, with most of the physical complications being as a result of laxative and purgative abuse.[22] Reports of major dissatisfaction among adolescent girls over their body shape and their associated eating behavior in South Africa showed that concern was shown by these girls over weight, desired weight loss, binge-eating, fasting, vomiting, and laxative usage.[23] A study was performed to assess the association between patients with anorexia nervosa and laxative abusers and non-abusers. This showed that the laxative abusing patients had higher ratings on the ineffectiveness, body-dissatisfaction and drive for thinness on the Eating Disorders Inventory, as well as more depressive and somatization symptoms. An association between laxative abuse and low-esteem was also noted.[24] In patients using laxatives for weight-loss, which appears to be on the increase, treatment has proven to be difficult.[18]

The common perception is that eating disorders afflict only white women, especially those in the upper- and middle-classes. While that demographic does constitute most reported cases, specialists believe that that all socio-economic and ethnic groups are affected. According to the National Eating Disorders Association, there are no reliable statistics on the prevalence of eating disorders among other members of the population due to under-representation in research of diverse communities. Because minority and poor women do not fit the profile, medical personnel often fail to assess them for eating disorders and they are overlooked. Also, ethnic groups have not had education efforts directed toward them, so early signs are often missed. Research over the last decade has found that eating disorders among minority and lower-income women have increased and may be becoming "an equal opportunity disorder".[24] A survey conducted in January 1994 found that Black girls may be especially vulnerable to developing eating disorders with binge eating featues.[24]

A study was performed to show the effect of urbanization on eating disorders. This showed that bulimia nervosa showed a dose-response relation with the degree of urbanization and was five times higher in the cities than in the rural areas, but anorexia nervosa showed no association with urbanization.[25]

Dietary change and attention to proper bowel habits are frequently the only therapy necessary for constipation. When laxative intervention is necessary, one of the milder agents should be employed over a short period of time. Chronic abuse of stimulant cathartics often deeply rooted in family or ethnic traditions is a significant problem and is often difficult to treat.[26]

Misuse of laxatives is widely found in our black population where patients are known to ingest these products for purposes other than those for which they are indicated. Traditional healers in South Africa now exceed 200 000. About 80% of the black population regards their advice and treatments as a primary source of health education. Treatments include any number of conditions ranging from sexually transmitted diseases to general medical check-up's to immunization against witchcraft. The most common medications dispensed by these healers are laxatives, enemas and emetics.[13]

Laxative misuse has been researched comprehensively with regard to eating disorders and weight loss, but literature on misuse and abuse of laxatives for other pharmacotherapeutic purposes appears to be overlooked.

1.5 ADVERSE EFFECTS OF LAXATIVES

The abuse of laxatives increases the incidence of intestinal and renal diseases. The loss of the protective intestinal mucous exposes the bowel to infection. Chronic abusers lose muscle tone in the bowel, causing retention of large amounts of faecal material.

Electrolyte imbalances like hypokalaemia can occur which may lead to severe cardiac arrhythmias and cardiac arrest. Other signs and symptoms include irritable bowel syndrome, sluggish bowel functioning, malabsorption of fat, protein and calcium, rectal bleeding, tumours of the colon and laxative dependence.[8]

Although stimulant laxatives have been proven to cause structural damage to surface epithelial cells, research has showed that there appears to be no convincing evidence that their chronic usage causes structural or functional impairment of enteric nerves or intestinal smooth muscle.[26] Nor is there reliable data to link chronic use of stimulant laxatives to colorectal cancer and other tumours. The researcher maintains that the risks of laxative abuse have been overemphasized.[27] Large doses of Senna pods infused to form an herbal tea may lead to acute hepatic failure and renal impairment. [28]

Laxative abusers tend to develop intestinal and renal disease more commonly than non-users.[3] This causes loss of muscle tone in the bowel, which tends to collect and retain large amounts of faecal material. The loss of protective intestinal mucous makes the bowel more vulnerable to infection. These patients tend to suffer from dehydration, tremours, weakness, irritable bowel syndrome, rectal bleeding, bowel tumours, malabsorption syndromes, osteomalacia and electrolyte imbalances – especially hypokalaemia, which in turn can cause cardiac abnormalities and even cardiac arrest.[29]

COMMON SIDE EFFECTS:

Bulk-Forming Laxatives:	Flatulence; Abdominal distension.
Osmotic Laxatives:	Cramps; Flatulence; Abdominal discomfort.
Stimulant Laxatives:	Fluid and electrolyte imbalance; Colonic atony; Abdominal cramps; Suppositories (e.g. bisacodyl) can cause local rectal irritation;
Faecal softeners and Lubricants:	Nausea; Tolerance with prolonged use; Anorexia; Abdominal cramps; Mineral oil may decrease absorption of fat-soluble vitamins; Mineral oil may also produce anal leakage causing Pruritis ani. [29;30]