

A Review on Extended Release Tablet of Lubiprostone for IBS-C

Mansvi patel¹

¹Student, Smt. B.N.B Swaminarayan Pharmacy college, Gujrat, India

Abstract: - Around 23 to 41 million people suffering from IBS. There are number of treatment to available treat IBS but some of them side effect of constipation. So we need drug to cure IBS as well as constipation. High dose of drug cause severe side effect in IBS condition. So to avoid this high potency drug required and use of other drug can cause side effect like constipation. Lubiprostone is high potency drug, low dose and give good therapeutic effect and also treat IBS with constipation. To improve patient compliance prepare extended release tablet.

Keyword: IBS, Lubiprostone, Therapeutic effect

INTRODUCTION

INTRODUCTION TO DISEASE :-

IRRITABLE BOWEL SYNDROME: - (1-4)

- The GIT (gastrointestinal system) consist of a hollow tube, divided into several parts, esophagus, stomach, small intestine and Large intestine.
- Irritable Bowel Syndrome (IBS) is a disorder which affecting intestine.
- **Irritable Bowel Syndrome** is a functional bowel disorder, in which abdominal pain is associated with a change in the bowel habit along with features of excretion and distension.

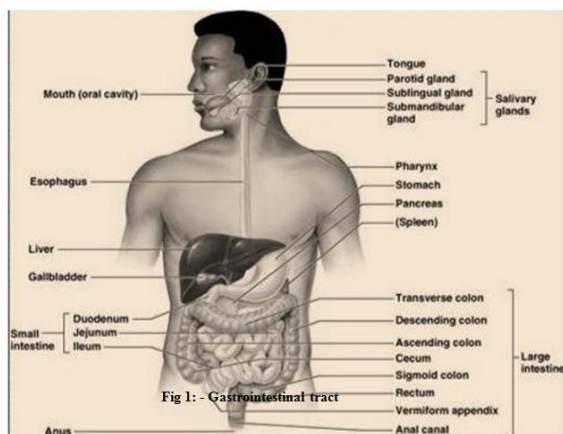


Fig 1: - Gastrointestinal tract

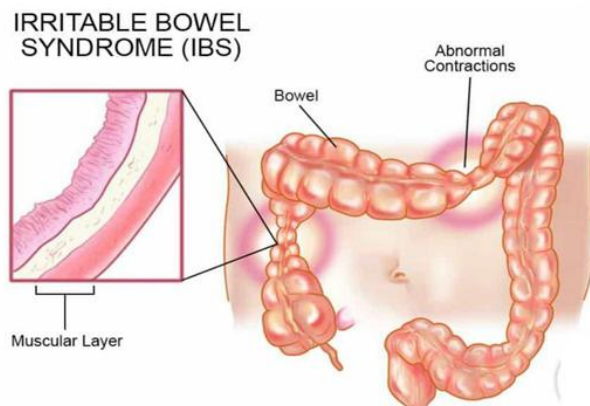


Fig 2: - Irritable Bowel Syndrome

1.1.2 ETIOLOGY: - (5-9)

- The combination of four factors lead to IBS: a genetic component, an environmental trigger, an imbalance of intestinal bacteria and an in appropriate reaction from the immune system.
- Immune cells normally protect the body from infection, but in people with IBS, the immune system mistakes harmless substances in the intestine for foreign substances and launches an attack, resulting in inflammation.
- Link between the brain and intestinal tract.

- Cramping pain
- Abnormal muscle contractions.
- Irritable bowel syndrome generally believed that most patients develop symptoms in the response to psychosocial factor, altered gastrointestinal motility, altered visceral sensation and luminal factors.

1.1.2(A) Psychosocial Factor: -

- About 50% patients meet criteria for a psychiatric diagnosis. A range of disturbance are Identified, including anxiety, depression somatisation and neurosis.

1.1.2(B) Altered Gastrointestinal Motility:-

- Patients with diarrhea as a predominant symptom exhibit cluster of rapid jejuna contraction waves, rapid intestinal transit and an increased number of fast and propagated colonic contractions.
- A range of motility disorders are found but none is diagnostic.

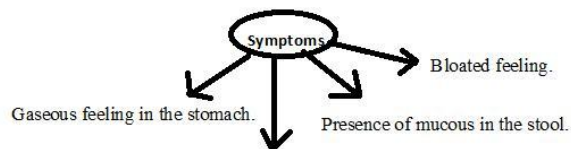
1.1.2(c) Abnormal Visceral Perception:-

- IBS is associated with the increased sensitivity to the intestinal distension induced by inflation of balloons in the ileum, colon and rectum.

1.1.2(D) Luminal Factors:-

- Some patients develop IBS following an episode of gastroenteritis.

1.1.3 Symptoms: - The common symptom observed in the patients is: (5,)



Alternate occurrence of diarrhoea and constipation.

1.1.4 EPIDEMIOLOGY: - (10)

- Irritable bowel syndrome is one of the most common gastrointestinal disorders with worldwide prevalence of up to **20%** and the reported prevalence of IBS in India is **4.2-7.9%**.

1.1.5 CLASSIFICATION OF IBS: - (3, 4) IBS can be classified as

- 1. IBS-C = Irritable bowel syndrome- constipation
- 2. IBS-D = Irritable bowel syndrome- diarrhea
- 3. IBS-M = Irritable bowel syndrome-mixed pattern
- 4. IBS-U = Irritable bowel syndrome- unspecified

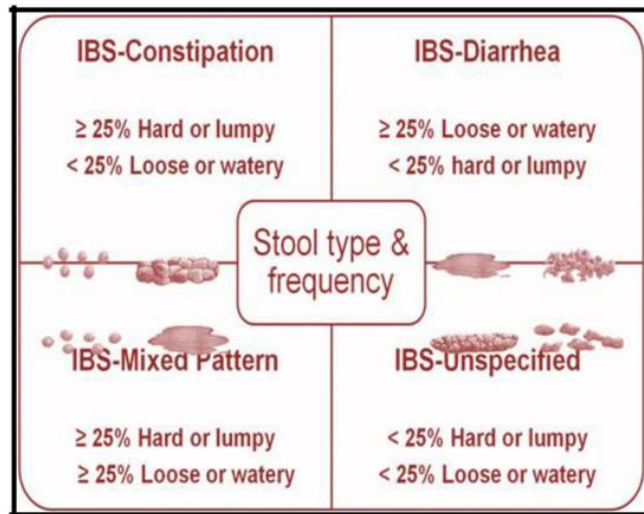
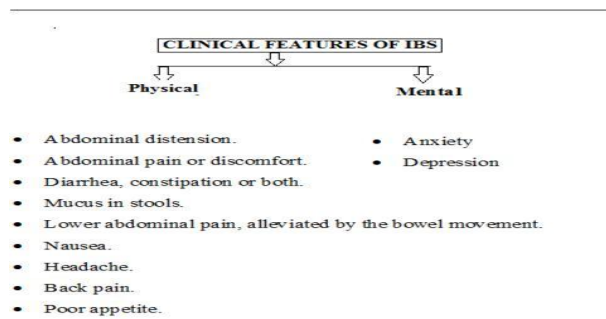


Fig 4:-Classification of IBS

1.1.6 CLINICAL FEATURES OF IBS (6, 7)

1.1.6 (A) Physical:

- Mucus in stools.
- Lower abdominal pain, alleviated by the bowel movement.
- Diarrhea, constipation or both.
- Abdominal pain or discomfort.
- Abdominal distension.
- Poor appetite.
- Nausea.
- Headache.
- Back pain.
- Depression
- Anxiet



1.1.7 PATHOGENESIS: - (11-14)

- Motor abnormalities of GI are detectable in some patients include increased frequency and irregularity of luminal contractions, prolonged transit time in constipation-predominant IBS, and an exaggerated motor response to cholecystokinin and meal ingestion in diarrhea-predominant IBS.
- Visceral hypersensitivity is frequent finding in IBS and results from stimulation of various receptors in the gut wall that transmit signals via afferent neural pathways to dorsal horn of spinal cord and ultimately to the brain.

These abnormalities are secondary to psychological disturbances rather than being of primary relevance.

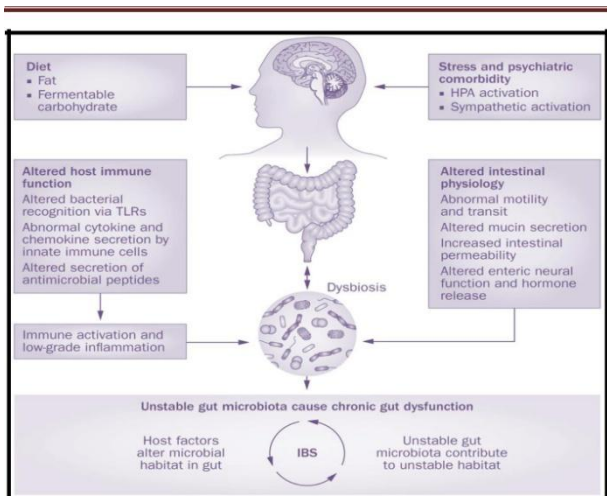


Fig 5: Pathogenesis of IBS

1.1.8DIAGNOSIS:- (4, 8, 10, 15)

- According to the complete medical history and physical examination the diagnosis of irritable bowel syndrome take place.

1.1.8(A) Additional tests

(a) Imaging tests:

- Flexible sigmoidoscopy. This test examines the lower part of the colon (sigmoid) with a flexible, lighted tube (sigmoid scope).

(b) Colonoscopy.

- Diagnostic test in which a small, flexible tube is used to examine the entire length of the colon.

(c) X-ray (radiography).

- X-rays, to obtain an image of the colon.

(d) Computerized Tomography (CT) Scans.

- CT scans produce cross-sectional X-ray images of internal organs. CT scans of your abdomen and pelvis may help your doctor rule out other causes of your symptoms, especially if you have abdominal pain.

- Lactase is an enzyme you need to digest the sugar found in dairy products. If you don't produce this enzyme, you may have problems similar to those caused by irritable bowel syndrome, including abdominal pain, gas and diarrhea.

(b)Breath Tests

- Breath test is perform to look for a condition called bacterial overgrowth, in which bacteria from the colon grow up into the small intestine, leading to bloating, abdominal discomfort and diarrhea.

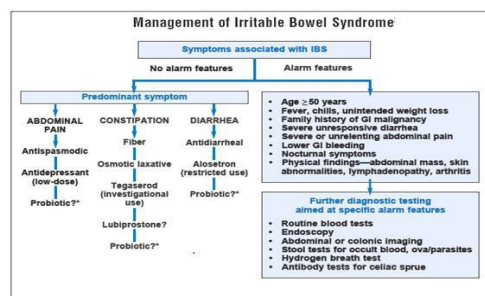
(c)Blood Tests

- Celiac disease is sensitivity to wheat, barley and rye protein that may cause signs and symptoms like those of irritable bowel syndrome. Blood tests can help rule out this disorder.

(d)Stool Tests

- In chronic diarrhea, examine stool for bacteria or parasites.

1.1.9 Management of IBS: - (7)



1.2 CONSTIPATION:- (16,17,18)

□ Constipation means having a hard, dry bowel motion (faeces) that are difficult to pass. It may cause straining, pain and discomfort. There may be slight bleeding from a small tear in the back passage.

□ Most people get constipated at some point in their lives. Constipation can be acute, which means sudden and lasting a short time, or chronic, which means lasting a long time, even years. Most constipation is acute and not dangerous.

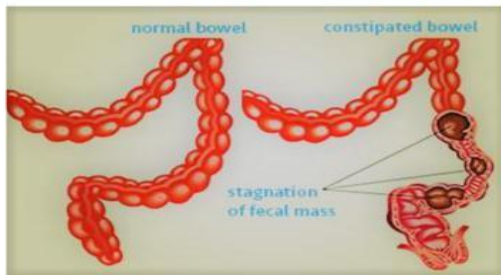


Fig 6: - Normal and constipated bowel

1.2.1 Symptoms of Constipation: - (19)

- The commonest complaint is that of infrequent bowel motions:
 - Excessive straining during bowel motions
 - Passing hard or lumpy stools
 - The feeling of incomplete evacuation or of a blockage

If stools are very hard, dry and large, it may cause a small split in the lining of the back passage (anal fissure) and result in pain and stinging in the area as well as some bright red bleeding, often seen on the toilet paper and sometimes also in the toilet.

1.2.2 Causes Constipation: - (20)

- Constipation is caused by stool spending too much time in the colon.
- The colon absorbs too much water from the stool, making it hard and dry.
- Hard, dry stool is more difficult for the muscles of the rectum to push out of the body.



Fig 7: - causes of constipation.

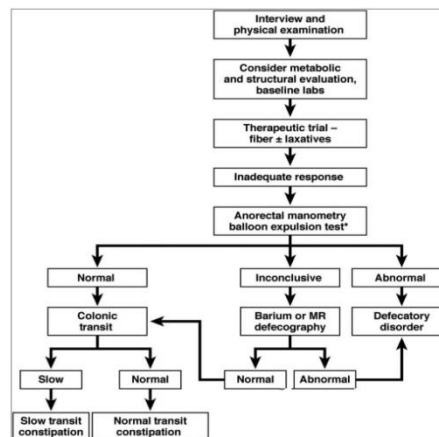
1.2.3 EPIDEMIOLOGY: - (21)

- The global prevalence of constipation varies between 7-14%, depending on the definition used.
- The prevalence is twofold higher in women than in men and tends to increase with age. Symptoms of chronic constipation overlap with those attributed to other disorder such as irritable bowel syndrome.

□ In addition, mood disorder such as depression is more prevalent in patients with chronic constipation than the general population.

1.2.4 Pathophysiology :- (22, 23, 24)

□ Constipation is often considered a natural part of aging but it is a disorder that is not caused by aging itself. Although changes in the gastrointestinal tract associated with aging may predispose one to develop constipation, the disorder usually has a multifactor etiology and may be a lifetime disorder.



□ Though bowel transit time and frequency of bowel movements do not change with aging, a number of co morbid conditions may contribute to the development of constipation.

□ Some data suggest that older adults perceive constipation as straining during defecation rather than decreased bowel frequency.

□ Another study of elderly individuals who reported constipation demonstrated that straining and hard bowel movements were the most frequent complaints.

□ Aging is associated with changes in the structure and function of the colon and defecator mechanisms. Regional differences in colonic properties and in neurotransmitter functions have implications for normal function and dysfunction.

□ Disordered defecation can occur as a result of injury to the pudendal nerve. The incidence of increased pudendal nerve terminal motor latency, an indicator of pudendal nerve dysfunction, is increased in elderly females.

□ Injury to the pudendal nerves can lead to abnormal perineal descent, which can impact rectal emptying by causing partial prolapse of the anal canal by the anterior rectal mucosa. Several types of anorectal abnormalities occur in older people with constipation including dysphasia and pelvic dyssynergia.

□ Dysphasia is characterized by reduced tone, increased compliance, and impaired sensation such that a greater degree of rectal distention is required to induce the defecator mechanism.

□ Seen most commonly in frail elders, these individuals have recurrent rectal impactions, a frequent consequence of which is fecal soiling. Fecal soiling affects 28% of older people. However, it is a problem that is not assessed by doctors or nurses.

□ Pelvic dyssynergia, also termed animus, involves a failure to relax the pelvic floor and external anal sphincter muscles during defecation.

1.3 IRRITABLE BOWEL SYNDROME WITH CONSTIPATION:- (25)

□ Irritable Bowel Syndrome with constipation, also referred to as IBS-C, is a distressing condition that can significantly affect the quality of life of those affected.

1.3.1 Symptoms of IBS-C : (26)

- abdominal pain or discomfort
- gas, bloating and abdominal distention
- straining when having a bowel movement
- a sense that something is blocking your rectum
- infrequent bowel movements (less than three per week)
- feeling like you have not completed your bowel movement

1.3.2 Causes of IBS-C (27)

- The cause of IBS-C is include:
 - Nerve Hyper-Sensitivity: Poorly coordinated signals between the brain and the gut can make your body overreact to the activities taking place during digestion causing increased sensitivity. This may explain why those with IBS-C experience abdominal pain and discomfort.

□ Intestinal motility: The walls of the intestines are lined with layers of muscles that contract and relax in a coordinated rhythm as they move food from your stomach to your intestines through a process called peristalsis. For those with IBS-C, contractions within the intestine may be reduced or delayed causing gas, bloating and stool to move slower than normal

□ Brain-bowel connection: There is a strong connection between our brain and bowel. This is sometimes called the brain-gut connection. In individuals with IBS-C, a possible disconnects or miscommunication between the mind and gut, may impact motility, pain sensitivity and fluid absorption. This disconnect may result in abdominal pain, discomfort and constipation.

□ Excess fluid absorption: Constipation results when the intestine absorbs too much

fluid from the stool, which can occur because of reduced or delayed contractions.

1.3.3 Risks Associated with IBS-C :-(28)

- If left untreated, IBS-C can potentially lead to additional health complications. These include:
 - Hemorrhoids: enlarged veins (blood vessels) in the rectum that may bleed or descend through the anus
 - Anal fissure: a crack in the lining of the anus caused when large or hard stools stretch the anal sphincter

- Fecal impaction: a mass of hard stool that cannot be excreted by a normal bowel movement and may need to be removed manually
- Rectal prolapsed: rectal tissue pushes out through the anus
- Lazy bowel syndrome: caused from frequent use of laxatives to have bowel function properly

1.4 TREATMENT AND MANAGEMENT (30, 31, 32)

(1) First –Line Treatment / Pharmacological:-

- (1) Anti-diarrhoeals e.g.: Loperamide
- (2) Visceral analgesics

e.g.: Kappa Opioid Agonists, Codeine

- (3) Laxatives

e.g.: **Lubiprostone** Methylcellulose Bisacodyl Senna

- (4) Antispasmodic/Anticholinergics

e.g.: Mebeverine, Clidinium Bromide, Dicyclomine, Peppermint Oil (Colpermine).

- (5) Antidepressants

e.g.: Amitriptyline, Clomipramin

- (6) Anxiolytics/Sedatives e.g.: Chlordiazepoxide

- 1) Cognitive behavioral therapy

- 2) Hypnotherapy

- 3) Psychotherapy.

- 4) Others :

- Yoga

- Stress Management Techniques.

- Meditation

- Exercise

1.5 INTRODUCTION TO DOSAGE FORM: - (33)

Solid medicaments may be administered orally as powders, pills, cachets, capsules or tablets. These dosage forms contain a quantity of drug which is given as a single unit and they are known collectively as solid unit dosage forms, even in the case of sustained action preparations which, technically, contain the equivalent of several normal doses of drug.

Tablet is defined as a compressed solid dosage form containing medicaments with or without excipients. According to the Indian Pharmacopoeia Pharmaceutical tablets are solid, flat or biconvex dishes, unit dosage form, prepared by compressing a drug or a mixture of drugs, with or without diluents. They vary in shape and differ greatly in size

and weight, depending on amount of medicinal substances and the intended mode of administration. It is the most popular dosage form and 70% of the total medicines are dispensed in the form of Tablet.

1.5.1 REPEAT ACTION TABLET: -

- It is a type of modified release dosage form.
- During GI disease uncontrolled and unpredictable gastric emptying is occur so repeat action tablet is based on this condition.
- It contains usually two doses of the drug, the first being released immediately following per-oral administration. The second dose is released later, when the layer of enteric coating is dissolved.

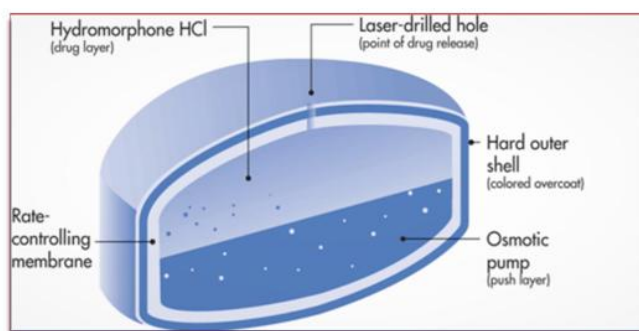


Fig 8: - repeat action tablet

1.5.1.1 Need of Repeat Action Tablet

- To control the drug delivery rate of either single or two different API.
- To separate incompatibility of API from each other and to control the release of API from one layer by utilizing the functional property of the other layer.
- Unpleasant odor and taste can be masked by coating technologies.
- As compared to other dosage forms cost is low.
- As compared to other dosage forms stability of chemical and microbial are greatest.
- Separation of incompatible components.
- Repeat action tablets can be designed and develop in such a manner as to modified release as either of the layers can be kept as sustained and the other as immediate release.
- Patient compliance is improved leading to improve drug regimen efficiency repeat action tablet is useful to reduce frequency of dose, prevention of direct contact of two or more

API and thus the efficacy of combination of two drugs will be increase.

1.5.1.3 Limitation of Repeat Action Tablet

□ Difficulty to swallow in case of children and unconscious patients.

□ Difficult to formulate or manufacture as a tablet that will still provide adequate or full drug bioavailability & Drugs with low poor wetting, dissolution properties and optimum absorption high in GIT may be difficult to formulate.

1.5.1.4 Preparation of Repeat Action Tablet (35)

□ Repeat action tablet formulation where double compression technique is involved.

□ One layer of drug for immediate release with the second layer designed to release drug extend, either as a second dose or in an extended release form are prepared by repeat action tablets.

□ The repeat action tablets with two incompatible drugs can also be prepared by compressing separate layers of each drug so as to minimize area of contact between two layers.

□ The compaction of a material involves both the compressibility and consolidation

□ Desired drug release profile and sufficient mechanical strength must be met.

□ Compression:

□ By eliminating voids and bringing particles into closer contacts as reduction in bulk volume is defined as compression.

□ Consolidation:

□ It is the property of the material in which there is increased mechanical strength due to interparticulate interaction (bonding). A major factor influencing tablet delamination was found to be by the compression force on layer 1.

□ Wide range of fluctuation Produce by Conventional dosage form in drug concentration in the blood stream and tissues with subsequent undesirable toxicity and poor efficiency.

□ The concept of controlled drug delivery systems led by this dynamic such as repetitive dosing and erratic absorption to The aim in designing sustained or controlled delivery systems is to decrease the frequency of the dosing or to

increase effectiveness of the drug by localization at the site of action, reducing the dose required or provide uniform drug delivery.

□ The main objective of sustained release drug delivery is to make sure safety and to improve effectiveness of drugs as well as patient compliance.

□ Formulation of layers are done by using more than one rate controlling polymer, thus enabling different types of drug delivery of one or more drugs where the drug may be released with a bolus and then at a controlled rate or by targeted drug delivery in the GI tract.

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