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Drugs in Development for Opioid-Induced Constipation

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1. Introduction

Opioid-induced bowel dysfunction (OIBD) is a collective term used to describe the gastrointestinal side effects of long-term opioid therapy in chronic pain patients. Constipation, nausea, vomiting, bloating, abdominal pain, and gastric reflux are among the most common gastrointestinal adverse effects. Within opioid-induced bowel dysfunction, a more specific subset exists, opioid-induced constipation, characterized by infrequent stools, straining, hard, dry stools, and incomplete evacuation. In these patients, the constipation can be so severe that they are willing to compromise their pain management by reducing their opioid analgesic dose, switch to a less potent opioid with inadequate pain relief, or completely discontinue their opioid medication all together. It is evident that opioid-induced constipation remains a significant barrier to achieving optimal pain management and represents a large unmet medical NEED.

Opioids induce gastrointestinal side effects indirectly through an effect on the central nervous system and directly through an effect on the gastrointestinal tract. Related to the indirect effect, it has been shown that intrathecal administration of opioids decreases gastrointestinal motility and intestinal secretion (Anderson, 2007). The direct effect is mediated through mu-opioid receptors in the neuronal plexi, located between the longitudinal and circular muscle layers (myenteric plexus) and within the submucosa (submucosal plexus). Within the myenteric plexus, the opioids induce relaxation of the longitudinal smooth-muscle layer and increase tonicity in the circular smooth-muscle layer. These effects are thought to be mediated through inhibition of acetylcholine release and inhibition of vasoactive intestinal peptide and nitric oxide release, respectively. The result of this differential effect on the longitudinal and circular intestinal smooth muscles is an increase in segmental contraction and a decrease in peristaltic activity.

Normal peristalsis in the small bowel occurs every 90 minutes in order to move the luminal contents from the duodenum to the ileum. Mass movements in the large bowel occurs less often, one to three times per day, sweeping its contents over longer distances. As a result of the reduced peristaltic activity, the transit time is significantly prolonged. The food stays in the stomach longer and the stool resides in the small and large bowel. The former causes gastric distension, resulting in nausea and gastric reflux, and the latter contributes to the constipation by allowing more time for fluid absorption, a predominant function of the large bowel in particular. A decrease in bowel-movement frequency is the primary symptom of

constipation, with secondary symptoms being hard, dry stool, the need for straining with bowel movements, and a sense of incomplete evacuation. Tertiary symptoms are abdominal bloating/distension, discomfort, and pain from stool or gas, borborygmi, flatulence, and dyspnea from interference of the abdominal stool and gas content with diaphragmatic contraction aiding inspiration. Aside from these physiologic effects exuded by the opioid analgesics themselves, the lifestyle of patients in chronic pain typically intensifies their condition. Chronic pain patients are often inactive and deconditioned. They are more likely to be overweight, have a poor diet, and get little to no exercise, exacerbating their constipation.

2. Prevalence

In 2010, it was estimated that approximately 250 million prescriptions were written for opioids in the United States (IMS Health 2010) and many studies indicate that a high percentage of patients receiving opioids experience gastrointestinal side effects. A systematic review was performed of 11 randomized, double-blind, placebo-controlled studies of oral opioids in the treatment of chronic non-cancer pain, given for periods ranging from 4 days to 8 weeks (Kalso et al., 2004). The opioids were morphine in five studies, morphine or methadone in one study, and oxycodone in four studies; all studies used inactive placebo except two in which benzotropine was given as active placebo. Of the 1,025 subjects randomized, 674 subjects completed the study they were in and 698 subjects were evaluable. Adverse events and lack of efficacy were the most frequent reasons for discontinuation during both opioid and placebo treatment. The mean final daily doses of the oral opioids varied from 30 to 120 mg for morphine, 20 to 45 mg for oxycodone (30 to 68.5 mg morphine equivalents), and 15 mg for methadone (45 mg morphine equivalents).

Constipation was the most common adverse event in the opioid-treated subjects, reported by 41% of the subjects in comparison to 11% of those treated with placebo, followed by nausea (32% versus 12%). The actual occurrence of constipation with oral opioid treatment in the range of 30 to 120 mg morphine equivalents per day is probably higher. The enriched nature of the studies excluded subjects from randomization who did not tolerate the medication or who did not find it effective in relieving their pain. The subjects who were not randomized because of the latter reason would also have discontinued the medication in practice; however, the subjects who were not randomized because of tolerability reasons would possibly have continued the treatment if the adverse event was constipation and this was effectively treated.

3. Available treatments

In 2008, the Food and Drug Administration approved a peripherally-acting mu-opioid-receptor antagonist (PAMORA), subcutaneous methylnaltrexone (Relistor®), for the treatment of opioid-induced constipation in patients with advanced illness who are receiving palliative care when response to traditional laxative therapy has been inadequate. Another peripherally-acting mu-opioid-receptor antagonist, alvimopan, was being studied as well but cardiovascular safety concerns, consisting of an increased risk of myocardial infarction, halted drug development. However, the Food and Drug Administration approved the medication in 2008 with a Risk Evaluation and Mitigation Strategy (REMS) for the indication of accelerating the time to upper and lower gastrointestinal recovery, following partial small- or large-bowel resection with primary anastomosis. The Risk

Evaluation and Mitigation Strategy restricts the use of the medication to short-term (15 doses) treatment in hospitalized patients and only in hospitals that have registered with the program and have met all the requirements.

Lubiprostone and tegaserod are Food and Drug Administration approved for the treatment of chronic idiopathic constipation in adults and can, of course, be used off label for this condition as well. Lubiprostone is an activator of the CIC-2 chloride channel, increasing water secretion in the lumen of the gastrointestinal tract, and tegaserod is a non-selective serotonin-4-receptor agonist. However, in 2007, upon request from the Food and Drug Administration, alleging increased risk of cardiovascular and cerebrovascular events, Novartis withdrew tegaserod from the market. Prior to its withdrawal, tegaserod was being studied for opioid-induced constipation. A prokinetic medication could be used as well, although not approved by the Food and Drug Administration for (opioid-induced) constipation, such as cisapride, a non-selective serotonin-4-receptor agonist, domperidone, a peripherally-acting dopamine-receptor antagonist, or metoclopramide, a dopamine-2-receptor antagonist and mixed serotonin-3-receptor antagonist/serotonin-4-receptor agonist. However, cisapride was withdrawn from the market because of long QT syndrome predisposing to arrhythmias, domperidone is not on the market in the United States, and the long-term, daily use of metoclopramide is not recommended because of potential extrapyramidal side effects, particularly tardive dyskinesia. Misoprostol, a synthetic prostaglandin E1 analogue, approved by the Food and Drug Administration for the prevention of gastric ulcers caused by the use of non-steroidal anti-inflammatory drugs (NSAIDs), also increases colonic transit and can be used off label as well.

Another strategy that is used to treat opioid-induced constipation is to switch to an opioid that, in general, causes less constipation as a side effect. From a constipation perspective and according to our experience, morphine, codeine, and hydrocodone tend to be worse and, for example, oxycodone and fentanyl better. Opioids that produce analgesia through other mechanisms, such as tramadol and tapentadol, which apart from being mu-opioid-receptor agonists also inhibit the presynaptic uptake of noradrenaline, tend to cause less constipation.

Over the counter constipation products in general can also be used for opioid-induced constipation, such as bulking agents (cellulose, psyllium), stool softeners (docusate), osmotic agents (lactulose, sorbitol, magnesium citrate, polyethylene glycol), and laxatives (senna, bisacodyl). Although traditional laxatives have proved efficacious at inducing bowel movements, they are a temporary, quick fix and frequently induce undesired side effects. For many patients a successful bowel movement requires a cumbersome combination of stool softeners, bowel stimulants, and osmotic agents. The unpredictable nature of stimulant laxatives are unappealing for patients as well. Aggressive laxative use does not come without the risk of serious side effects, including metabolic abnormalities, and the long term safety and relief of abdominal symptoms has yet to be revealed. One exception is Miralax (polyethylene glycol) which demonstrated sustained efficacy in long-term studies. Furthermore, traditional laxatives are not specifically approved by the Food and Drug Administration (FDA) for opioid-induced constipation.

4. Drug development

Given the paucity of FDA-approved medications and the sub-optimal efficacy of over the counter options for the treatment of opioid-induced constipation, a new drug class,

peripherally-acting mu-opioid receptor antagonists (PAMORAs), has evolved that directly targets the mechanism of opioid-induced constipation. The first two drugs to enter the market were subcutaneous methylnaltrexone (Relistor®) in April 2008 and an oral formulation of alvimopan (Entereg®) in May 2008. However, both drugs were FDA-approved in a specific sub-population, palliative care patients and post-surgical patients, respectively. Thus, the treatment for the general population with opioid-induced constipation remained limited. Since 2008, several pharmaceutical companies have developed peripherally-acting mu-opioid receptor antagonists that are now undergoing various phases of clinical studies with the specific indication of opioid-induced constipation in chronic pain patients.

Peripherally-acting mu opioid-receptor antagonists are an improvement to the traditional non-specific opioid-antagonists, naloxone and naltrexone. The novelty behind the new class resides with its restricted activity to the peripheral mu-opioid receptors in the enteric system and increased specificity to the mu-receptors versus the kappa- and delta-receptors. As a result, the constipating effects of opioids on gastrointestinal function and motility are inhibited without crossing the blood-brain barrier and reversing the central analgesic effects of opioids.

Among the drugs currently being developed, the oral formulation is the most popular. While subcutaneous methylnaltrexone (Relistor) has already been approved by the Food and Drug Administration, clinical studies with the oral formulation are underway. Other oral, peripherally-acting mu-opioid receptor antagonists in development for opioid-induced constipation are ADL5945 (Adolor), ALKS37 (Alkermes), NKTR-118 (AstraZeneca), S-297995 (Shionogi), and TD-1211 (Theravance). Lubiprostone, already FDA-approved for other types of constipation, is undergoing development for opioid-induced constipation as well. Medications that are in development for chronic constipation and may ultimately also be developed for opioid-induced constipation are the selective serotonin-4-receptor agonist, prucalopride (Johnson & Johnson), and the guanylate-cyclase C-receptor agonists, linaclotide (Ironwood) and plecanatide (Synergy).

4.1 Methylnaltrexone

Methylnaltrexone is a quaternary derivative of naltrexone, synthesized by adding a methyl group to the nitrogen atom of the molecule. Quaternary opioid antagonists are constructed to have more polarity and, therefore, less lipid solubility than their parent compounds. The reduced ability to penetrate the blood-brain barrier allows the medications to block opioid-induced constipation peripherally, without antagonizing the centrally-mediated opioid analgesia or causing central opioid withdrawal.

Methylnaltrexone was initially tested in an intravenous formulation. A laxation response was seen in 11 subjects with methadone-induced constipation who were treated with methylnaltrexone IV, compared to no laxation response in the 11 subjects in the placebo group ($P < 0.001$)². Along with the 100% response rate in the methylnaltrexone recipients, no central opioid withdrawal was observed and no significant adverse events were reported. At the same time, the oral-cecal transit time was decreased by 77.7 minutes from baseline in the methylnaltrexone group, while only by 1.4 minutes in the placebo group ($p < 0.001$). Subsequently, subcutaneous administration was studied, potentially enlarging the target population for this treatment.

In a double-blind, randomized, placebo-controlled study in healthy volunteers, oral-cecal transit time was significantly reduced after 0.3 mg/kg subcutaneous methylnaltrexone plus morphine, compared with placebo plus morphine ($P < 0.05$) (Yuan et al, 2002). As an intervention for opioid-induced constipation in advanced illness, 0.15 mg/kg subcutaneous methylnaltrexone caused a laxation response within 4 hours in 48% of 62 subjects in the methylnaltrexone group, compared to 15% of the 71 subjects in the placebo group ($p < 0.001$). Fifty two percent of the subjects had laxation without the use of a rescue laxative within 4 hours after two or more of the first four doses, as compared to 8% in the placebo group ($P < 0.001$) (Thomas et al, 2008). The treatment did not affect centrally-mediated analgesia and did not precipitate opioid withdrawal. Abdominal pain and flatulence were the most common adverse events.

A similar study in opioid-induced constipation in advanced illness used a single subcutaneous injection of methylnaltrexone, 0.15 mg/kg or 0.3 mg/kg, or placebo (Slatkin et al, 2009). Sixty two percent and 58% of the subjects treated with methylnaltrexone 0.15 mg/kg and 0.3 mg/kg, respectively, had a laxation response within 4 hours, compared to 14% of the subjects in the placebo group ($P < 0.0001$; each dose *versus* placebo). Adverse events were slightly more common in the subjects treated with 0.15 mg/kg than in those treated with 0.3 mg/kg, particularly abdominal pain, flatulence, nausea, and dizziness. Due to a comparable efficacy profile, the results suggest the lower dose, 0.15 mg/kg, to be most optimal.

Methylnaltrexone in a dose of 12 mg subcutaneous was given once daily or every other day for 28 days in a randomized, double-blind, placebo-controlled study, which involved a total of 469 subjects with opioid-induced constipation (Slatkin et al, 2009). Compared to placebo, the medication given once daily significantly improved rectal symptoms ($P < 0.05$), stool symptoms ($P < 0.001$), and global constipation scores ($P < 0.001$), while given every other day significantly improved stool symptoms ($P < 0.05$) and global constipation scores ($P < 0.05$). The changes from baseline in abdominal symptoms and pain scores between the two methylnaltrexone groups and placebo were not significant.

Although the intravenous and subcutaneous formulations produced promising results, they are impractical for the general population. An intravenous administration can only be administered under the supervision of health care professionals, and while the subcutaneous injections are more safe and convenient, they either require self-administration or frequent assistance. An oral formulation is the most favorable as a pill is generally more convenient and affordable. Fortunately, phase 3 studies have commenced, assessing the safety and efficacy of oral methylnaltrexone for opioid-induced constipation in chronic pain patients.

4.2 ADL5945

ADL5945 is an oral peripherally-acting mu-opioid-receptor antagonist in development by Adolor with two randomized, double-blind, placebo-controlled studies recently completed in subjects with chronic non-cancer pain and opioid-induced constipation. In the first study, two doses of ADL5945 (0.10 mg and 0.25 mg) were given twice daily *versus* placebo to 130 subjects (43 per treatment arm) over 4 weeks. The second study was of similar design, with the exception that only one dose of ADL5945 (0.25 mg) was given and only once daily *versus*

placebo to 80 patients (40 per treatment arm). The primary endpoint in both studies was the change from baseline in the mean number of spontaneous bowel movements per week over the 4-week treatment period. The results demonstrated a statistically significant and clinically relevant effect of the 0.25 mg dose in particular, without tolerability issues and evidence of central opioid withdrawal or reversal of opioid analgesia. Adolor's backup compound for opioid-induced constipation is the peripherally-acting mu-opioid-receptor antagonist, ADL7745, which recently successfully completed preclinical studies.

4.3 ALKS37

ALKS 37 (RDC-1036) is an oral peripherally-acting mu-opioid-receptor antagonist in development by Alkermes for the treatment of opioid-induced constipation, with a randomized, double-blind, placebo-controlled, multi-dose study recently completed (Alkermes website, 2011). The study treated opioid-induced constipation in subjects with chronic non-cancer pain with doses of 1 to 100 mg taken once daily. Subjects were eligible to participate in the study if they were taking opioid analgesics at doses of 30 mg or more morphine equivalents per day and had fewer than three spontaneous bowel movements per week.

The primary endpoint was a change from baseline in the average number of spontaneous bowel movements per week. A clear dose-response relationship was demonstrated with a statistically significant increase in the average number of spontaneous bowel movements per week in the subjects receiving 100 mg of the medication once daily, compared to those receiving placebo (4.5 *versus* 0.7) ($p = 0.006$). The results also demonstrated a statistically significant increase in the average number of complete spontaneous bowel movements per week, compared to subjects receiving placebo (3.5 *versus* 0.8) ($p = 0.007$). Overall, ALKS 37 was well tolerated and the most commonly reported adverse events were gastrointestinal in nature, including abdominal pain (25%) and diarrhea (22%), mostly occurring in the higher and most effective doses (30 mg and 100 mg). There was no indication of reversal of opioid analgesia, that is, there was no increase in average daily pain score or opioid use (Alkermes Press Release, 2011).

4.4 NKTR-118

NKTR-118, also known as PEG-naloxol, is a combination of naloxol, a derivative of the opioid antagonist, naloxone, and a polyethylene glycol moiety. The purpose of the PEGylation is twofold, that is: 1. altering its metabolism, thereby reducing the first-pass effect and increasing its bioavailability, and 2. modifying its distribution to reduce penetration into the central nervous system. A randomized, double-blind, placebo-controlled, multiple-dose study was performed, evaluating the safety and efficacy of NKTR-118 in subjects with opioid-induced constipation (Webster, L., 2009). Eligible subjects were defined as having opioid-induced constipation with fewer than three spontaneous bowel movements per week and on a stable analgesic opioid regimen of 30 mg to 1000 mg morphine equivalents per day for a minimum of 2 weeks. A total of 208 subjects were randomized to NKTR-118 or placebo in three sequential cohorts. The first week they received a once daily dose of single-blind placebo, followed by 4 weeks of NKTR-118 once daily in doses of 5, 25, or 50 mg, or placebo.

The primary endpoint was achieved in both the 25-mg and 50-mg treatment groups, with a significant increase in the mean number of spontaneous bowel movements per week over the first week. Subjects receiving 25 mg NKTR-118 had an average of 5.0 spontaneous bowel movements during the first week (1.4 at baseline) *versus* 3.1 in the placebo group (1.2 at baseline) ($p = 0.002$). Subjects receiving 50 mg NKTR-118 had an average of 6.0 spontaneous bowel movements during the first week (1.6 at baseline) *versus* 3.3 in the placebo group (1.3 at baseline) ($p = 0.0001$). The increase in bowel movements was sustained at a statistically significant level throughout the 4 weeks in both dose groups ($p = 0.002$ and $p < 0.0001$, respectively). The medication was well tolerated and adverse events were dose-dependent, occurring most frequently in the 50-mg group, and were primarily gastrointestinal in nature, particularly abdominal pain, cramps, diarrhea, and nausea. The majority of the adverse events were rated as mild or moderate in intensity. Reversal of opioid analgesia was not observed in the study, as measured by numerical pain rating and opioid requirement.

4.5 S-297995

Shionogi has developed an oral peripherally-acting mu-opioid-receptor antagonist, S-297995. Initially, it was designed to alleviate a spectrum of opioid-induced side effects (constipation, nausea, and vomiting) but the more recent studies have focused primarily on its effects on opioid-induced constipation. S-297995 may prove more favorable than existing treatments, given its efficacy at lower doses in alleviating not just opioid-induced constipation but also nausea and vomiting (Shionogi website, 2011).

In 2011, a randomized, double-blind, placebo-controlled, single-ascending dose study was completed to evaluate the safety and efficacy of S-297995 in opioid-induced constipation. Subjects were eligible to participate in the study if they had chronic pain requiring 90 mg or more morphine equivalents daily for a minimum of 3 months, opioid-induced constipation, and physical opioid dependence. Seventy five subjects were randomized to one of six S-297995 cohorts (0.01 mg, 0.03 mg, 0.1 mg, 0.3 mg, 1.0 mg, or 3.0 mg). Preliminary results demonstrate a statistically significant and dose-dependent increase from baseline in the number of spontaneous bowel movements at 24 hours post-dose, starting at doses of 0.3 mg ($p = 0.0011$ in the 0.3-mg group and $p < 0.001$ in both the 1.0-mg and 3.0-mg groups). The medication was generally well tolerated with predominantly mild or moderate gastrointestinal adverse events. There was no evidence of central opioid withdrawal and there was no impact on the analgesic effect of the opioids or a change in pupil size (Shionogi Annual Report, 2011).

4.6 TD-1211

TD-1211 is a multivalent compound designed by Theravance to block the effects of opioids on the gastrointestinal mu-opioid receptors, without mitigating their central analgesic properties. In preclinical studies, the medication demonstrated oral bioavailability with no evidence of activity in the central nervous system. A randomized, double-blind, placebo-controlled, dose-escalation study assessed the efficacy and safety of the medication in subjects with non-cancer pain and opioid-induced constipation (Theravance Press Release, 2011). The latter was defined as fewer than five spontaneous bowel movements during a 2-week baseline period and at least one additional symptom of constipation. A total of 70 subjects were randomized to receive oral 0.25, 0.75, 2.0, 5.0, and 10.0 mg doses of TD 1211 daily, or placebo.

The primary endpoint was the change from baseline in the average spontaneous bowel movements per week over the 2-week treatment period. Proof of efficacy was achieved in a dose-dependent fashion, specifically with the 5 and 10 mg doses. In the subjects who received the 5 mg dose, the mean number of spontaneous bowel movements increased by 3.2 (from 1.1 at baseline to 4.3 over the 2-week treatment period; confidence interval: 1.5-5.0). Similarly, in the subjects who received the 10 mg dose, the mean number of spontaneous bowel movements increased by 4.9 (from 1.4 at baseline to 6.3 over the 2-week treatment period; confidence interval: 3.1-6.7). However, in the placebo-treated group, the increase in the mean number of spontaneous bowel movements was not statistically significant (from 1.7 at baseline to 3.3 over the 2-week treatment period; confidence interval: 0.6-2.5).

Regarding the median time to first spontaneous bowel movement after the first dose of TD-1211, a dose-dependent reduction was observed in the subjects receiving the 5 and 10 mg doses, with the time reduced to 8.6 and 3.6 hours, respectively, *versus* 28.7 hours in the placebo group. Overall, TD-1211 was well tolerated with the majority of the gastrointestinal adverse events mild or moderate in intensity, occurring early in treatment and resolving within days. There was no evidence of central opioid withdrawal with the medication or reversal of opioid analgesia.

4.7 Lubiprostone

Lubiprostone is an activator of the CIC-2 chloride channel, increasing water secretion in the lumen of the gastrointestinal tract, approved by the Food and Drug Administration for the treatment of chronic constipation and constipation-predominant irritable bowel syndrome (IBS). It is in development for opioid-induced constipation and two randomized, double-blind, placebo-controlled studies with this indication have been completed (Sucampo website, 2009). The two studies are identical phase 3 trials in which a total of 875 subjects with opioid-induced bowel dysfunction were randomized to 12-week treatment with lubiprostone, 24 mcg twice daily. The subjects were taking opioid medications for chronic non-cancer pain, including fentanyl, methadone, morphine, and oxycodone, for at least 30 days prior to screening and continued to take these medications for the duration of the study. During the 2-week baseline period before randomization, they were required to have fewer than three spontaneous bowel movements per week. The overall adverse-event rate for the combined studies was 54.9% for lubiprostone and 51.6% for placebo, with nausea being most common (15.0% *versus* 7.5%), followed by diarrhea (8.5% *versus* 3.7%).

The primary endpoint of the studies was the change from baseline in the frequency of spontaneous bowel movements at week 8 of treatment, which was met in one of the studies (OBD0631) but not in the other (OBD0632). The change from baseline in the frequency of spontaneous bowel movements in the first study was from 1.42 to 4.54 for lubiprostone and from 1.46 to 3.81 for placebo; in the second study, these changes were from 1.60 to 4.10 for lubiprostone and from 1.60 to 3.95 for placebo. An interesting post-hoc sub-analysis revealed that subjects taking methadone and randomized to lubiprostone experienced a lower increase in the frequency of spontaneous bowel movements than lubiprostone-treated subjects on other opioids. Methadone was subsequently found to interfere with the mode of action of lubiprostone at the level of the CIC-2 chloride channel. A third randomized, double-blind, placebo-controlled study with the exclusion of methadone users is currently being conducted.

5. Conclusion

Opioid-induced gastrointestinal dysfunction results predominantly from the effect of opioids on the mu-opioid receptors in the gastrointestinal tract. Constipation and nausea are its most common symptoms, probably occurring in at least half of the patients treated with oral opioids. The constipation in particular is not an uncommon reason for patients to discontinue the medication or to take it at a dose that is much lower than required for adequate pain relief. In addition, it can further decrease the quality of life in patients whose quality of life is generally already significantly impaired by chronic pain. With the exception of subcutaneous methylnaltrexone for a subset of patients, there are no medications on the market for the general population with opioid-induced constipation. Prospective treatments are in development and will undoubtedly obtain marketing approval from the Food and Drug Administration within the next several years. With the emergence of these novel medications that specifically target the pathophysiology of OIC, there is hope for patients who suffer not only from chronic pain but the adverse effects of their opioid pain medication.

6. Acknowledgements

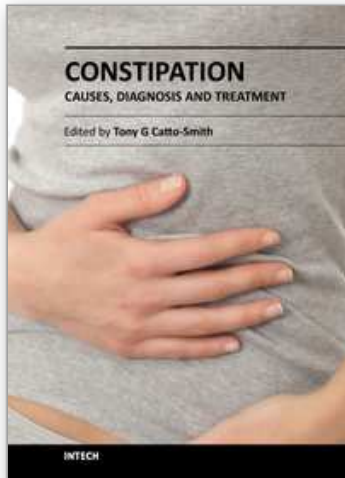
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Constipation is common in both adults and children. Estimates would suggest a median prevalence of around 12-16% in the general population. While regarded as a minor nuisance in some cases, its consequences can be severe, with a substantial impact on quality of life. Secondary faecal soiling has a profound psychological effect at all ages. This book provides contributions from authors with a range of backgrounds which clarify the pathogenesis, diagnosis, and therapy of constipation for the general population and also for certain high risk groups.

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