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Gastrointestinal tract as a side-effect target of medications

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World Health Organization (WHO) defines adverse drug reaction (ADR) as "a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological function". ADRs are a serious problem of contemporary pharmacotherapy. Expenditures for treatment of ADRs in the United States may cost up to 30.1 billion dollars annually. Factors affecting the development of ADRs are: age, gender, body weight, polypharmacy. About 10% of ADRs is associated with gastrointestinal tract (GIT). ADR can affect every part of GIT. Xerostomia is the most common ADR occurring in oral cavity. ADRs affecting esophagus include irritation and inflammation of the mucosa. Approximately one-third of all cases of esophageal inflammation results from administration of non-steroid anti-inflammatory drugs (NSAIDs). The main cause of ulcerations involving stomach and small intestine are NSAIDs. Drug-induced diarrheas are the most common adverse effect accounting for approximately 7% of all observed cases of ADRs. They may be triggered by antibiotics, magnesium salts, laxatives and others. On the other hand, some groups of medications may induce constipation. These drugs comprise opioids, diuretics, calcium channel blockers, cholinolytics and others. Proton pump inhibitors, metformin, orlistat and colesevelam may lead to restricted absorption of certain vitamins and minerals. Physicians' knowledge about most popular and well documented ADRs can improve patients' safety and make pharmacotherapy more comfortable for them.

Światowa Organizacja Zdrowia (WHO) definiuje niepożądaną reakcję na lek (ADR) jako "odpowiedź na lek, która jest szkodliwa i niezamierzona i która pojawia się przy dawkach stosowanych zazwyczaj u człowieka w profilaktyce, diagnostyce , leczeniu choroby lub modyfikacji funkcji fizjologicznej."

Działania niepożądane są poważnym problemem współczesnej farmakoterapii. Wydatki na leczenie działań niepożądanych w Stanach Zjednoczonych mogą sięgać nawet do 30,1 miliardów dolarów rocznie.

Czynniki wpływające na rozwój działań niepożądanych to: wiek, płeć, masa ciała, polipragmazja. Około 10% ADR jest związanych z przewodem pokarmowym (GIT). ADR może wpływać na każdą część GIT. Kserostomia jest najczęstszym ADR występującym w jamie ustnej. Działania niepożądane obejmują podrażnienia przełyku i zapalenia błony śluzowej. Około jednej trzeciej wszystkich przypadków zapalenia przełyku wywołuje podawanie niesteroidowych leków przeciwzapalnych (NLPZ). Główną przyczyną owrzodzeń zlokalizowanych w żołądku i jelicie cienkim są NLPZ. Biegunki polekowe są najczęstszym działaniem niepożądanym, stanowią około 7% wszystkich zaobserwowanych przypadków działań niepożądanych. Mogą być wyzwalane przez antybiotyki, sole magnezowe, środki przeczyszczające i inne leki. Z drugiej strony, niektóre grupy leków, mogą powodować zaparcia. Leki te obejmują opioidy, leki moczopędne, blokery kanału wapniowego, cholinolityki i inne. Inhibitory pompy protonowej, metformina, orlistat i kolesewelam może prowadzić do ograniczonego wchłaniania niektórych witamin i minerałów. Wiedza lekarzy o najbardziej popularnych i dobrze udokumentowanych działaniach niepożądanych, może poprawić bezpieczeństwo pacjentów i uczynić farmakoterapię lepiej dopasowaną do ich potrzeb.

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Introduction

World Health Organization (WHO) defines adverse drug reaction (ADR) as "a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological function"

[1,2]. Virtually all the drugs may cause side effects of varying severity. ADR is a serious problem of modern pharmacotherapy. In the United States in 2004, ADR was the cause of 180,000 deaths and over a million hospitalizations. The treatment costs of ADR are high - in the United States they amount to $ 3 billion a year.

The expenses might be also generated by a phenomenon called "prescribing cascade." It consists in the fact that ADR is diagnosed and treated as a new disease, for instance: arthritis → NSAIDs → hypertension → calcium channel blocker (amlodipine) → swollen ankles → diuretic (indapamide) → gout (allopurinol). In this way, the patient was diagnosed incorrectly with three diseases which are actually side effects of drugs. Whereby, instead of switching of the basic drug, the patient received the next three medications, what was followed by the next adverse reactions [1,3].

The occurrence of ADR is influenced by many factors, such as amount of drugs, age and sex of the patient. The gastrointestinal tract (GIT) is very often the locus of ADR - about 10% of all reported cases [1,4,5]. In this article we will try to bring the most common and best known ADR associated with the GIT [1,5].

Oral cavity

The oral cavity is the first segment of the gastrointestinal tract and similarly as its consecutive segments, it is at risk of damages of its structures resulting from adverse effects of some pharmaceuticals.

Ulceration of the oral mucosa may be triggered by cholinolytic agents, potassium-containing preparations, as well as acetylsalicic acid. The risk of such damages is particularly high in patients who prolong keeping medications in their mouth, what results in active substances being released from a tablet already at this stage. Adverse effects of topical preparations containing antiseptics, anesthetics and antibiotics are most commonly associated with the patient developing redness and irritation of the mucous membrane of the cheeks [1].

Table II provides a list of medications, which - when no appropriate oral hygiene is employed - may result in drug-induced gingival overgrowth. Such injuries usually appear one to three months following initiation of therapy with one or several of the above pharmaceuticals. Most commonly, the lesions are situated in the region of the anterior labial gingiva. Treatment consists in discontinuation of the causal preparation or employing a replacement medication that does not evoke gingival hyperplasia [1,6,7].

Xerostomia is dryness of the oral cavity, which is a result of reduction or complete lack of saliva secretion. It is estimated that more than 500 medications may result in the pathology; the most important preparations are presented in table III. The symptoms of reduced saliva secretion include a sense of dryness of the oral cavity, difficulties when swallowing (dysphagia), discomfort when talking, taste abnormalities and injuries of the oral mucosa. Prolonged xerostomia leads to development of fungal infections, burning sensation in the mouth, dental caries and profound pain [8-10]. Oral dryness is an adverse effect, which in the majority of cases is resolved following therapy discontinuation or a change in pharmacotherapy [8,9].

On the other hand, reduced taste and dysgeusia may represent adverse effects of such medications as tetracyclines, griseofulvin, or lithium preparations [11].

Esophagus

The most common adverse effects occurring within the esophagus include irritation and inflammation of the mucosa, which in their most severe form may lead to esophageal ulceration or stricture [12-14].

A cause of esophageal inflammation may lie in a premature release of the active agent from a tablet or capsule. The phenomenon is caused by the pill being lodged in this segment of the gastrointestinal tract. The reason underlying the medication being lodged in the esophagus may include its anatomical structure, dysphagia resulting from a disease (e.g. abnormal intestinal peristalsis, neurological conditions, the presence of an obstacle) or too small an amount of fluid used while swallowing a tablet/capsule [1]. Some authors maintain that capsules are prone to be more frequently lodged in the esophagus [16]. Blunt pain situated in the chest or arm and developing soon after having taken a medication or a meal may be the only presenting symptom reported by the patient [17]. Substances that are the most common agents causing irritation of the esophageal mucosa include acetylsalicic acid (and other non-steroid anti-

Table I
Risk factors for adverse drug reactions.
Czynniki ryzyka występowania niepożądanych reakcji na lek.

Risk Factors For Adverse Drug Reactions
Age (>65 years)
Gender (women)
Body weight and fat distribution
Pregnancy and Breastfeeding
Alcohol drinking
Smoking
Polypharmacy
Drug dose and frequency
Renal failure
Liver disease

Tabela II
List of medications associated with gingival enlargement.
Leki związane z wystąpieniem przerostu dziąseł.

List Of Medications Associated With Gingival Enlargement	
Category of a medication	Name of the drug
Anticonvulsants	phenytoin sodium valproate phenobarbitone vigabatrin carbamazepine
Immunosuppressants	cyclosporine
Calcium channels blockers	nifedipine isradipine felodipine amlodipine verapamil diltiazem

Tabela III
List of medications causing xerostomia.
Leki mogące powodować kserostomię.

List of Medications causing xerostomia	
Category of a medication	Name of the drug
Diuretics	chlorothiazide hydrochlorothiazide
Antidepressants	amitriptyline imipramine reboxetine bupropion hydrochloride
Antihistaminic agents	clemastine
Neuroleptics	derivatives of phenothiazine butyrophenone thioxanthene
Bronchodilators	B2-adrenomimetics inhalatory glucocorticoids inhalatory cholinolytics (ipratropium)
Anxiolytics	benzodiazepine derivatives: diazepam, oxazepam, lorazepam
Cholinolytic agents	atropine homatropine scopolamine
Hypotensive agents	angiotensin-converting enzyme inhibitors: enalapril, caplopril, lysinopril, perindopril
Opioids	morphine codeine methadone pethidine
Immunomodulators	interferon-alpha
Appetite suppressants	sibutramine
Antimigraine drugs	rizatriptan

-inflammatory drugs), potassium chloride, tetracycline, doxycycline, vitamin C, iron, quinidine, bisphosphonates, theophilline and captopril [12,18,19].

The most common cause of mucosal injury is a release - in contact with the mucous membrane - of a large amount of an irritant (a strong acid or a strong base) or a hyperosmolar character of concentrated salts (e.g. potassium chloride) [1,20-22].

Tetracyclines, and in particular doxycycline, may cause esophageal inflammation, mainly in young patients, who employ the medications as anti-acne therapy. The cause of such a phenomenon is a release of tetracyclines in the form of an acid at the site where a tablet or a capsule dissolves [13,14].

The symptoms of mucosal irritation usually resolve spontaneously within several days, and in case of severe ailments that interfere with eating, pain may be alleviated employing sucralfate or lidocaine suspension [17].

To avoid a tablet or capsule being lodged in the esophagus, one should follow several fundamental principles: medications should be taken with the patient in a vertical position, taking the pharmaceutical should be preceded by drinking several sips of fluid to moisture the throat, and the medication should be washed down with approximately 240ml of fluid [1,17]. A vertical position is particularly important in case of biphosphonate therapy. Patients taking drugs from this group should be also reminded of the necessity of taking the medication on an empty stomach (approximately 30 minutes before a meal) and washing it down with a glass of water. Maintaining a vertical position (sitting or standing) for at least 30 minutes following taking the medication decreases the probability of developing ulcers [23,24]. As it follows from studies, third generation bisphosphonates (sodium risedronate) less commonly cause ulceration as compared to earlier pharmaceuticals (alendronate) [1,23,24].

Patients who develop esophageal inflammation due to potassium chloride administration (often taken by individuals who are on diuretics) may be recommended microencapsulated preparations, which are safer in this respect as compared to slow release tablets [12].

Approximately one-third of cases of esophageal inflammation result from administration of non-steroid anti-inflammatory drugs (NSAIDs), mainly acetylsalicic acid [1]. NSAIDs are also a common cause of esophageal and peptic ulcers [18,25,26]. Adverse effects of NSAIDs are associated with a direct and indirect effect exerted by the preparations on the mucosa [26,27]. Direct mucosal irritation by NSAIDs weakens its resistance to toxic substances via disturbances of its integrity [12,28,29]. At the same time, NSAIDs - inhibiting the activity of cyclooxygenase 1 (COX 1) - cause a decrease in production of prostaglandins that are necessary for normal mucosal function. A decrease in the amount of prostaglandins leads to:

- a decreased production of mucin that is responsible for protecting the mucosa against the activity of digestive enzymes and corrosive substances,
- poor blood circulation, with a resultant decrease in the amount of oxygen transported to the mucosal cells [20,30].

The result of adverse effects of NSAIDs may be not only superficial injuries, but also ulcers and bleeding, as well as perforation [5,31-33]. The symptoms reported by the patient are non-specific (vomiting, diarrhea, nausea) and they do not always reflect the true degree of the mucosal damage [33].

In patients from the risk group, it is recommended to use NSAIDs being selective COX 2 inhibitors to avoid disturbances in prostaglandin production [34].

Medication-induced injuries of the esophageal mucosa may be triggered indirectly by pharmaceuticals, the adverse effect of which is disturbances of the normal pressure tension of the lower esophageal sphincter (LES). A decreased LES pressure results in altered peristalsis and may be a cause of gastroesophageal reflux [35-37].

Medications that may lead to this type of disturbances include sildenafil, tricyclic antidepressants, diazepam, calcium channel blockers, cholinomimetics, nitrates, morphine, theophilline and progesterone [36].

Oral iron preparations may cause damages of the esophageal as well as gastric and duodenal mucosa. Lesions in the upper gastrointestinal tract resulting from chemical irritation of the mucosa by iron are seen microscopically in necrotic epithelial tissue as brown-black crystals. The highest risk of injuries induced by iron preparations is seen in bed-ridden patients with coexisting disturbances of saliva production [38,39].

Stomach

Use of NSAIDs leads to the same side effects both in the esophagus as in the stomach.

Adverse effects of treating hepatic tumors with chemotherapy and irradiation therapy administered in intra-arterial infusions are ulcerations, mainly peptic ulcers [40,41]. A characteristic microscopic finding includes atypical nuclei that are increased in numbers and seen in the ulceration zone [41].

Pseudodysplasia may also develop in patients with gout who take colchicine, or in individuals who are on paclitaxel cancer therapy. Both medications inhibit mitosis via inhibition of microtubule formation resulting from inhibiting tubulin polymerization [40,42]. Colchicine induces the above-mentioned symptoms predominantly in the gastric antrum and duodenum, usually in individuals with kidney dysfunction. or who has overdosed the pharmaceutical [42]. Paclitaxel may be a cause of injuries situated in the esophagus, more rarely in the stomach or intestines [40,41].

The most common adverse effects of pharmaceuticals include nausea and vomiting, usually concomitant with the onset of therapy. Administration of antiemetic agents may prove necessary when the symptoms are severe and there is a risk of electrolyte disturbances or dehydration.

Drugs that have specific emetogenic activity include chemotherapeutics. They induce vomiting in the mechanism of indirect and direct stimulation of the vomiting center in the brain stem and the vomiting center in the solitary tract [43]. The indirect mechanism consists in a reaction to damaging stimuli, which induce serotonin release from enterochromaffin cells of the gastrointestinal epithelium, what results in stimulation of 5-hydroxytryptamine receptors (5-HT3) in the vagal nerve, from where the signal is transmitted to the vomiting centers. The other mechanism is direct stimulation of the central nervous system by cytostatic drugs [43]. Chemotherapeutics may be divided with respect to their emetogenic potential. Medications with the highest potential include such agents as cisplatin, altretamine and carmustine, while the lowest potential is shown by e.g. alemtuzumab, vinblastine and interpheron α [43].

In the majority of cases, employing an appropriate premedication schedule allows for avoiding cytostatic treatment-induced vomiting [44].

Nausea and vomiting may be also a symptom of a toxic activity of a pharmaceutical, resulting from overdosage, observed in case of taking preparations containing e.g. theophilline and digoxin [1].

Small intestine

Similarly as in the case of the esophagus and stomach, medication-induced mucosal damage may develop also in the small intestine resulting from a direct contact with a therapeutic agent in consequence of taking gastro-resistant capsules.

The main cause of ulcerations involving the small intestine, similarly as in the case of the upper gastrointestinal tract, are NSAIDs. At particular risk are patients who are on chronic NSAIDs therapy. The highest risk of mucosal damage involving the small intestine, regardless of the route of administration, is demonstrated by indomethacin and also by other NSDAIDs that pass through the hepato-intestinal circulation [45-47]. The clinical symptoms include anemia caused by iron deficiency and latent blood in stool, which results from intestinal bleeding [46].

Diagnostic management of injuries of the small intestine mucosa has become possible due to the use of video capsule endoscopy.

In some cases, inflammation of the small intestine caused by a long-term usage of NSAIDs leads to development of diaphragm disease. Diaphragm disease is narrowing of the small intestine lumen resulting from barrier-forming scarring produced in the course of mucosal healing [48,49]. The most common symptoms of diaphragm disease include weight loss with concomitant diarrhea; the most severe cases of intestinal obstruction require surgical interventions [48].

Decelerated small intestine motility may be induced by taking medications belonging to the group of opioids, tri-cyclic antidepressants, phenotiazine derivatives, calcium channel blockers, anti-parkinsonism drugs, as well as large doses of cholinolythics. Disturbances of small intestine motility usually resolve following discontinuation of treatment with the above-mentioned pharmaceuticals.

Ischemia of the small intestine may be

Tabela IV
Antibiotics associated with clostridium difficile associated disease (CDAD).
Antybiotyki związane z wystąpieniem CDAD.

ANTIBIOTICS ASSOCIATED WITH CLOSTRIDIUM DIFFICILE ASSOCIATED DISEASE (CDAD)		
MOST FREQUENTLY ASSOCIATED:	**FREQUENTLY ASSOCIATED:**	**LESS FREQUENTLY ASSOCIATED:**
CLINDAMYCIN SECOND- AND THIRD-GENERATION CEPHALOSPORINS FLUOROQUINOLONES BROAD-SPECTRUM PENICILLINS WITH INHIBITORS	TICARCILLIN/CLAVULANATE PIPERACILLIN/TAZOBACTAM AMOXICILLIN AMPICILLIN TRIMETHOPRIM/SULFAMETHOXAZOLE MACROLIDES TIGECYCLINE CARBAPENEMS	AMINOGLYCOSIDES FIRST GENERATION CEPHALOSPORINS TETRACYCLINES VANCOMYCIN METRONIDAZOLE RIFAMPICIN CLOXACILLIN PENICILLIN NITROFURANTOINE

an adverse effect of such medications as digoxin, preparations employed in hormone therapy, diuretics and antihypertensives [1].

Colon

The most common adverse effect accounting for approximately 7% of all observed cases of adverse drug reactions (ADR) are drug-induced diarrheas [50]. They may be triggered among others by antidiabetic agents, thyroid hormones, immunosuppresants, anti-inflammatory medications and diuretics [1]. The WHO defines diarrhea as a minimum of three watery stools occurring over at least two consecutive days [51]. The mechanisms underlying drug-induced diarrheas are variable and not fully understood. Osmotic diarrheas are caused by inhibition of water absorption from the large bowel due to increased osmotic pressure of colonic content. They may be induced by preparations taken to neutralize gastric acid, containing inorganic magnesium salts, and laxatives, such as lactulose, macrogol, sodium phosphates. Antibiotic-induced diarrheas are particularly common, resulting among others from disturbances of intestinal bacterial flora; such diarrheas are seen in 25-30% of patients on antibiotic therapy and are caused by overrepresentation of resistant strains and their excessive growth [52].

Broad-spectrum antibiotics, such as ampicillin, clindamycin, cephalosporins, amoxicillin/clavulanic acid, are the predominant cause of antibiotic-induced diarrheas. Development of diarrhea is independent of the route of drug administration, and for this reason, in case it occurs, changing the antibiotic rather than route of its administration is justified [52].

Pathological growth of *Clostridium difficile* (CD) is the cause of 15-25% of antibiotic-induced diarrheas. Approximately 3% of healthy population members are CD carriers. Diarrheas may be concomitant with abdominal cramps, fever and gastrointestinal bleeding [52,53].

The basic diagnostic management consists in determining A and B Clostridium difficile toxins in a stool sample. Antibiotics are divided into three groups with respect to the risk of CD infection development. The highest predisposition to evoke Clostridium difficile-associated disease (CDAD) is characteristic of clindamycin, II and III generation cephalosporins, fluoroquinolones and broad spectrum penicillins. The complete division of antibiotics is presented in Table 4 [54].

Tabela V
Risk of gastrointestinal complications with nonsteroidal anti-inflammatory drugs.
Ryzyko powikłań ze strony przewodu pokarmowego po zastosowaniu niesteroidowych leków przeciwzapalnych.

RISK OF GASTROINTESTINAL COMPLICATIONS WITH NONSTEROIDAL ANTI-INFLAMMATORY DRUGS		
Low risk	Medium risk	High risk
Celecoxib Rofecoxib Ibuprofen (not at higher doses -> 1,800 mg/day)	Diclofenac Meloxicam Naproxen Indomethacin	Piroxicam Ketoprofen Ketorolac

Tabela VI
Common causes of drug-induced constipation.
Najczęstsze przyczyny zaparć polekowych.

COMMON CAUSES OF DRUG-INDUCED CONSTIPATION:
Calcium Channel Blockers: Verapamil
Diuretics: Furosemid
Antacids Containing Calcium or Aluminium
Antidepressants: Tricyclic and Inhibitors of MAO
Cholinolytic Drugs: Tolterodine, Oxybutynin, Trospium
Anticonvulsive Drugs
Opioids: Morphine
Iron Supplements
Antiparkinson Drugs: Levodopa, Bromocriptine, Pramipexol, Amantadine
Neuroleptic Agents: Trifluoperazine, Chlorpromazine:
Antispasmodic Drugs: Dicyclomine, Hyoscine

Toxins produced by CD are the cause of pseudomembranous colitis in every fourth patient with severe course of antibiotic-induced diarrhea [55].

Discontinuation of treatment with the antibiotic that is the cause of CDAD is recommended in patients with mild infection course; in 23% of patients, it results in symptom resolution after 48-70 hours [56]. If antibiotic therapy cannot be discontinued, one should consider changing the antibiotic to another drug from this group that is associated with a lower CDAD risk. In patients with moderate and severe forms of CDAD, the first line therapy is oral metronidazole, while in severe cases, oral vancomycin proved to be more effective; the latter is also the first line medication in recurrent CD infections [57]. Complications, such as megacolon toxicum, intestinal perforation or refractory colitis often require surgical interventions.

As it follows from studies, probiotics taken during and after antibiotic therapy may significantly decrease the risk of CDAD diarrhea development [58]. Chronic administration of proton pump inhibitors (PPIs) may result in an increased risk of CD-induced diarrhea [59]. The problem was addressed in the Food and Drug Administration (FDA) communication issued in 2012 [60].

Cytostatic drugs are also a common cause of gastrointestinal mucosal inflammations. Mucosal inflammation occurs in 5-15% of patients treated with standard chemotherapy. The most commonly inflammation-causing medications include methotrexate, edothrexate, idarubicin, doxorubicin, daunorubicin, 5-fluorouracil, cytosine arabinoside, cisplatin [61]. Treatment with cytostatic medications may lead to neutropenic colitis, which is characterized by mucosal damage and secondary infections (bacterial, fungal or viral) [62]. Symptoms that may be presented in neutropenic colitis include fever above 38°C, pain, muscle guarding, diarrhea and vomiting [63].

Adverse effects of NSAIDs may occur in the colonic mucosa, similarly as it happens in the upper gastrointestinal tract. NSAIDs may be the cause of both exacerbation of the existing conditions and development of new diseases. Most commonly, adverse effects occur in patients on chronic NSAIDs treatment, but they may also develop as soon as after a several-day therapy. Diseases, in which the condition of the patient may deteriorate in consequence of NSAIDs administration include diverticulosis and inflammatory bowel diseases (IBD).

In diverticulosis, which occurs (often in an asymptomatic form) in approximately one-third of the population above 45 years of life, NSAIDs increase the risk of bleeding, especially originating in the diverticula. Colonic ulceration, perforation and narrowing are a group of conditions that may be induced by long-term NSAIDs usage [64].

Administration of NSAIDs, in particular meclofenamate and mefenamic acid, may lead to nonspecific colitis accompanied by abdominal pain and bloody diarrhea [1].

Constipation is estimated to occur in 12-19% of adults, being twice as common in females as in males; the incidence increases with age to 30-40% among individuals above 65 years of life. Constipation is defined as fewer than three bowel movements per week [69]. Among causes of constipation are ADR [70]. Groups of medications that may induce constipation include e.g. opioids, diuretics, calcium channel blockers, cholinolytics and other pharmaceuticals, which are presented in table VI together with some examples.

Drug-induced constipation may necessitate discontinuation of therapy with a given medication or changing its dosage; in some cases, it is necessary to introduce laxatives [71]. The recommended management strategies are presented in table VII.

The elderly and patients on palliative therapy are at the highest risk of gastrointestinal adverse effects of opioids, i.e. constipation, abdominal pain, incomplete bowel movement and bloating, nausea, vomiting and loss of appetite [1]. Opioid bowel dysfunction (OBD) is a syndrome of intestinal disturbances associated with taking opioid medications; it may affect from 70 to 90% of oncological patients and is most commonly induced by morphine. The constipation-causing activity of opioids results predominantly from activation of peripheral opioid μ and κ receptors. The consequence is a prolonged intestinal passage time and inhibition of propulsive contractions. Increased intestinal water absorption leads to formation of hard stools. In addition, recital sensitivity to stretching is decreased, while the tension of the anal sphincter increases, what weakens the feeling of a need to defecate. With an increasing duration of opioid therapy, problems with defecation become intensified. In case of OBD, symptomatic treatment is usually of little effectiveness. A method of alleviating opioid-induced constipation may consist in changing the route of administration, decreasing the dose, or changing the drug to another medication with a weaker constipation-inducing effect [72].

Another cause of drug-induced constipation may lie in improper use of laxatives. Fiber belongs to preparations that increase stool mass. The effectiveness of fiber depends on consuming adequate amounts of fluid and for this reason, especially in the elderly who do not feel thirsty, fiber may lead to constipation or exacerbate the already existing condition. Additionally, fiber may cause bloating and flatulence. A significant possible adverse effect of fiber is decreased absorption of medications (aspirin, warfarin, digoxin) and microelements (calcium, iron, magnesium) [1,72].

Constipation may also develop in consequence of intestinal atony resulting from chronic use of laxatives that stimulate colonic motility (i.e. bisacodyl, senna and other anthraquinone compounds-containing preparations) [1,72]. Another adverse effect of long-term administration of large contact doses of laxatives is melanosis coli. Melanosis coli is characterized by brownish coloring of the mucosa resulting from accumulation of macrophages filled with lipofuscin pigment. The effect is reversible and resolves several months following discontinuation of therapy.

Tabela VII

Recommendations for the treatment of drug-induced constipations.

Zalecenia dotyczące leczenia zaparć polekowych.

RECOMMENDATIONS FOR THE TREATMENT OF DRUG-INDUCED CONSTIPATIONS:	
Drug induced constipation:	Proposal for modification of therapy:
Oral iron preparations	Intramuscular or intravenous iron or laxative agent
Antacids containing calcium or aluminium	Proton pump inhibitors or antacids containing magnesium or laxative agent
Calcium channel blockers	Angiotensin-converting-enzyme inhibitor or beta-blockers
Tricyclic antidepressants	Serotonin reuptake inhibitors
Opioids	μ-opioid receptors antagonist or laxative agent
Anticonvulsive drugs	Laxative agent
Antiparkinson drugs	
Neuroleptic agents	

Anus and rectum

Adverse effects of medications seen in the anus and rectum include ulceration following using ergotamine suppositories or NSAIDs [1].

Drugs associated absorption abnormalities

Proton pump inhibitors (PPIs) constitute a group of medications that inhibit hydrogen ion release to the canaliculi of gastric parietal cells. PPIs are irreversibly bound to H+/K+-ATPase. The enzyme activity may be reinitiated only when a new particle is synthesized. Long-term depression of acid release by parietal cells may lead to restricted absorption of certain vitamins and minerals, as well as to an increased risk of some infectious diseases [73,74].

An acid environment is necessary for pepsin activation, which allows for releasing protein-bound cyanocobalamin. Free vitamin B_{12} may be subsequently absorbed in the ileum in the process involving the intrinsic factor (IF) [75]. A statistically significant effect of PPIs on vitamin B_{12} levels in patients have not been demonstrated in all investigations [74]. Thus, it seems reasonable to monitor its concentration in patients from risk groups (the elderly, patients on vegetarian diets) who are on chronic PPI therapy. Henry et al. demonstrated a decrease in serum vitamin C levels following a 4-week omeprazole treatment (40mg/day) [76].

PPIs may also affect absorption of such minerals as calcium, magnesium or iron. Investigations addressing an increase in the risk of fractures in association with PPI administration have culminated in contrary results [74,77]. In 2010, FDA issued a communication on an increased risk of fractures involving the hip, wrist and spine following PPI usage. In 2011, FDA updated the warning, which then referred only to PPI-containing prescription medicines. As it can be seen in the warning, an increased risk of fractures is mostly noted when the group of medications is administered at large doses for a period exceeding one year (for this reason, over-the-counter (OTC) medications have been excluded from the alert) [78].

Acidic gastric environment affects favorably the process of iron absorption, particularly in its non-heme form [74]. Sarzyński et al. demonstrated a negative effect of more than one-year omeprazole administration on hematological parameters, such as hematoglobin level or hematocrit [79]. Chronic (more than a year) usage of PPIs may also cause magnesium deficit [80]. This problem was emphasized by FDA in the communication of 2011. At the same time, the Agency stressed the fact that 25 % of hypomagnesemia cases were resistant to magnesium supplementation [81].

Another medication that may cause depressed absorption is metformin, which is the first line drug in treating type 2 diabetes. Its mechanism of action is complex, and its most important elements include improved cell insulin sensitivity and inhibition of hepatic gluconeogenesis [82]. Metformin shows a negative effect on vitamin B_{12} absorption from the gastrointestinal tract, what may result in vitamin B_{12} deficiency [83]. A derivative of biguanide depresses absorption of the factor-cyanocobalamin complex in the ileum. The process is calcium ion-dependent. Bauman et al. demonstrated that administration of calcium ions at the dose of 1200mg/day may reverse the negative effect of metformin on vitamin B_{12} absorption [84].

Drug-induced absorption disturbances may also involve folic acid; its deficits are noted in patients treated with sulphasalazine [85,86].

Medications that inhibit fat absorption or bile acid-binding – Orlistat (tetrahydrolipstatin – therapy of obesity), colesevelam (therapy of hypercholesterolemia) - may theoretically restrict absorption of fat soluble vitamins– A,D,E,K [87,88]. As it was demonstrated by McDuffie et al. in case of Orlistat, particular attention should be paid to vitamin D, especially in view of its highly common deficit [87].

Conclusion

ADRs are a major problem of modern

pharmacotherapy. Rapid recognition of ADR gives a chance to change a therapy, avoid "prescribing cascade" as well expensive diagnostic procedures. Physicians' knowledge about potential as well the most common ADRs is important to improve patients' safety and reduce expenditures on health care.

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