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Modern Possibilities of Using Lactulose in Clinical Practice

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Aim: to present an overview of current literature data on the possibilities of application of lactulose in clinical practice.
Key points. Lactulose is a synthetic disaccharide belonging to the class of osmotic laxatives. Officially permitted indications for its appointment in Russian Federation are functional constipation (including in children, the elderly and senile, pregnant women and women in postpartum period), an obstipation type of irritable bowel syndrome, the need to soften the consistency of feces in hemorrhoids and anal fissures, after operations on the colon and anorectal area, as well as hepatic encephalopathy. Other indications include preparation for colonoscopy, treatment and prevention of disorders of the intestinal microbiota, prevention of constipation in oncological patients receiving narcotic analgesics, as well as patients on artificial lung ventilation.
Conclusion. Lactulose is a highly effective and safe drug, which combines osmotic laxative effect with expressed prebiotic action and is used in a wide clinical practice.
Keywords: lactulose, functional constipation, obstipation type of irritable bowel syndrome, hepatic encephalopathy
Conflict of interest: the authors declare that there is no conflict of interest.

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Современные возможности применения лактулозы в клинической практике

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Цель: представить обзор современных данных литературы о возможностях применения лактулозы в клинической практике.
Основные положения. Лактулоза является синтетическим дисахаридом, относящимся к классу осмотических слабительных. Официально разрешенными показаниями к ее назначению в Российской Федерации служат: функциональный запор (в том числе у детей, лиц пожилого и старческого возраста, беременных и женщин в послеродовом периоде), обстипационный вариант синдрома раздраженного кишечника, необходимость смягчения консистенции кала при геморрое и трещинах заднего прохода, после операций на толстой кишке и аноректальной области, а также печеночная энцефалопатия. Другие показания включают в себя подготовку к колоноскопии, лечение и профилактику нарушений состава кишечной микробиоты, профилактику запоров у онкологических больных, получающих наркотические анальгетики, а также у пациентов, находящихся на искусственной вентиляции легких.
Заключение. Лактулоза является высокоэффективным и безопасным препаратом, сочетающим осмотический слабительный эффект с активным пребиотическим действием, широко применяющимся в повседневной клинической практике.
Ключевые слова: лактулоза, функциональный запор, обстипационный вариант синдрома раздраженного кишечника, печеночная энцефалопатия
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Lactulose (4-O-ß-D-galactopyranosyl-D-fructose) belonging to the group of osmotic laxatives, is a synthetic disaccharide consisting of residues of fructose and galactose molecules, which is not broken down by the digestive enzymes of the small intestine and enters the large intestine in unchanged form. In the lumen of the colon, it is broken down by saccharolytic bacteria with the

formation of short-chain fatty acids (lactic, butyric, acetic, propionic acid), which reduce the pH of the contents of the colon and increase the osmotic pressure in its lumen, which leads to the passage of water into the lumen of the colon, an increase in intestinal volume contents and its softer consistency, stimulates peristalsis and ultimately provides a laxative effect [1].

The most common indications for the use of lactulose are *primary (idiopathic, functional) constipation* and *obstipation variant of irritable bowel syndrome (IBS)*, as well as secondary constipation that occurs with various diseases and taking certain medications. Lactulose has been used in clinical practice as a laxative since 1959, and its properties have been well studied over the past period. Recent researches have confirmed the high efficiency and safety of lactulose in the treatment of patients with constipation.

Thus, a double-blind, placebo-controlled study conducted in Japan confirmed a significantly higher frequency of bowel movements when using lactulose compared to placebo, with mild side effects and relatively rare occurrence of diarrhea [2]. Results from a randomized multicenter trial of 363 patients with functional constipation showed that the effectiveness of paraffin-embedded lactulose for 4 weeks was comparable to that of polyethylene glycol (PEG) [3].

Much attention is paid to the use of lactulose in the treatment of functional constipation in *pediatric patients*. Y. Cao et al. [4] compared the effectiveness of using lactulose at a dose of 5 mL daily in pediatric patients for six weeks with placebo in the treatment of chronic constipation. Lactulose significantly increased stool frequency ($p < 0.01$) and improved its consistency ($p < 0.01$). However, the frequency of side effects did not differ in both groups.

U. Poddar et al. [5] observed 316 children with functional constipation (mean age — 44 months) treated with lactulose or PEG. The effect was evaluated after three months. The efficacy of both medicinal products was similar. R. Velvizhy et al. [6] showed that in India, when treating constipation in children, the main place in the arsenal of laxatives is occupied by lactulose and PEG, which are prescribed in 26.8 and 24.6 % of cases, respectively, indicating a greater preference for lactulose.

Significant prevalence in the *elderly* (20–36 %) and association with a high risk of cardiovascular disorders are known to be important aspects of constipation. A review of published papers suggests that lactulose can be used for treating constipation in the elderly [7]. In 2021, *Russian Journal of Gastroenterology, Hepatology, Coloproctology* published a consensus opinion of the following experts: gastroenterologists (V.T. Ivashkin et al.), coloproctologists (P.V. Tsarkov et al.), gerontologists (Yu.V. Kotovskaya et al.), cardiologists (Yu.N. Belenkov) on diagnosis and treatment of elderly patients, and it was concluded that the use of lactulose in elderly and senile patients is effective and safe [8].

The issue of treating constipation in *pregnant women* in which the incidence is as high as 40 % is still relevant. Lactulose is considered the drug of choice in such cases [9]. Food and Drug Administration (FDA) has officially authorized the use lactulose during pregnancy as it has no side effects for the mother and the fetus.

Lactulose is indicated for constipation treatment in women in the *postpartum period*. P. Huang et al. [10] studied the efficacy and safety of oral lactulose in the treatment of constipation in the postpartum period. Women received lactulose 15 mL once daily, followed by a maintenance dose of 5 to 15 mL/day depending on the efficacy. The quality of life was assessed using SF-36 Questionnaire. The treatment lasted for six weeks. In the female patients group receiving lactulose compared to the women in control group who were not prescribed this medication, constipation resolved faster ($p < 0.05$), bowel movements were shorter in duration ($p < 0.05$), a greater number of constipation-free days was observed ($p < 0.05$) and significantly better quality of life parameters by SF-36 score were reported ($p < 0.05$).

S. Meng et al. [11] conducted a randomized controlled study of efficacy of lactulose use in the treatment of constipation during the postpartum period. Women in the study group ($n = 100$) received lactulose 20 mL twice daily during four weeks, patients in the control group adhered to adequate drinking regimen, kept a diet and performed exercises. The efficacy of treatment in the study and control groups was reported in 92 and 21 % of cases, respectively, while the constipation recurrence rate in female patients followed-up during 120 days was 4 and 18 % ($p < 0.001$), suggesting very good remote effect of the medication.

The results of a multicenter study which included the analysis of the findings from a survey conducted in 4,781 women who were taking lactulose for two weeks during the postpartum period suggested that the frequency of stool increased while the duration of bowel movements decreased while on treatment. Herewith, the therapeutic effect was maintained even after the end of therapy [12].

Widely recognized indications for prescribing lactulose also include the need to soften the consistency of feces in *hemorrhoids, anal fissures, after operations on the colon and anorectal area*.

A big number of studies are dedicated to the efficacy of lactulose use for treatment and prevention of *hepatic encephalopathy*, the incidence of which in liver cirrhosis is up to 70 % [13]. Hepatic encephalopathy (HE) is a complex of potentially reversible neuropsychiatric disorders resulting from liver failure and/or portosystemic blood shunting [14]. The key factor for its development is failure of the liver to convert the ammonia formed in the intestine into the urea, which results in its increased blood concentration followed by neuronal damage and neurological disorders development.

Depending on the presence or absence of clinical signs, HE falls into a masked (latent, minimal) form found by special psychometric tests and coordination tasks (making a star with six matches, number matching test) and overt (manifested) one with sleep disorder, loss of concentration, depression or euphoria, mnestic disorders, flapping tremor (asterixis) at early stages, and characterized by stuporous state, confusion, pain reflexes suppression and coma development at the end stage.

Short-chain fatty acids formed during the breakdown of lactulose in the intestines prevent the growth of pathogenic bacteria that form ammonia, and its laxative effect leads to the removal of nitrogen-containing substances from the intestines. Moreover, under the acidic condition of the intestinal contents formed during lactulose administration, ammonia (NH^{3+}) is converted into ammonia ions (NH^{4+}) characterized by poor absorption [15].

Lactulose efficacy was studied both in latent and overt forms of HE. A multicenter randomized study conducted in China in 11 hospitals showed that two months use of lactulose significantly eliminated the manifestations of latent HE compared to the control group and facilitated improvement in the physical status of patients [16]. A meta-analysis of 25 studies which included 1563 patients with minimal HE allowed to conclude that lactulose was the only medication which removed manifestations of minimal HE, prevented development of overt HE signs, reduced ammonia levels in the body, improved the quality of life and had no significant side effects [17].

Overt hepatic encephalopathy is associated with the need for hospitalization of patients with increased risk of lethal outcome [18]. A review of eight papers demonstrated that lactulose used as monotherapy in patients with overt HE for more than six months decreased the risk of HE relapses and reduced the need in hospitalization of such patients [19].

A gastrointestinal haemorrhage is a significant factor for HE development in patients with cirrhosis. The provided systematic review of researches dedicated to studying lactulose efficacy in preventing HE development in patients with cirrhosis who had had gastrointestinal haemorrhage demonstrated that the incidence of HE in patients receiving lactulose was 7 % while in those without lactulose treatment the incidence was 26 % ($p = 0.01$) [20].

A number of researches were dedicated to studying the efficacy of lactulose use in HE compared to local antibiotic rifaximin and in combination with thereof. A systematic review and meta-analysis of 16 studies which included 1,376 patients with overt HE receiving either lactulose or rifaximin showed that lactulose significantly improved the overall quality of life of patients related to health, social functioning, sleep, while the therapeutic effect of rifaximin was not significant [21].

M.A. Moneim et al. [22] found that the use of lactulose and rifaximin combination in patients with cirrhosis resulting from viral hepatitis C aimed at secondary prevention of HE at the dose of 30 to 45 mL 3 times a day and 400 mg 3 times a day, respectively, vs. control patients group receiving lactulose monotherapy resulted in more prolonged HE remission which lasted 18.84 and 14.0 weeks ($p = 0.002$) and lower incidence of overt HE relapses (46 and 70 %; $p = 0.005$), respectively. Lactulose in combination with rifaximin decreased ammonia production in patients with cirrhosis by 20 % [23]. A meta-analysis of seven randomized controlled studies which included 843 patients with HE showed that the use of lactulose and rifaximin combination facilitates greater reduction in HE mortality vs. lactulose monotherapy [24].

However, higher efficacy of lactulose and rifaximin combination compared to lactulose monotherapy was not reported in all the papers. Thus, N.I. Butt et al. [25] studied two groups of patients with decompensated chronic hepatic diseases, 65 patients in each one. One group received 30 mL of lactulose 3 times a day for 10 days, the other received lactulose in the same dose in combination with rifaximin 550 mg 2 times a day. Positive changes over time in the severity of HE symptoms were similar (in 58.46 and 67.69 % of patients, respectively; the difference was insignificant, $p = 0.276$).

K. Ahire and A. Sonawale [26] compared the efficacy of lactulose and rifaximin combination to lactulose monotherapy in overt HE. In both groups, positive changes over time were noted in mental status, asterixis grade, serum ammonia level, number matching test results, HE index.

No statistically significant differences in the obtained results between both groups were found. Finally, S. Hasan et al. [27] performed a follow-up of 96 patients with overt HE and demonstrated that improvement in the neurological status for lactulose monotherapy (especially at initial stages) was more pronounced than that when using lactulose and rifaximin combination.

Taking into account the ambiguity of the results obtained, a more fair point of view seems to be that considers lactulose monotherapy as first-line therapy, and the combination of lactulose and rifaximin as a second-line treatment regimen, for which there must be appropriate indications [18]. Thus, the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases consider lactulose as the first choice drug for treatment and prevention of episodic overt HE. Rifaximin is added for prevention of overt HE relapses [28].

All the above lactulose indications are considered as officially approved in the Russian Federation. The below indications are considered as off-label indications in our country but are registered in a number of other countries.

It has been shown that low doses of lactulose can be used as a *prebiotic*, facilitating increased bifidobacteria and lactobacilli levels in the intestine, inhibiting the growth of pathogenic microorganisms (*Clostridia, Salmonella, Campylobacter, etc.*) and strengthening the protective barrier of the intestinal mucosa [29, 30].

Antibiotic azithromycin is known to induce the growth of pathogenic bacteria (in particular, *Streptococcus*) in the intestine. 16S-ribosomal RNA sequencing method showed that co-administration of lactulose increases the contents of saccharolytic bacteria (*Lactobacilli, Enterococci, Anaerostipes*) and prevents, in such cases, intestine colonization with opportunistic pathogenic flora [31]. Positive effect of lactulose on intestinal microbiota also determines the advisability of its use in patients with type 2 diabetes mellitus [32].

A randomized controlled study conducted by H. Yuanchao et al. [33] demonstrated that adding lactulose to PEG when *preparing to colonoscopy* significantly improved colon cleansing and the incidence of further adenomas detection (especially with the size of less than 5 mm) compared to preparation to colonoscopy using PEG in combination with placebo.

A meta-analysis of 18 studies which included 2,274 patients confirmed that preparation to colonoscopy using PEG and lactulose combination turned out to have higher quality compared to isolated PEG use. Moreover, in cases where PEG and lactulose combination was used, the incidence of abdominal pain, nausea and vomiting in patients was lower [34]. Two comparative studies demonstrated that lactulose is superior to PEG in terms of the quality of preparation to colonoscopy and tolerability [35, 36].

Constipation is often observed in patients receiving *narcotic analgesics*. The use of lactulose 10 mL twice daily effectively prevented constipation in patients with malignancies receiving narcotic analgesics due to severe pain syndrome [37, 38].

Constipation is also a serious problem in patients in intensive care units on *artificial lung ventilation (ALV)*. It has been shown that in such patients administered with lactulose compared to patients not receiving lactulose significantly higher rate of bowel movements per day (1.3 and 0.7; $p < 0.0001$, respectively), significantly lower percentage of bowel movements-free days (33.1 and 62.3 %; $p < 0.0001$), more pronounced decrease in Sequential Organ Failure Assessment (SOFA) scale (–4 and –1, respectively; $p = 0.036$) were reported [39].

Impaired intestine function is a common complication at early stage of *acute pancreatitis*. In a randomized controlled study conducted in 73 patients with moderately severe acute pancreatitis, improvement in the intestinal function after seven days of treatment was reported in patients receiving lactulose. Herewith, inflammatory cytokines serum levels reduced, the intestinal mucosa permeability index decreased, bifidobacteria and short-chain fatty acids levels increased [40].

The advantages of lactulose include a high safety profile (in particular, the absence of drug interactions, which is especially important in comorbid patients), as well as the possibility of long-term use.

Thus, in addition to the officially approved indications for the use of lactulose in the Russian Federation, which include functional constipation (including that in pediatric patients, the elderly, pregnant women and women in postpartum period), constipation predominant type of irritable bowel syndrome, the need to soften the consistency of feces in hemorrhoids and anal fissures, after operations on the colon and anorectal area, a number of indications are planned for authorization (preparation for colonoscopy, treatment and prevention of disorders of the intestinal microbiota, prevention of constipation in oncological patients receiving narcotic analgesics, as well as in patients on ALV). It is possible that over time, considering the high efficacy and safety of lactulose, these indications will also become officially approved in Russia.

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