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Selection of Medications in Comorbidity

Abstract

New classification divides medications on five classes by influence on comorbid diseases and conditions and rates drug's effects as favorable (A), possible (B), neutral (C), undesirable (D), and unfavorable (X). Class A includes drugs used in treatment of comorbid disease, class B embraced drugs with positive influence, class C includes drugs without significant influence or contradictory influence, class D consist of drugs with possible non-severe adverse effects, and class X includes drugs with severe adverse effects. The more universal drug classification according to influence on comorbid diseases can include and unite other classifications. Classification may help unify marks of positive and negative influences drugs on comorbidity and help practitioners in selection of effective and safe treatment.

Key words: comorbidity, treatment, classification of medicines

In clinical settings, the choice of medication for patients with comorbid diseases and conditions often presents challenges, since it is necessary to take into account the scattered and often contradictory information provided in the instructions for use, clinical guidelines and articles. Few works systematize information on the treatment of diseases in comorbid conditions.

Instructions for use in the sections of side effects, contraindications, special instructions, and use in cases of renal and hepatic dysfunction are not sufficiently adapted for making clinical decisions and are often outdated. Sections of comorbidity in different guidelines are concise, not always informative enough, or may not be available at all. Specialized articles describe the problem in more detail, but the probability of inaccurate statements is higher.

For convenient information handling, classifications that group objects with similar characteristics are widely used. The study of the problem of choosing medications for the treatment of diseases in the conditions of comorbidity allowed us to propose a classification that includes five classes with a favorable, possible, neutral, undesirable and unfavorable effect on comorbid diseases and conditions [1].

In order to improve and make it easier to use, this paper proposes to supplement the classification with letters that are used in many international classifications and are familiar to medical practitioners (Table 1). A similar approach is used in the classifications of the safety of medication in pregnancy, first proposed by the United States Food and Drug Administration (FDA), and the FORTA classification (Fit fOR The Aged), which separates

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Table 1. *Classification of medicines by their effect on comorbid diseases and states*

Class	Effect of the medicine	Effect on comorbid diseases and conditions
A	FAVORABLE	The medicine can be used as a monotherapy
B	POSSIBLE	Moderate therapeutic effect
C	NEUTRAL	The medicine does not have a significant effect or there are not enough data to assess the effect
D	UNDESIRABLE	Rare risk of deterioration
X	UNFAVORABLE	High incidence of life-threatening complications

medicines according to their effectiveness and safety in elderly and senile patients [2].

The proposed classification of medicines by their effect on comorbid diseases and conditions is more versatile and allows us to include well-known specialized classifications.

The main problem with correct ranking of medicines is the lack of more reliable randomized controlled trials in patients with severe comorbid diseases. The latter are usually excluded from clinical trials in order to more objectively assess the effect of the medicine and reduce the number of adverse side effects [3]. Therefore, the main source of information is the findings of less accurate observational studies and registers. In recent years, mathematical techniques have been used more often to improve the accuracy of observational research results by leveling differences in patient groups [4]. The opinion of expert groups is widely used, which prevails in modern guidelines. For example, in influential American and European cardiac guidelines, only 8–14% of the statements confirmed in a large randomized study or meta-analysis of the latter can be considered reliable, while 41–55% are based only on the opinion of experts.

Practitioners often experience difficulties when choosing medications to treat diseases in patients with concomitant liver disease. Information on such clinical situations is more difficult to find than in such combinations as hypertension and renal dysfunction or atrial fibrillation in patients with coronary syndromes.

Here we consider the use of classification when choosing treatment for patients with various types of chronic coronary syndrome, heart failure, and mental disorders in combination with severe chronic liver disease at the stage of cirrhosis. The urgency of the problem relates to the fact that cardiovascular diseases significantly increase mortality, and mental disorders reduce the quality of life of patients with liver cirrhosis and persist in a significant part of patients after liver transplantation [5–8].

The paper does not set a task to justify in detail and strictly justify the assignment of medicine in different categories, which may be the subject of discussion due to the lack of reliable research, but to demonstrate the practical feasibility, principles of development and the possibility of applying the classification.

Classification of the medicines for the treatment of coronary heart disease in combination with liver cirrhosis is presented in Table 2.

Class A includes non-selective beta-blockers that reduce portal venous pressure by narrowing the vessels and reducing cardiac output. These medicines are essential for primary and secondary prevention of bleeding from enlarged esophageal veins, and can reduce mortality and the risk of hepatocellular carcinoma [9, 10].

Among nitrates, it is preferable to use isosorbide mononitrate, since isosorbide dinitrate is converted to active mononitrate in the liver and has variable bioavailability (10–90%). The effect of isosorbide mononitrate on portal pressure is lower than non-selective beta-blockers, and so the medicine is used in combination with beta-blockers [11].

Table 2. *Classification of medicines for the treatment of chronic coronary syndrome according to the effect on liver cirrhosis*

Class	Medicines
A	Non-selective beta blockers
B	Beta$_1$-blockers, isosorbide mononitrate, statins
C	Calcium antagonists, molsidomine, nitrates, nicorandil, trimetazidine
D	Antiaggregants
X	Ranolazine, rivaroxaban

There is a very common wariness among patients and doctors about possible liver damage when using statins. At the same time, many studies show a positive effect of statins on the course of even very severe liver diseases, which allowed the medicines to be classified in class B. Statins have been shown to reduce the severity of liver fibrosis, the frequency of decompensation of liver cirrhosis, and even mortality [12, 13]. Statins can also slightly reduce portal hypertension by reducing intrahepatic vascular resistance [14]. According to a meta-analysis of observational studies, treatment with statins was associated with a 37% reduction in the risk of developing hepatocellular carcinoma [15]. A change in the stance on statins has been noted in the latest recommendations on liver cirrhosis [16].

Antiaggregants that are assigned to class D may increase the risk of bleeding in case of vitamin K-dependent coagulopathy, thrombocytopenia, esophageal varices, erosive ulcerative lesions of the stomach, which are usually found in the setting of severe liver cirrhosis.

Ranolazine, which has antiarrhythmic properties along with antiischemic effect, is contraindicated in case of liver cirrhosis, because the concentration of medicine increases by 80% already in moderate liver dysfunction with a 3-fold increase in QT prolongation frequency. The latter is especially dangerous in the presence of heart diseases.

A recently completed COMPASS study raised a question regarding the possibility of applying rivaroxaban in small doses in patients with stable atherosclerosis. In this case, it should be taken into account that rivaroxaban is not recommended in patients with liver cirrhosis, even in Child-Pugh class B, because the exposure of medicine increases more than twice and the risk of large bleeding increases [17, 18].

Table 3 presents a classification of medicines for the treatment of chronic heart failure with concomitant liver cirrhosis. Along with cardiogenic heart failure, cirrhotic cardiomyopathy should be noted [19].

One of the frequent life-threatening complications of liver cirrhosis is bleeding from the esophageal varices. Non-selective beta-blockers are recommended for primary and secondary prevention of varicose bleeding and mortality reduction, of which only carvedilol is approved for treatment of

Table 3. *Classification of medicines for the treatment of chronic heart failure according to their effect on liver cirrhosis*

Class	Medicines
A	Diuretics, carvedilol, spironolactone
B	Beta$_1$-adgeneric blockers, eplerenone
C	Digoxin, ivabradine
D	Angiotensin converting enzyme inhibitors, angiotensin II receptor blockers

systolic heart failure. The latter reduces portal pressure, also due to the alpha-blocking effect. Diuretics and spironolactone are used to correct ascites caused mainly by portal hypertension and hypoalbuminemia. Eplerenone can be prescribed during development of painful gynecomastia in patients taking spironolactone [20].

Angiotensin converting enzyme inhibitors and angiotensin II receptor blockers can reduce portal pressure and fibrosis development, but there is an increased risk of hypotension and renal dysfunction with decompensation of liver disease [21–23]. It is obvious that the proposed classification is not without shortcomings, and as a result of consideration and discussion can be significantly improved, including clarification of the criteria for assigning a medicine to a particular class, as well as verification of systematically collected evidence-based medicine data. It was important to show the principles and approaches to the development and use of the original classification.

The proposed classification of medicines by their effect on comorbid diseases and conditions allows us to unify the assessment of the positive and negative impact of treatment of the main disease, can significantly facilitate the work of the doctor and optimize the treatment of patients, taking into account the principles of individual approach.

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