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DRUG-RELATED PROBLEMS IN COMORBID PATIENTS WITH ANXIETY-DEPRESSIVE DISORDERS

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Drug-related problems (DRPs) pose a significant threat to patient safety, especially in conditions of comorbidity and polypharmacy. DRPs can manifest as adverse reactions, drug interactions, etc., potentially negatively affecting the effectiveness and safety of treatment. Since most DRPs are potentially predictable if timely detection and correction of pharmacotherapy are provided, the role of the clinical pharmacist is increasing, who can be included in the interdisciplinary team of specialists and, within the framework of pharmaceutical counselling, contribute to their minimization.

The aim: *The aim of our study was to assess the frequency and nature of DRPs in comorbid patients with anxiety and depressive disorders to develop a model of pharmaceutical counselling.*

Materials and methods: *A retrospective analysis of 55 medical histories of comorbid patients who were inpatients in the therapeutic department of a multidisciplinary hospital in Kyiv and were treated for the main disease and anxiety-depressive disorders was conducted. Most patients (67%) had 3–4 concomitant diseases, including anxiety-depressive disorder, in addition to the main one.*

The analysis of potential drug-drug interactions was carried out using the DrugBank database and official instructions for medical use of medicines.

Statistical analysis included correlation analysis to assess the relationships between variables and comparison of qualitative indicators using the Pearson χ^2 test. The level of statistical significance was taken as $p < 0.05$. Data processing was carried out using the Microsoft Excel package.

Results: *The total frequency of DRPs per patient was 3.73 ± 2.58, polypharmacy was detected in 84% of patients. A significant correlation ($p < 0.05$) was found between the patient's age and the number of comorbid conditions ($r = 0.48$), as well as between the patient's age and the number of medications he received ($r = 0.45$).*

Patients were significantly more likely to receive benzodiazepines than antidepressants (89.1% vs. 38.2%; Pearson's $\chi^2 = 30.80$, $p < 0.001$).

Conclusions: *Among comorbid patients with anxiety and depressive disorders who were treated in a somatic hospital, a significant prevalence of drug-related problems was found. The number of drugs per course of treatment correlated with the age of the patients. Almost all patients received benzodiazepines, including the majority of elderly patients, which is dangerous due to the risk of increasing cognitive impairment. In addition, clinically significant drug-drug interactions were found in 42% of patients, and in 29% – the prescription of drugs in the presence of restrictions or contraindications. The results of the study emphasize the importance of individualizing pharmacotherapy considering age, comorbidity and potential interactions and justify the need to involve a clinical pharmacist in a multidisciplinary team to minimize the risk of drug-related problems*

Keywords: *drug-related problems, comorbid patients, antidepressants, sedative drugs, polypharmacy*

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1. Introduction

Comorbid patients are at high risk of DRPs due to the need for complex pharmacotherapeutic regimens, which makes it difficult to predict treatment outcome [1]. According to a report by the US Institute of Medicine, complications associated with pharmacotherapy, including adverse drug reactions and avoidable medication errors, are responsible for 44,000 to 98,000 deaths each year [2]. A prospective cohort study conducted in an emergency department analyzed 1039 patient presentations, of which a significant proportion had at least one DRP related to the treatment of the underlying disease [3].

In the context of the treatment of patients with anxiety-depressive disorders, who often have concomitant chronic diseases and receive several medications at the same time, it becomes important not only the effectiveness of drugs with anti-anxiety effect, but also the safety of therapy, which can be ensured through a personalized approach to the patient [4, 5]. This will allow considering the characteristics of the metabolism, comorbid conditions, concomitant drug therapy and harmful habits of the patient. That is, there is a need for well-coordinated pharmaceutical strategies aimed at optimizing prescriptions and reducing the risk of drug complications. This role can be played by a clinical pharmacist integrated into an interdisciplinary team of

health care system specialists, which is fragmentarily described in the international literature [6–9].

Assessment of prescriptions, identification of DRPs and provision of substantiated recommendations for therapy correction by the pharmacist, according to the study by Stuhec M. (2021), contributed to increasing the effectiveness and safety of treatment, as well as improving the quality of life of patients with anxiety-depressive disorders [7]. And given the increase in the frequency of mental disorders and the resulting increase in the use of antidepressants among Ukrainians against the background of the full-scale war unleashed by the Russian Federation in Ukraine, consideration of the model of cooperation between doctors and clinical pharmacists is becoming increasingly relevant [10–12]. An almost twofold increase in sales of antidepressants was noted (2024 compared to the pre-war year 2021: the increase is 78% or a coefficient of 1.8). The most popular antidepressants in Ukraine remain escitalopram, amitriptyline, fluoxetine, sertraline, and paroxetine (Proxima Research, Ukraine, 2025) [13]. Despite the widespread clinical use of the above-mentioned antidepressants in the treatment of depressive and anxiety disorders, their use is accompanied by a potential risk of DRPs. Such problems include, in particular: serotonin syndrome (especially in combination therapy with serotonergic drugs), hepatotoxicity, cardiotoxicity (for tricyclic antidepressants such as amitriptyline) [14, 15], interaction with anticoagulants, antipsychotics, antiepileptic drugs, other psychotropic drugs, which leads to an increased risk of adverse drug reactions (ADRs) or changes in the effectiveness of treatment [16, 17].

The prevalence of DRPs in the treatment of anxiety and depressive disorders is due to both the pharmacokinetic and pharmacodynamic properties of drugs [4, 18]. Antidepressants are mainly metabolized in the liver with the participation of the CYP450 enzyme system, which makes them highly sensitive to interactions with strong inducers or inhibitors of this enzyme, and also requires special attention in patients with impaired liver function [19]. Genetic variants of metabolism, in particular polymorphisms of CYP2C19 and CYP2D6 enzymes, affect the pharmacokinetics of antidepressants such as escitalopram, fluoxetine and paroxetine. This leads to an increased risk of DRPs in a certain category of patients [20, 21].

Systematic assessment of risk factors for the development of DRPs is a key condition for increasing the effectiveness of pharmaceutical interventions aimed at their detection and minimization. The use of international classification systems, in particular PCNE (Pharmaceutical Care Network Europe), contributes to the identification of types and causes of DRPs, as well as the formation of a structured approach to further clinical pharmaceutical support of patients. When assessing DRPs according to the PCNE classification, attention is paid to accurately defining the type of problem (efficacy, safety, or other), establishing its cause (e.g., drug choice, dose, duration, patient behaviour), and documenting planned interventions [22].

Methods for assessing DRPs in the management of anxiety and depressive disorders follow generally accepted approaches in clinical pharmacy and medical practice and include:

– interview and/or history taking with a detailed questioning of the patient regarding adherence to medication regimens, adherence to regimens in general, information about allergic reactions, self-made changes in therapy, assessment of complaints related to medication treatment [23];

– use of a classification model to determine the type of DRPs, for example, the above-mentioned PCNE or any other (DOCUMENT, GSASA, Westerlund) [24];

– analysis of prescriptions and medical documentation, which will make it possible to verify compliance of prescriptions with treatment standards, analysis of possible interactions, dosage, duration of administration, duplication of drugs, the presence of potentially dangerous combinations, especially in patients with polypharmacy [25];

– identification, assessment and recording of adverse reactions that may be a manifestation of DRPs, with subsequent analysis of their relationship with symptoms of anxiety-depressive disorders or deterioration of the patient's condition [22];

– use of checklists and algorithms for the application of structured tools to assess the risk of DRPs, especially in complex clinical cases, for example, in patients with comorbidities, cognitive impairment, low adherence to treatment [26];

– planned periodic audit of prescriptions and treatment outcomes in order to identify errors and develop preventive measures [4, 22].

It should be noted that the diagnosis of DRPs in the management of anxiety-depressive disorders has its own specifics due to the increased risk of medication non-adherence, the difficulty of communication with the patient and symptom assessment, and the frequent presence of polypharmacy [27].

Often, the use of complex pharmacotherapeutic regimens (polypharmacy) in comorbid patients is the main cause of DRPs in the treatment of anxiety-depressive disorders. The prevalence of polypharmacy among patients with depression is about 46.9% compared to individuals without depression (19.7%) [28]. Among elderly patients with anxiety disorders, the frequency of polypharmacy can reach 75% [29]. Another study described that patients with anxiety and depressive disorders in inpatient units have a higher level of polypharmacy, reaching 76%, and among patients with serious mental disorders, up to 91% of cases of polypharmacy are associated with psychotropic drugs [30].

Although there are many fragmentary studies on DRPs in clinical practice, issues related to comorbid patients with anxiety-depressive disorders remain poorly understood. In particular, little attention is paid to the analysis of the impact of polypharmacy on the risk of developing DRPs in this cohort. There is also a lack of standardized approaches to identifying DRPs and effective pharmaceutical intervention algorithms relevant to Ukraine in wartime conditions.

Therefore, the aim of our study was to conduct a retrospective analysis of discharges of inpatients with anxiety-depressive disorders and comorbidities to determine the nature and frequency of DRPs, identify risk factors for their occurrence, and develop an algorithm for managing

the adverse effects of DRPs with subsequent implementation of prospective pharmaceutical counselling in practice.

2. Planning (methodology) of research

1. The aim of the study was to assess the frequency and nature of DRPs in comorbid patients with anxiety and depressive disorders to form a model of pharmaceutical counselling.

2. The criteria for including patients in the study, data sources (hospital discharges) were determined, and compliance with the ethical requirements of the study was ensured.

3. Primary information was collected through retrospective analysis of medical histories, data on anamnesis, comorbidity, diagnostic and laboratory data, a list of prescribed medications with an indication of doses, frequency and duration of administration were systematized.

4. DRPs were analyzed by frequency and nature of occurrence, in particular polypharmacy, duplication of drugs, use of drugs with existing contraindications, potential drug interactions.

5. Based on the data obtained, an algorithm was formed for the pharmacist to assess the risk of DRPs for further pharmaceutical counselling within the framework of interdisciplinary interaction.

3. Materials and methods

The study was conducted during 2025 and involved a retrospective analysis of medical records for 2017–2018. 55 case histories of comorbid patients who were inpatients in the therapeutic department of a multidisciplinary hospital in Kyiv and were treated for the underlying disease and anxiety-depressive disorders were analyzed. The selection of this number of cases is due to the compliance of clinical documentation with the inclusion criteria, a sufficient level of completeness of data and their representativeness for solving the research tasks. The data were anonymized in accordance with ethical requirements.

The study was approved by the Commission on Bioethical Expertise and Ethics of Scientific Research at the Bogomolets National Medical University on 02/24/2025.

Data collection in the study was carried out through a thorough analysis of medical records containing information on patients' medical history, medical history, prescriptions, and laboratory test results. Other relevant clinical factors included: age, gender, allergic history, and results of additional examinations. Such a comprehensive approach allowed us to obtain a complete clinical picture of the patients' condition and the characteristics of their treatment.

Patient inclusion criteria: persons over 18 years of age with diseases of internal organs who were diagnosed with anxiety-depressive disorder according to ICD-10 (F41.2) (Table 1) by a psychiatrist in an inpatient department and prescribed pharmacotherapy with drugs with anxiolytic and/or antidepressant effects. Patients were aged from 35 to 82 years; the mean age was 61.6 ± 13.7 years for women and 60.9 ± 10.0 years for men. The gender distribution showed a predominance of women – 35 people (64%) compared to 20 men (36%).

Table 1

Main and concomitant diseases in the studied sample of patients (n = 55)

Nosology, clinical condition	Number of patients (n, %)	
	Value	%
Anxiety-depressive disorder	55	100%
Hypertension	40	73%
Heart failure	34	62%
Ischemic heart disease	26	47%
Chronic cholecystitis	12	22%
Diabetes mellitus	12	22%
Autonomic dysfunction	10	18%
Chronic pancreatitis	9	16%
Chronic gastritis	9	16%
Osteoarthritis	6	11%
Other liver diseases	4	7%
Fatty liver disease	3	5%
Chronic colitis	3	5%
Ulcer disease	3	5%
Postcholecystectomy syndrome (PCS)	2	4%
Gastrointestinal (GIT) cancer	2	4%
Chronic pyelonephritis	2	4%
Pulmonary failure	2	4%
Acquired renal cyst	2	4%
Chronic anemia of gastrogenic origin	2	4%
Atherosclerosis obliterans	2	4%
Atrial fibrillation	1	2%
Chronic obstructive pulmonary disease (COPD)	1	2%
Chronic rheumatic disease	1	2%
Lumboischialgia vertebrogenic syndrome	1	2%
Aortic insufficiency	1	2%
Hemorrhoids	1	2%
Cardiosclerosis	1	2%
Cataracts	1	2%
Chronic kidney disease	1	2%
Chronic renal failure	1	2%

Descriptive statistics were used to describe the sample and assess the frequency and nature of DRPs. Comparison of indicators was carried out by grouping patients by age, sex, number of comorbidities, number of prescribed medications. Analysis of potential drug-drug interactions was carried out using the DrugBank database [31] and official instructions for medical use of drugs. Statistical analysis included correlation analysis to assess the relationships between variables and comparison of qualitative indicators using the Pearson χ^2 test. The level of statistical significance was taken as $p < 0.05$. Data processing was carried out using the Microsoft Excel package.

4. Results

The total number of prescribed drugs reached 393, which included both anti-anxiety drugs (N = 80) and drugs for the treatment of primary and comorbid diseases (N = 313). The average number of prescribed drugs per person was 7.15 ± 1.91 (range: 3 to 12 drugs), indicating a high level of polypharmacy in the study group.

Polypharmacy was the most common DRP, in particular the prescription of five or more drugs, which

was observed in 46 patients (83.6%). The second most frequently detected problem was the problem of prescribing benzodiazepines to elderly patients – 26 patients (47%). In addition, 23 patients (42%) were identified as being at risk of clinically significant drug-drug interactions.

The prescription of drugs, including antidepressants and drugs of other groups, to patients with existing restrictions or direct contraindications (heart failure, ischemic heart disease, impaired liver or kidney function) was recorded in 16 people (29%). This emphasizes the need for a more careful approach to the choice of pharmacotherapy. Among the less common, but no less significant problems, the following were noted:

– need for dose adjustment – 16%;

– risk of QT interval prolongation – 15%;

– lack of documented indications for prescribing the drug – 11%;

– prescribing several drugs with the same active ingredient or from the same pharmacological group – 9%;

– risk of decreased metabolism of antidepressants, and therefore their accumulation, due to impaired liver function or potential drug-drug interactions – 9% (Fig. 1).

Age analysis confirmed the known pattern: patients with fewer comorbid conditions (1–2) had the lowest mean age (47.1 ± 7.9 years), while patients with the highest number of comorbid conditions (≥ 5) had the highest mean age (67.4 ± 7.2 years). Women predominated in all groups (Table 2).

A significant correlation ($p < 0.05$) was found between the patient's age and the number of comorbid conditions ($r = 0.48$), as well as between the patient's age and the number of medications he received ($r = 0.45$).

Patients were significantly more likely to receive benzodiazepines than antidepressants (89.1% vs. 38.2%; Pearson's $\chi^2 = 30.80$, $p < 0.001$).

Considering the established sex-age characteristics of the sample and clinical features, the structure of pharmacotherapy prescribed to patients with anxiety-depressive disorders was analyzed. Of the 393 prescribed medications, 80 (20.4%) were drugs with anti-anxiety effects. Benzodiazepines were most frequently prescribed – 49 prescriptions (61%), among which gidazepam dominated – 47 prescriptions. After benzodiazepines, the second most frequently used antidepressant from the group of selective serotonin reuptake inhibitors paroxetine was prescribed in 10 cases (13%). Less common were the antipsychotics sulpiride and thioridazine, as well as the atypical antidepressant agomelatine – each of them was prescribed 4 times (5%, respectively). The detailed distribution is presented in Fig. 2.

The main drugs that were prescribed to patients for the treatment of comorbid diseases included: cardiovascular drugs (ACE inhibitors, beta-blockers, sartans, statins, anticoagulants, antiplatelet agents), antidiabetic drugs, drugs for the treatment of gastrointestinal diseases (proton pump inhibitors, antispasmodics, antacids), diuretics (diuretics), nootropics and antioxidants, vitamin complexes.

The total frequency of DRPs per 1 patient was 3.73 ± 2.58, which is a high indicator.

Based on the results obtained, an algorithm for assessing the risk of DRPs by a pharmacist was developed, which allows for a systematic identification of the main types of problems accompanying pharmacotherapy and the justification of the need for its correction. The proposed approach can be implemented in the practical activities of a clinical pharmacist as a member of an interdisciplinary team to increase the effectiveness and safety of drug treatment (Fig. 3).

Table 2

Sample characteristics by age and gender depending on the number of comorbid conditions

Number of comorbid conditions	Number of patients (*n*, %)	Average age (years)	Proportion of women (*n*, %)	Average age of women (years)	Proportion of men (*n*, %)	Average age of men (years)
1–2	10 (18%)	47.1 ± 7.9	6 (60%)	41.3 ± 2.9	4 (40%)	55.8 ± 2.9
3–4	37 (67%)	63.9 ± 11.6	23 (62%)	64.8 ± 11.8	14 (38%)	62.5 ± 11.6
≥5	8 (15%)	67.4 ± 7.2	6 (75%)	69.8 ± 6.6	2 (25%)	60.0 ± 1.4

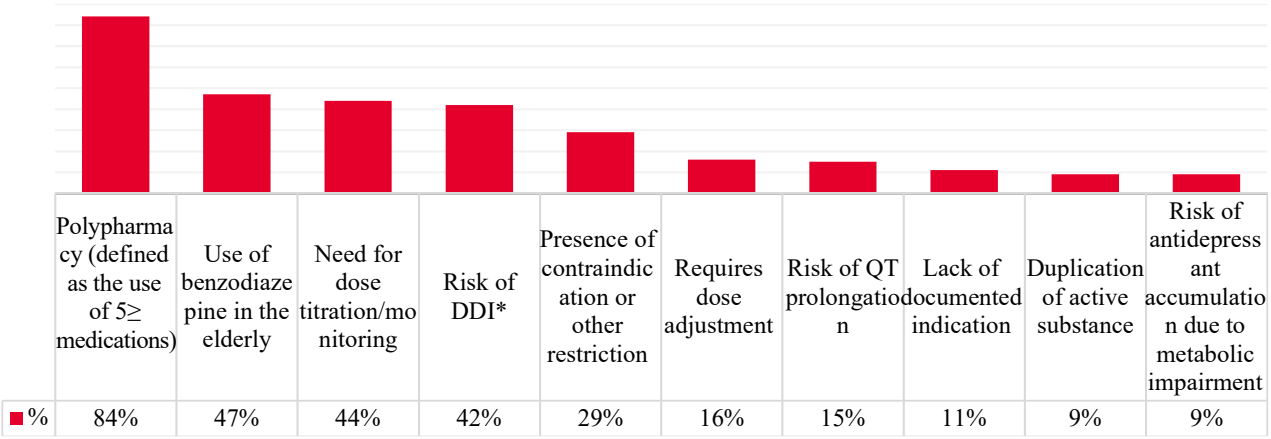

Fig. 1. Frequency of DRPs in the study population. The potential risk of drug-drug interactions (DDI) was assessed using the DrugBank database

Main stages of the algorithm:

1. Collection of clinical information. At this stage, a comprehensive collection of data about the patient is carried out, including the history of the disease, the results of laboratory and diagnostic examinations, and, if necessary, pharmacogenetic tests (in particular, CYP2D6 or CYP2C19).

2. Initial screening of DRPs. This stage involves checking the prescribed pharmacotherapy for polypharmacy (≥5 simultaneously prescribed drugs), which may increase the risk of side effects and interactions. Additionally, the efficacy and safety of prescribed drugs and dietary supplements that the patient is taking at the time of the examination are assessed. It is also important to identify prescriptions without clearly documented clinical indications. Particular attention is paid to potentially dangerous combinations (for example, interactions that may cause QT prolongation), as well as duplication of active substances or the use of irrational treatment regimens.

3. Classification of DRPs by category:

– efficacy issues – insufficient therapeutic effect of the prescribed drug or potential risk of reduced efficacy due to concomitant conditions (e.g., liver or kidney dysfunction affecting drug metabolism);

– safety issues – increased risk of adverse reactions, presence of contraindications, need for dose or regimen adjustment;

– compliance problems – complexity of the treatment regimen, high risk of missed doses, lack of a clear description of the regimen for the patient, which may reduce adherence to treatment.

4. Quantification of the frequency of DRPs. The total number of DRPs detected in a particular patient is counted. The data are recorded in the relevant documentation for further analysis and comparison between patients or groups of patients. This approach allows to estimate the frequency of DRPs and to identify the most common types of problems.

5. Formulation of recommendations for the necessary correction of pharmacotherapy. This stage includes the development of possible options for interventions, in particular, optimization of drug dosages, replacement of potentially dangerous combinations or correction of the treatment regimen. Recommendations are formed considering the individual characteristics of the patient and are prepared in a convenient form for the doctor, who makes the final decision on further therapy. Such a patient-oriented approach contributes to increasing the effectiveness and safety of treatment.

6. Documentation and routine monitoring. At this final stage, all identified DRPs and recommendations proposed by the pharmacist are subject to mandatory recording in the medical documentation. This ensures transparency of the decision-making process and creates a basis for further analysis. During the following consultations, the effectiveness of the changes made is assessed: it is checked whether the expected therapeutic effect has been achieved, whether the risk of adverse reactions has decreased, and whether the patient's adherence to treatment has improved. Thus, routine monitoring allows not only to track the dynamics, but also to make additional adjustments to pharmacotherapy in a timely manner.

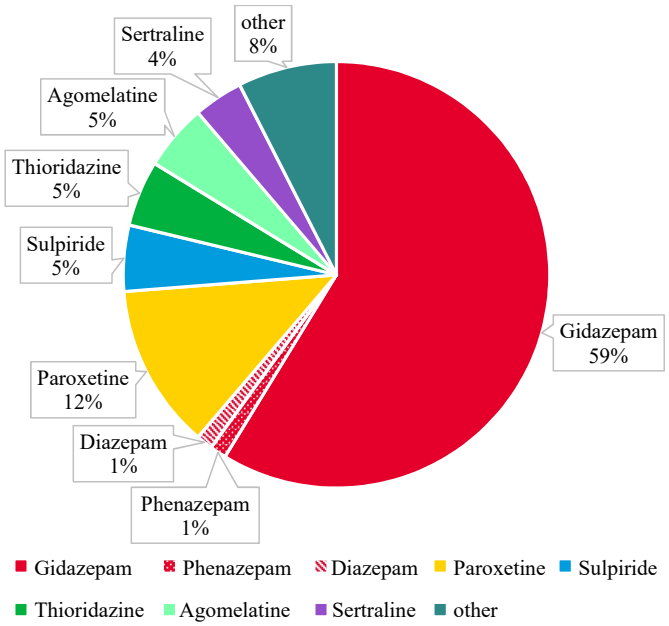

Fig. 2. Frequency of prescribing psychotropic drugs to comorbid patients with anxiety-depressive disorders

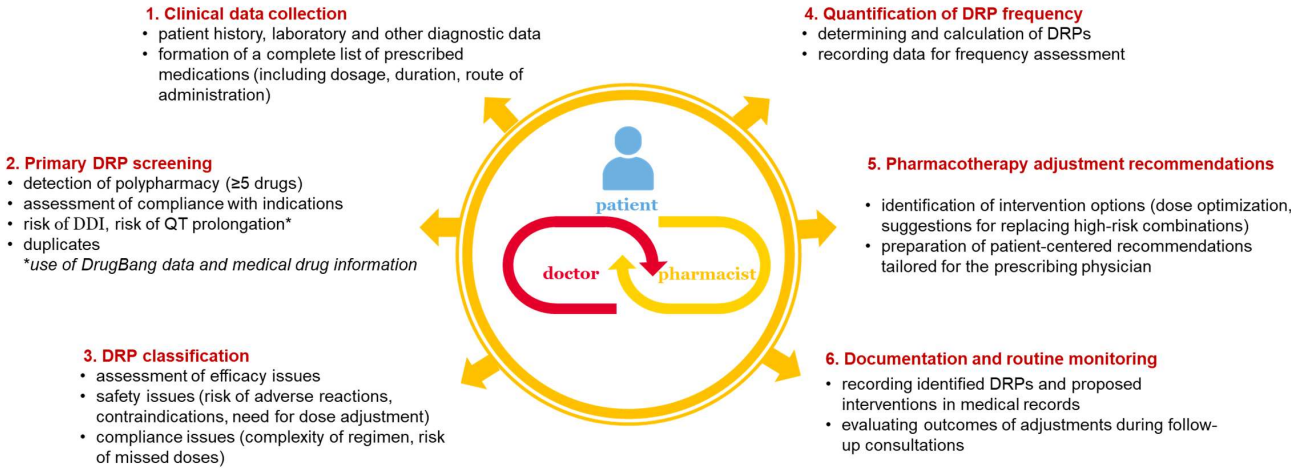

Fig. 3. Algorithm for pharmacist assessment of the risk of DRPs

The application of the proposed algorithm allows not only to standardize the approach to the detection and analysis of DRPs in clinical practice, but also to quickly respond to key problems of drug therapy, strengthen cooperation between the clinical pharmacist, physician, and other members of the multidisciplinary team, and reduce risks for the patient associated with irrational or potentially dangerous use of drugs.

5. Discussion

A significant correlation was established between the patient's age, the number of comorbid conditions and the number of drugs per course of therapy, which is consistent with the literature [29].

It was found that patients with anxiety-depressive disorders received benzodiazepines (mainly gidazepam) much more often than antidepressants, which does not meet current recommendations; it is especially worrying that most elderly patients also received benzodiazepines, which is dangerous due to the risk of increasing cognitive impairment.

Current guidelines indicate the need to limit or completely avoid prescribing benzodiazepines to elderly people, especially if alternative methods of treating insomnia, anxiety or other mental disorders are available, due to the high risk of developing cognitive impairment, falls, addiction, as well as the negative impact of these drugs on the functional state and quality of life of elderly patients [32].

The study showed that the frequency of polypharmacy among patients with multimorbidity is almost 84%, which is in the upper range of international data for hospitalized patients (46–84%) [33, 34] (Table 4). In many countries, polypharmacy is more common in women and older people, which is also confirmed by the results of our study [35, 36].

International studies also show that the number of DRPs is directly proportional to the number of prescribed medications and the level of comorbidity [37]. In patients with comorbidity who take ≥4 medications, the risk of hospitalization related to DRPs reaches 40% or more [38].

Table 4

Comparison of key indicators of the DRP with international data

Indicator	Our study	International range (sources)
Polypharmacy	84%	27–84% [33, 34, 36, 39, 40]
DRPs per patient	3.73 ± 2.58	2.5–5.0 [38]
Use of benzodiazepine in the elderly	47%	7–34% [32]
Lack of documented indication	11%	7–20% [41]
Risk of QT prolongation	15%	6–20% [42–44]

This practice is consistent with international trends, where the frequency of such prescriptions among patients with anxiety-depressive disorders ranges from 7% to 20%. The lack of justified indications for prescribing drugs increases the risk of DRPs, including side effects, treatment failure, and reduced adherence to therapy [41].

Another important aspect is the risk of QT prolongation, which was found in 15% of patients in our sample. According to some international reviews, the frequency of QT prolongation among patients receiving psychotropic therapy may reach 6–20%. Particular attention should be paid to antidepressants with a known risk of QT prolongation, including citalopram, escitalopram, and tricyclic antidepressants (e.g., amitriptyline). Given these data, it is advisable to conduct ECG monitoring before starting and during antidepressant therapy in patients with anxiety-depressive disorders, especially in the presence of polypharmacy or concomitant cardiopathology [42–44].

The role of pharmacogenetic tests for personalized pharmacotherapy is especially important when using antidepressants [45].

Practical significance. The results of the study can be used in the practice of psychiatrists and clinical pharmacists for the timely detection and correction of DRPs in patients with anxiety and depressive disorders. The proposed algorithm for assessing the risk of DRPs by a pharmacist can be implemented in the internal protocols of medical institutions to increase the effectiveness and safety of pharmacotherapy. The scope of application of the results is not limited to the examples given and is determined by the authors considering the specifics of the study.

Study limitations. This retrospective analysis has several limitations, namely: a relatively small sample size and the lack of documented long-term clinical consequences of the identified DRPs.

Further research prospects. In the future, it is advisable to conduct prospective studies to assess the dynamics of DRPs and the effectiveness of pharmaceutical interventions over time. Expanding information on clinical and laboratory diagnostic data will help increase the accuracy of DRPs detection.

6. Conclusions

The analysis of medical records conducted by us within the framework of this retrospective study, which included the medical histories of 55 comorbid patients with anxiety-depressive disorders (ICD-10: F41.2), showed a high level of polypharmacy (393 prescriptions of drugs; average number per patient – 7.15 ± 1.91). The leading position in prescriptions among drugs with anti-anxiety effect (N = 80) was occupied by benzodiazepines (N = 49, 61%) with the priority of gidazepam (N = 47), while antidepressants were prescribed much less often (mainly paroxetine – 13%). The problem of using benzodiazepines in the elderly (47%) is relevant, as well as the issue of safety of pharmacotherapy (risk of adverse reactions, QT prolongation, use of drugs from the same pharmacological group, etc.).

The results of the study are consistent with international data on the high prevalence of DRPs in patients

with comorbidity. The data indicate the need for standardization of pharmacotherapeutic approaches and strengthening the role of the clinical pharmacist in interdisciplinary interaction in the treatment of comorbid patients with anxiety and depressive disorders. The involvement of the clinical pharmacist may be one of the key areas of increasing the effectiveness and safety of pharmacotherapy of such patients to minimize the risks of DRPs, especially in today's conditions.

Conflict of interest

The authors declare that they have no conflict of interest regarding this study, including financial, personal, authorship, or other, that could influence the study and its results presented in this article.

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Availability of data

Data will be provided upon reasonable request.

Use of artificial intelligence

The authors confirm that they use artificial intelligence technologies to search for international studies. All data and analysis have been verified and conducted.

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