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Research Article

# Pharmacoepidemiological analysis of drug therapy for asthenic syndrome as provided in Kaliningrad region

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## Abstract

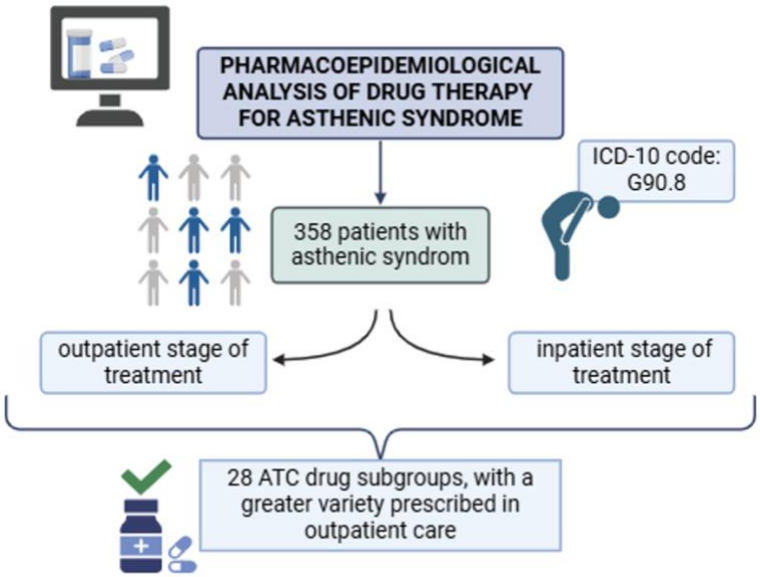
**Introduction:** Asthenic syndrome (AS) is increasingly prevalent, especially post-COVID, but its treatment lacks standardization due to unclear pathogenesis and diagnostic challenges. Current approaches rely on physician experience, underscoring the need for pharmacoepidemiological studies to optimize therapy.

**Materials and Methods**: This study analyzed AS drug therapy (ICD-10 G90.8) in Kaliningrad region. A retrospective cross-sectional study of 358 patients (82 males, 276 females) evaluated outpatient and inpatient treatment using healthcare database records. Data were processed using Microsoft Access, Excel, and Statistica 13.3, with descriptive statistics (mean, median, mode, etc.).

**Results and Discussion:** Showed 77% of AS patients were female, with monotherapy predominant (69.3% outpatients, 61.8% inpatients). Key drug subgroups included N07XX (48% outpatients, 66% inpatients – mainly succinic acid combinations) and N06BX (18% outpatients, 23% inpatients – primarily vinpocetine).

**Conclusion:** Overall, 28 ATC drug subgroups were used, with greater variety in outpatient care. Common medications were ethylmethylhydroxyperidine succinate (EMHPS) and combinations of inosine, nicotinamide, and riboflavin. The findings highlight inconsistent prescribing patterns and the need for standardized protocols to reduce polypharmacy and improve outcomes.

# Graphical Abstract





# Keywords

asthenia; pharmacotherapy; pharmacoepidemiological study; real-world clinical practice


# Introduction

Asthenic syndrome (AS) is currently among the most pressing and challenging issues faced by physicians across all specialisations. In general medical practice, the prevalence of AS ranges from 45% to 90% in patients with chronic somatic diseases in outpatient care, reaching 55% in those with acute pathologies. The frequency of seeking medical help for asthenia is approximately 30% in general practice and rises to as high as 80% in neurological practice (Chutko and Surushkina 2020; Shmyrev et al. 2023).

Post-infectious asthenia, characterised by a combination of physical and mental fatigue with prolonged tiredness, is particularly relevant at present. Caused by previous viral or bacterial infections, this condition has become a particular area of focus in the post-pandemic context of COVID-19.

The urgency of diagnosing and treating AS has also increased in the post-pandemic period due to the high prevalence of post-infectious syndrome, of which AS is a component (Alkodaymi et al. 2022; Medvedev et al. 2021). In addition to COVID-19, other infectious diseases can induce post-infectious AS, with a frequency of up to 65% (Ebzeyeva et al. 2023).

Although clinical recommendations for the treatment of senile asthenia have been developed in Russia, therapy for other forms of asthenic syndrome remains unstandardized (Tkacheva et al. 2020). The lack of unified views on the pathogenesis of AS, along with the absence of clear clinical recommendations and difficulties in defining and diagnosing the condition, determines the vast variety of pharmacological approaches used. The literature describes the application of a wide range of pharmacological groups in AS therapy, based on the empirical experience of physicians from various specialities (Khaibullina and Maksimov 2023). Similar patterns are confirmed by studies based on surveys of general practitioners and neurologists (Belousova et al. 2024).

The analysis of pharmacoepidemiological (PE) study data is a crucial step in developing recommendations to optimise pharmacotherapy (Crescioli et al. 2022). In recent years, the format of pharmacoepidemiologic studies to assess physicians' knowledge and preferences in a particular area, also known as a “knowledge/preference cross-section”, has gained increasing attention. In addition to the previously mentioned PE studies, “real-world clinical evidence” and “evidence from real-world evidence” based on their analysis are also important. These areas are also the focus of a significant amount of scientific work, and interest in them is growing

(Bontsevich 2024). Our team has previously conducted a cross-sectional knowledge/preference survey on the choice of therapy for asthenic syndrome among physicians of general practitioners and neurologists. Also, we found out what ICD-10 code they prefer to code this diagnosis with (Belousova et al. 2024). However, the lack of unified approaches in AS therapy makes the issue highly relevant and provides a basis for research aimed at obtaining objective data on current AS pharmacotherapy practices, primarily using the methodology of PE studies.

The present research was conducted to analyse the real clinical practice of drug use in AS at medical and prophylactic centres in Kaliningrad region.

# Materials and Methods

### Study design

A retrospective, cross-sectional, non-interventional PE study was conducted to analyse data on the pharmacotherapy of outpatients and inpatients diagnosed with ICD-10 code G90.8. The data were exported from the BARS medical information system, which constitutes the Kaliningrad regional segment of the national unified healthcare information system. A purpose-designed individual registration card recorded patients' demographic details, ICD-10 diagnosis codes and the treatment provided, including the mode of administration (dose, frequency, and route of administration) at both inpatient and outpatient stages. Solvents used for drug administration, such as isotonic sodium chloride solution and 5% glucose solution, were excluded from the analysis. Drugs were coded according to the ATC drug classification system.

In accordance with the results of our previous study, where a survey of neurologists and general physicians showed that asthenic syndrome was most commonly coded under ICD-10 code G90.8, 'Other disorders of the autonomic nervous system', the criterion for including a patient's medical history in the study was the presence of a diagnosis with ICD-10 code G90.8. (Belousova et al. 2024). Data from 1950 individual registration card with the specified ICD-10 code were analysed, where men and women were represented in a ratio of 41.8% men to 58.2% women, probably due to the fact that women are more likely to seek medical assistance. These patients received both outpatient and inpatient treatment at the rehabilitation department of the Central Hospital and the outpatient clinic of City Hospital No. 3 in Kaliningrad.

### Ethical review

The study was approved by the Independent Ethical Committee of Immanuel Kant Baltic Federal University (Minutres No. 31 of 30.05.2022) and was conducted from September to November 2022.

### Statistical analysis

The obtained data were processed using software based on the Microsoft Access database management application, as well as Microsoft Excel and Statistica 13.3 (Statsoft, Inc., US). Descriptive statistical methods were employed to analyse quantitative characteristics. Specifically, the arithmetic mean, median and mode were calculated to assess central tendency. To evaluate the spread of values around the arithmetic mean, the standard error of the mean, as well as the minimum and maximum values, were used.

# Results

According to the results of the study, of all the data we reviewed, the diagnosis of G90.8 was found in 276 women, representing 14%, and in 82 men, representing 4%. Comparative statistics revealed a higher frequency of occurrence of the sought diagnosis in women ($p < 0.001$). There were 358 patients in the study aged 18 to 95 years, with a mean age of 58 (± 17.03) years. In the rehabilitation inpatient hospital, 251 people were treated, and 107 people were treated at the outpatient stage. Also, it should be noted that upon discharge from the hospital, patients received recommendations on taking medications for AS at the outpatient stage.

Figure 1 demonstrates the number of patients receiving between one and six different medications at the inpatient and outpatient stages. Analysis of the number of drugs prescribed per patient showed that the majority of patients (69.3% ± 6.3) received one drug at the outpatient stage, while at the inpatient stage, this proportion reached 61.8% ($p>0.05$). Two different drugs were received by 34.7% and 19.3% ($p <0.001$) of patients at the inpatient and outpatient stages, respectively. Among inpatients, the maximum number of medications prescribed per patient per course of treatment was four. However, only 0.4% of patients received this number of drugs, while 1.8% of patients were prescribed six drugs during outpatient treatment ($p<0.05$).

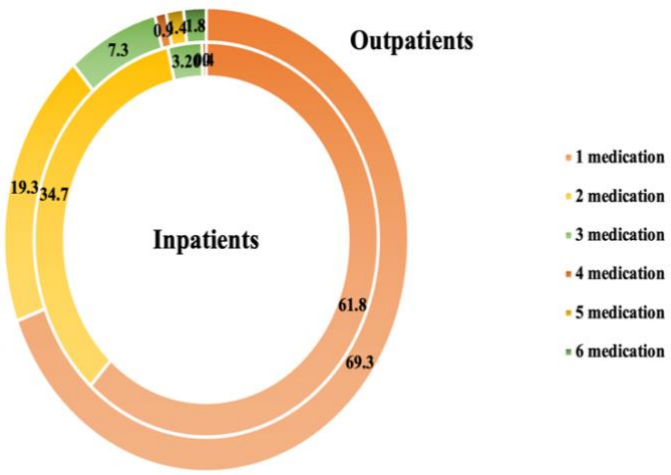



**Figure 1.** Number of patients receiving varying numbers of drugs during one course of AS treatment (%).

Figure 2 illustrates the drug prescription pattern at the inpatient stage, based on the ATC classification. The most frequently prescribed drug subgroup was N07XX, 'Other nervous system drugs', accounting for 66% of all drug subgroups ($p>0.05$). Subroup N06BX, 'Other psychostimulants and nootropic drugs', accounted for 23% of all drug subgroups prescribed at the inpatient stage. In subgroup N07XX, the majority of prescriptions were for a combination drug containing succinic acid, inosine, nicotinamide and riboflavin, which made up 90%, while the remaining 10% was accounted for by EMHPS. In subgroup N06BX, the prescriptions were distributed as follows: 64% vinpocetine, 31% piracetam, and 5% citicoline. Additionally, drugs from subgroup A16AX, 'Various alimentary tract and metabolism products', subgroup N05BX, 'Other anxiolytics' and subgroup N07CA, 'Antivertigo preparations', were prescribed, each accounting for 3%.

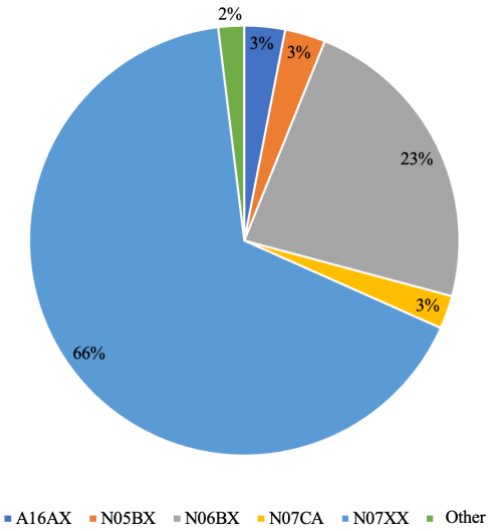



**Figure 2.** Structure of drug prescription for inpatient AS therapy according to ATC classification.

Figure 3 shows the drug prescription pattern at the outpatient stage, based on the ATC classification. The most frequently prescribed drug subgroup was also N07XX, 'Other nervous system drugs', accounting for 48% of all the subgroups ($p>0.05$). In this subgroup, the majority of prescriptions (90%) were for a combination drug containing succinic acid, inosine, nicotinamide and riboflavin, while EMHPS accounted for 6% and B vitamin complexes – for 4%. Moreover, subgroup N06BX, 'Other psychostimulants and nootropic drugs', comprised 18% of all medication groups prescribed to outpatients. This group included a large range of drugs, as presented in Table 1. Subroup N07AX, 'Other parasympathomimetics', accounted for 7% and was exclusively represented by choline alphoscerate. The remaining 25 ATC classification groups encompassed drugs prescribed for AS therapy in fewer than 5% of cases.

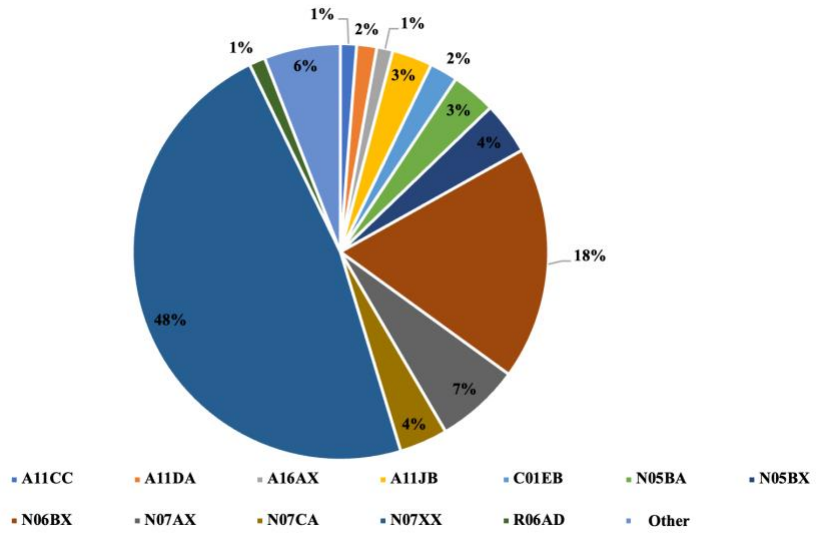



**Figure 3.** Structure of drug prescriptions for AS therapy in outpatient care according to ATC classification.

**Table 1**. Structure and frequency of using N06BX subgroup medications

| Name of drug in group N06BX | Frequency of use (%) |
|---|---|
| Aminophenylbutyric acid | 26 |
| Vinpocetine | 5 |
| Glycine | 12 |
| Hopatenic acid | 2 |
| Antibodies to brain-specific protein S-100 affinity purified + antibodies to endothelial NO synthase affinity purified | 2 |
| Polypeptides of the cortex of cattle | 16 |
| N-nicotinoyl-gamma-aminobutyric acid sodium salt | 10 |
| Piracetam | 7 |
| Piracetam + cinnarizine | 9 |
| Antibodies to brain-specific protein S-100 affinity purified | 3 |
| Methionyl-glutamyl-histidyl-phenylalanyl-prolyl-glycyl-proline | 2 |
| Cerebrolysin concentrate | 2 |
| Citicoline | 5 |

# Discussion

The PE study revealed a high prevalence of polypharmacy in AS therapy. The research identified 28 ATC-classified drug groups used in the treatment of AS, highlighting the considerable diversity of prescribed medications. The data obtained align with the findings of Kotova and Akarachkova (2016) who reported the use of over 40 different drugs for the treatment of AS, including adaptogens, general tonic and metabolic agents, vitamin and mineral complexes, nootropics, antioxidants and antihypoxants, with effectiveness varying based on the level of evidence evidence (Kotova and Akarachkova 2016).

Monotherapy was identified as the predominant treatment approach for asthenic syndrome (AS), utilised in 69.3% of outpatients and 61.8% of inpatients ($p>0.05$). However, the prescription of two drugs was noted in 34.7% of inpatients and 19.3% of outpatients ($p>0.05$). The data obtained align with the literature, particularly the work by Dyukova (2012), which highlights the widespread use of combinations of different pharmacological groups in AS therapy. The high level of polypharmacy may stem from concomitant pathologies, including depressive and anxiety disorders. The present study revealed that inpatient rehabilitation for AS therapy was characterised by a limited number of concurrently prescribed drugs, with no more than four medications used during the course of treatment. In contrast to hospital rehabilitation therapy, outpatient practice showed a tendency for more diverse drug use, with the maximum number of concurrently prescribed drugs reaching six, as observed in 1.8% of patients ($p>0.05$). This variation may be attributed to the relatively short duration of hospital rehabilitation

compared to the longer period of observation and rehabilitation in outpatient care, which involves several courses of AS therapy. These findings are consistent with the results obtained by Abakumov and Tyurenkov (2011) who analysed physicians' preferences when prescribing nootropic drugs and reported the average use of four nootropic drugs concurrently in a patient.

Analysis of the structure of drug therapy of AS in outpatient and inpatient rehabilitation settings revealed two drugs whose frequency of prescription exceeded 50% at both stages of treatment. The most commonly prescribed drug in Kaliningrad region was a combination preparation containing inosine, nicotinamide, riboflavin and succinic acid, with the second most frequently used medication being EMHPS. A comparison with the findings by Dovgun and Demidova (2012) on the structure of nootropic drug prescriptions in patients after a cerebrovascular accident (CVA), where the same combination drug and EMHPS were prescribed to 66% of patients, confirms the prevalence of these drugs in neurorehabilitation practice, despite the limited number of PE studies on AS. It is worth noting that the use of these drugs is supported by existing clinical guidelines for the treatment of post-CVA patients, and it is possible that clinical guidelines for the diagnosis and therapy of AS will be developed in the near future, potentially including these drugs.

# Conclusion

A wide range of drugs, represented by 28 ATC subgroups, is used for AS therapy, with significant intragroup diversity. Differences in pharmacotherapeutic approaches were observed when comparing therapy during inpatient rehabilitation (10 ATC subgroups used) and outpatient treatment (28 ATC subgroups used). The most commonly prescribed drugs at both stages of rehabilitation were a combination medication (inosine, nicotinamide, riboflavin and succinic acid) and EMHPS. The absence of established therapeutic algorithms and the high frequency of polypharmacy in outpatient practice highlight the need to develop standardised approaches to AS treatment, focused on evidence-based medicine, with the aim of optimising pharmacotherapy and reducing the risk of polypharmacy.

# Additional Information

### Conflict of interest

The authors declare the absence of a conflict of interests.

### Funding

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### Acknowledgments

The authors have no support to report.

### Data availability

All of the data that support the findings of this study are available in the main text.

### Ethics statements

The study was approved by the Independent Ethical Committee of Immanuel Kant Baltic Federal University (Minutres No. 31 of 30.05.2022) and was conducted from September to November 2022.

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