

REVIEW

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*(Internal member of the Scientific Jury, approved by Order No. P-109-94/12.02.2026 of the
Rector of MU-Varna)*

Subject: Procedure for the defense of a dissertation for obtaining educational and scientific degree "Doctor", FHE 7. Healthcare and sports, PF 7.3. Pharmacy, in the doctoral program "Pharmacoeconomics and Pharmaceutical regulation".

Topic of the dissertation:

"Evaluation of Pharmaceutical Care for Improving Therapeutic Outcomes and Preventing Complications in Patients with Ankylosing Spondylitis"

Author of the dissertation:

LADA ALEKSANDROVA ANDREEVA, MScPharm – PhD student in individual studies at the Medical University of Varna.

Supervisor:

Assoc. Prof. Anna Hristova Todorova, MScPharm, PhD

Scientific consultant:

Prof. Valentina Petkova-Dimitrova, MScPharm, PhD, DSc

Brief biographical data: Lada Alexandrova Andreeva graduated summa cum laude from the German Language High School "Friedrich Schiller", Ruse, in 2001. She is fluent in German and English. In 2007, she obtained a Master's degree in Pharmacy from the Medical University - Sofia, also with full honors, and was awarded the "Golden Galenus" award.

Her professional qualification was supplemented with a postgraduate specialization in Clinical Pharmacy, a course in homeopathy at the Medical University-Sofia, numerous participations in additional training and scientific conferences, as well as a course in first aid for life-threatening incidents in children.

In 2023, she won a competition for the academic position of "assistant" at the Department of "Health Care" at the Faculty of "Public Health and Health Care" of the "Angel Kanchev" University of Ruse. Since her graduation, she has been working in a community pharmacy, starting her professional career in Sofia and currently holding the position of pharmacy manager in Ruse. For the past three years, she has been a supervisor of pharmacy students during their state pre-graduate internship.

Significance of the topic: The topic of pharmaceutical care to improve therapeutic outcomes and prevent complications in patients with Ankylosing Spondylitis (AS) is particularly relevant due to the chronic and progressive nature of the disease, which leads to pain, limited mobility and reduced quality of life. The disease mainly affects young people and requires long-term and often complex treatment.

The therapy of ankylosing spondylitis includes various drug groups, all very well described by the doctoral student, such as non-steroidal anti-inflammatory drugs, biological medicinal products and other immunomodulatory therapies. All of them may be associated with the risk of adverse drug reactions, drug interactions and problems with adherence to therapy. In this context, pharmaceutical care has a key role in optimizing pharmacotherapy by monitoring the effectiveness and safety of treatment, identifying drug-related problems and providing consultations to patients.

Despite the potential of the pharmacist as an accessible and reliable health professional, his/her possibilities for contributing to the care of patients with AS remain insufficiently studied and implemented in Bulgaria. The dissertation draws attention to this untapped resource opportunity — the pharmacist can participate in early screening, in the prevention of problems related to drug therapy, and in the optimization of treatment, in accordance with the principles of Good Pharmaceutical Practice of the WHO and the International Federation of Pharmacists.

Relevance of the developed topic: Lada Andreeva's dissertation is dedicated to studying the possibilities of pharmaceutical care for improving therapeutic outcomes and preventing complications in patients with ankylosing spondylitis. The disease has been continuously increasing in its prevalence in recent years. This is not only due to better diagnostics — it actually affects more and more people, with data showing a steady increase trend throughout the world. In Bulgaria, between 20,000 and 30,000 people are sick, but the real number is probably higher due to the massive undiagnosis. In addition, patients with ankylosing spondylitis are exposed to an increased risk of complications and extra-articular manifestations, which requires a complex and multidisciplinary approach. Through the active participation of the pharmacist in the health team, adherence to therapy can be improved, the risk of complications can be reduced, and better clinical outcomes can be achieved. Therefore, the development of pharmaceutical care in AS is an important tool for increasing the quality of treatment and the long-term prognosis of patients with the disease. From a public health and economic perspective, the effective implementation of pharmaceutical care can lead to a reduction in the incidence of complications, hospitalizations and costs to the healthcare system, as well as to an improvement in the work capacity and social activity of patients.

Structure of the dissertation: The dissertation work of Lada Andreeva is very well-formed and structured in terms of its main parts and fully complies with the Regulations for RAS of MU-Varna. It begins with an introduction and contains the following sections:

- Literature review;
- Aim, tasks and scientific hypotheses;
- Materials and methods;
- Results and discussion;
- Conclusions;
- Recommendations;
- Conclusion;
- Contributions;
- Appendices.

Finally, the literature used is listed. The dissertation covers a total of 145 standard typewritten pages, including 4 figures and 38 tables. 254 literary sources are cited, of which, however, only 20 are in Bulgarian.

The literature review contains a sufficient volume of summarized and analyzed scientific material, which reflects a lot of data and information about scientific research on the topic to date. It is systematically presented and reveals a very good knowledge of the material related to the disease Ankylosing spondylitis and justifies the choice of the topic for the dissertation. The literature review is divided into several parts, which sequentially examine: the essence and characteristics of the disease Ankylosing spondylitis, therapeutic approaches and good pharmaceutical practice.

The doctoral student excellently describes the pathogenesis of AS, which is associated with genetic predisposition - over 90% heritability, with HLA-B27 being the leading genetic risk factor carried by 90-95% of patients. Key inflammatory pathways are indicated, including TNF- α , IL-23 and IL-17. It is exhaustively indicated how the diagnosis is made by a rheumatologist according to the modified New York criteria, combining clinical and radiographic data. A significant problem is the diagnostic delay - an average of 5 to 7 years from the onset of symptoms to receiving the diagnosis, and in women it reaches 8.8 years. It is explained how disease activity is assessed using validated BASDAI and ASDAS indices.

The treatment of AS is presented very comprehensively in the literature review, which is complex and includes non-pharmacological and pharmacological methods. Non-pharmacological approaches include individualized physiotherapy, analytical exercises, hydrotherapy and ergotherapy. In advanced cases, spinal surgery or joint replacement is applied.

Pharmacological treatment follows a stepwise algorithm according to the updated ASAS/EULAR recommendations from 2022. The first line is NSAIDs, applied according to the principles of chronopharmacology - taking into account the circadian rhythm of pain and stiffness, characteristic of the night and early morning hours. In case of failure after at least two NSAIDs, biological agents are used: TNF-inhibitors (infliximab, adalimumab, golimumab, etanercept, certolizumab) and IL-17 inhibitors (secukinumab, ixekizumab, bimekizumab). Targeted synthetic disease-modifying drugs — JAK-inhibitors (upadacitinib) — represent a new therapeutic option with the advantage of oral administration. Standard DMARDs (sulfasalazine, methotrexate) are used mainly in peripheral forms. The choice of biological therapy is based on the extra-articular manifestations — in uveitis and inflammatory bowel disease, monoclonal TNF-inhibitors are preferred, in psoriasis — IL-17 inhibitors. The review examines in detail the adverse drug reactions of each therapeutic group — gastrointestinal, cardiovascular, hematological toxicity in NSAIDs and standard DMARDs, infectious risk and immunogenicity in biological therapies.

L. Andreeva provides a very comprehensive review of the Concept of Pharmaceutical Care, which has existed for more than 30 years, but its integration into daily practice remains limited. Pharmacies serving the population are an easily accessible point of the health system, with pharmacists gradually moving from activities of drug suppliers to active participants in health care.

I accept the conclusions drawn by the doctoral student that the role of the pharmacist in AS covers three main areas:

- o First — early screening: prepared with knowledge of the characteristic inflammatory pain and early symptoms, the pharmacist can identify suspect patients and refer them promptly to a rheumatologist, shortening the diagnostic delay.
- o Second — optimization of pharmacotherapy: applying the principles of chronopharmacology and individualized pharmaceutical care, the pharmacist selects the appropriate NSAID, dosage form and time of administration, minimizes adverse reactions and interactions, and manages polypharmacy in comorbid patients.
- o Third — improvement of adherence: according to WHO data, adherence to therapy in chronic diseases is on average only 50%. Proper pharmacist-patient communication, training and regular follow-up can significantly improve this indicator, and hence — therapeutic outcomes.

The literature review examines in detail comorbidity in AS — hypertension (16.4%), peptic ulcer (13.9%), osteoporosis, cardiovascular diseases — as a factor requiring special attention in the management of drug therapy. Current international and national priorities are also presented: Bulgaria's National Health Strategy 2030 envisages increased participation of pharmacists in

screening, prevention and monitoring of chronic diseases, and the European document "Pharmacy 2030" of PGEU outlines the future role of pharmacy pharmacists as integrated participants in the multidisciplinary healthcare team.

In conclusion, the literature review identifies and describes three incompletely studied aspects that motivate the research in the dissertation: the level of competence and attitudes of pharmacists in implementing pharmaceutical care in AS, the extent to which patients recognize the pharmacist as a resource for optimizing treatment, and the potential of the pharmacy network for conducting early screening and monitoring of therapy.

The main aim of the dissertation is to study the attitudes and competencies of pharmacists in providing pharmaceutical care to patients with ankylosing spondylitis and to analyze the potential for integrating the pharmacist into the multidisciplinary approach to prevent complications and optimize therapeutic outcomes.

The tasks are 6 in total and arise from the set goal. They are formulated precisely and are logically justified, and their implementation enables the achievement of the defined goal.

The doctoral student formulated **two scientific hypotheses**:

- The attitudes and competencies of pharmacists to provide pharmaceutical care to patients with AS are related to their personal and professional characteristics and determine the potential for the effective integration of the pharmacist in the multidisciplinary approach to prevention, care and optimization of the treatment of the disease.
- Unfavorable, potentially influenced by pharmaceutical care, health-behavioral factors and low adherence to drug therapy are associated with higher disease activity and lower quality of life in patients with AS.

The subjects of the study in the developed dissertation were master pharmacists practicing in pharmacies serving the population and patients diagnosed with the disease ankylosing spondylitis.

The methods used in the study are classical and have been selected in view of its specificity:

- Documentary method
- Sociological method
- Statistical methods

The overall design of the study is evidence of the doctoral student's in-depth knowledge and mastery of modern methodological approaches in pharmaceutical care and social pharmacy. It is a good impression that the methods used are diverse and in different directions.

The results obtained are presented clearly and are well structured for each aspect of the study, and are accompanied by numerous tables and figures.

L. Andreeva's research includes two independent components - a survey among 260 master pharmacists and an interview among 66 patients with ankylosing spondylitis from the Ruse region. Results of the study among master pharmacists

The participants are mostly women (77%), with almost every second one having acquired their education more than 10 years ago, and 87% do not have a postgraduate specialization. In terms of attitudes and readiness, 84% of pharmacists consider the participation of the pharmacist in the complex care of AS to be necessary, and the implementation of IFG would bring professional satisfaction to 88% of them. However, 55% are either unsure or do not feel sufficiently prepared to consult patients with AS. Nearly 70% cannot or are unsure whether they can differentiate inflammatory from compression pain, and 47% would refer a patient with inflammatory pain to a neurologist instead of a rheumatologist. Eighty percent of pharmacists regularly see patients with low back pain.

The main barriers to the implementation of IFG are: lack of sufficient time (76%), insufficient awareness of the disease (70%), lack of a special designated place (63%) and lack of payment for the service (53%).

The correlation analysis found that work experience was the most significant factor — recently graduated pharmacists were significantly better acquainted with the concept of IFG ($\rho = 0.353$; $p = 4.99 \times 10^{-9}$), more confidently assessed their own knowledge and more clearly realized the need for pharmacist participation in the care of patients with AS. The ability to differentiate inflammatory from compression pain is significantly associated with readiness for IFG (OR = 2.19; $p = 0.006$). Gender and place of education do not have a statistically significant influence.

I highly appreciate the practical algorithm for pharmaceutical care in patients with AS, a quick screening questionnaire of 7 questions for pharmacy use and training materials for pharmacists, developed based on the results.

Among the more important results of the study among patients with AS, I would highlight those that in nearly two thirds the diagnosis was made more than 5 years after the onset of complaints, and in more than half - between the ages of 21 and 30. HLA-B27 was positive in 92.4%.

The doctoral student has extremely successfully selected and used validated questionnaires in her dissertation to assess various aspects of the health status of patients with AS, respectively for:

- o *Disease activity (BASDAI)*: 70% of patients were at or above the clinical threshold for starting biological therapy (BASDAI ≥ 4), and 12% had very high activity (BASDAI > 8). The mean value was 5.53. Statistically significantly higher disease activity was found in women (6.22 vs. 5.02 in men; $p = 0.031$), in patients with comorbidities (6.40 vs. 3.42; $p = 0.000001$), in smokers (6.70 vs. 4.61; $p \approx 3.5 \times 10^{-5}$), in patients without biological therapy

(6.73 vs. 4.57; $p = 0.000006$), in physically inactive patients (6.07 vs. 5.05; $p = 0.019$) and in those sleeping less than 6 hours ($p = 0.029$). Biological therapy is the only factor with a clear and significant reducing effect on disease activity.

o *Quality of life (EQ-5D-5L)*: The mean value is 0.803, and the median 0.83 — in the category of good health, but statistically significantly lower than the reference population value ($t = -7.98$; $p < 0.0001$; Cohen $d \approx -0.98$). The subjective self-assessment on VAS is on average 68.6/100. Most of the studied health-behavioral factors do not show a statistically significant influence on EQ-5D-5L. An important exception: in women a significant negative correlation between disease activity and quality of life was found ($r = -0.47$; $p = 0.012$), which is absent in men.

o *Comorbidity and behavioral profile*: 71% of patients have at least one comorbidity, among which diabetes mellitus, elevated lipids and gout (over 60%), osteoporosis and cardiovascular diseases predominate. 44% are smokers, 70% sleep less than 6 hours, 53% are overweight ($BMI \geq 25$). 65% are on biological therapy, 60% also apply non-pharmacological methods. Over 90% report at least one adverse drug effect, and 47% take nutritional supplements on their own initiative.

o *Adherence to therapy (MMAS-8)*: 54.5% of patients have a low level of adherence, 33.3% — moderate, and only 12.1% — high level. The average value is 5.70. Education is a significant factor — paradoxically, patients with higher education show the lowest adherence ($p < 0.001$; $\eta^2 \approx 0.43$). Gender, comorbidities and type of therapy do not have a statistically significant influence. A moderate positive correlation was found between Morisky and BASDAI ($r = 0.45$; $p < 0.001$), especially pronounced in women ($\rho = 0.39$; $p = 0.038$), indicating that more severe disease motivates stricter adherence, and not the other way around.

o *Patients' attitudes towards pharmaceutical care*: 88% of patients would benefit from IFG, none responded negatively. 89.4% assessed the need for FG with a score of 8–10 out of 10. However, over 60% of them would not consult a pharmacist about the nutritional supplements they use, which reveals a gap in the implementation of this willingness in practice.

All the results obtained are original and reliable, supported by a large volume of analyzed and summarized scientific material.

Conclusions. Specific conclusions have been formulated from the conducted studies, which have a practical focus and are in accordance with the collected and analyzed data. I believe that all the conclusions made objectively reflect the results obtained by the doctoral student.

The recommendations are well structured. They are aimed at different institutions and levels of the health system. In general, the recommendations are logically justified by the results, but differ in the degree of specificity and realism of implementation.

Contributions to the dissertation

The presented contributions are divided into those with original, scientifically applied and confirmatory nature.

SCIENTIFIC-THEORETICAL

- ❖ *The study enriches theoretical knowledge about the role of the pharmacist in early recognition and comprehensive care for patients with ankylosing spondylitis, by identifying specific knowledge gaps and factors affecting professional readiness;*
- ❖ *For the first time, a comprehensive characterization of patients with ankylosing spondylitis has been carried out on a regional scale, including socio-demographic profile, comorbidities, health-behavioral habits, types of applied therapies, disease activity, quality of life and degree of adherence to drug therapy;*
- ❖ *Key dependencies between modifiable health-behavioral factors (smoking, physical activity, sleep) and disease activity have been proven, contributing to a deeper understanding and control of the clinical course of the disease.*

SCIENTIFIC-PRACTICAL

- ❖ *Practical algorithms, a screening checklist and training materials have been developed, meeting the identified educational and practical needs of the surveyed pharmacists, which support pharmacists in real pharmacy practice in early referral to a specialist rheumatologist and implementation of pharmaceutical care in patients with AS;*
- ❖ *Factors of practical importance for the control of disease activity have been determined, which allows for targeted and individualized care;*
- ❖ *A high risk of low adherence to the prescribed therapy and the role of educational programs in improving patient compliance have been identified;*
- ❖ *Arguments have been formulated in support of the active participation of the pharmacist in the comprehensive care of patients with AS;*

Abstract and publications. The abstract has been prepared in accordance with the requirements of the Regulations for the Development of the Academic Staff of the Medical University of Varna and correctly reflects the results obtained and the scientific contributions of the dissertation work.

Five publications in scientific journals and three participations in scientific conferences related to the topic of the dissertation work are presented. In all articles, the doctoral student is the first author, which shows his personal participation in the development, discussion and presentation of the results obtained. In addition, one of the articles has been published in an international specialized journal with IF, which is indisputable evidence of the significance of the conducted research.

Conclusion. I positively evaluate the dissertation work of Lada Andreeva and believe that in terms of content and scientific contributions it fully meets the requirements of the LDAS in the Republic of Bulgaria and the Regulations for the Development of the Academic Staff of MU-Varna. The

good methodological preparation, in-depth theoretical knowledge and the accumulated practical experience of the doctoral student in the field of Pharmaceutical Care are an excellent prerequisite for her future successful development as a scientist. All this gives me reason to confidently recommend to the members of the esteemed Scientific Jury to award **LADA ALEXANDROVA ANDREEVA** the educational and scientific degree of "**Doctor**".

Varna
2 April 2026

Заличено на основание чл. 5,
§1, б. „В“ от Регламент (ЕС)
2016/679

Member of the Scientific Jury:.....

(prof. Evgeni Evgeniev Grigorov, MScPharm, PhD)

By signing here, I declare that I am not related to the doctoral student, and that I have no private interest that could affect the impartial and objective implementation of the opinion in the current procedure for acquiring ESD "Doctor".