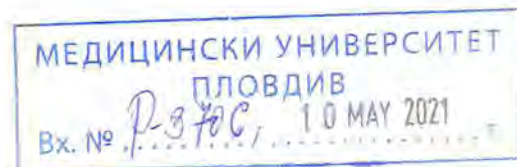


To the Chairman of the Scientific Jury  
designated by Order No. P-496/07.04.2021 of the  
Rector of the Medical University of Plovdiv.



## REVIEW

by Prof. Dr. Rosen Gospodinov Kolarov, PhD,  
Medical University of Varna, Faculty of Dental Medicine, Department of Oral Surgery of a  
dissertation for receiving a doctoral degree

Sphere of higher education: 7. Healthcare and sports

Professional field: 7.2. Dental medicine

Doctoral programme: Oral Surgery

Author: Dr. Tanya Ivanova Sbirikova, self-training PhD student

Department: Oral Surgery

Theme:

Control of postoperative pain – psychological, fMRI and immunological studies

Academic supervisor: Assoc. Prof. Dr. Deyar: Zdravkov Neychev, PhD, Medical  
University of Plovdiv, Faculty of Dental Medicine, Department of Oral Surgery

## **1. General presentation of the procedure and the doctoral candidate**

This review was prepared on the basis of Order of the Rector of the Medical University of Plovdiv No. **P-496/07.04.2021**, with appointed Scientific Jury under the procedure for public defence of the dissertation above mentioned.

The presented set of materials in both paper and electronic form is in accordance with Art. 115 (I) of the Procedure for Awarding Doctoral Degrees at the Medical University of Plovdiv, set in the Regulations of the Medical University of Plovdiv of 06 Nov 2014, and was provided to me within the legal deadline.

The doctoral candidate has enclosed 3 scientific publications printed in scientific journals and 2 participations in scientific forums related to the theme of the dissertation.

All documents were duly prepared and presented.

## **2. Biographical notes of the doctoral candidate**

Dr. **Tanya Ivanova Sbirikova** was born on 04 December 1981.

In 2000 she graduated from the French Language School "Antoine de Saint-Exupery", Plovdiv.

In 2000 she was admitted to the Faculty of Dentistry of the Medical University of Plovdiv. Graduated in dentistry in 2006.

Since February 26, 2007 and until now Dr. Sbirikova is an assistant at the Department of Oral Surgery of the FDM, MU - Plovdiv.

Since March 27, 2012 and until now Dr. Sbirikova has been working in AGPPPDMD "Charisma" Ltd.

For the period 01.11.2012 - 01.02.2014, works in the University Hospital "St. Georg" at the Clinic of Maxillofacial Surgery, as an oral surgeon.

Dr. Sbirikova is a leading researcher in a research project on "Objectification of postoperative pain control after extraction of impacted third mandibular molars."

Dr. Sbirikova has a total work experience of 14 years as a lecturer.

In 2011, she acquired a specialty in Oral Surgery.

Dr. Sbirikova's latest assessment in the attestation process is "good".

Dr. Sbirikova is a member of:

- Bulgarian Dental Association (BDA),
- Bulgarian Scientific Dental Society (BNSD)
- Union of Scientists in Bulgaria (USB).

She has a good command of English and French.

### **3. Significance of the theme and appropriateness of the objectives and tasks set**

The theme of the dissertation addresses a significant and important problem for the dental science and practice. The objective is clearly stated, and the tasks are defined correctly and implemented using modern research methods.

### **4. Knowledge on the problem**

In her dissertation, Dr. Tanya Ivanova Sbirikova shows in-depth knowledge of the theme, namely: Control of postoperative pain – psychological, fMRI and immunological studies.

The doctoral candidate has made a thorough critical analysis of the literature, formulating unsolved problems on the theme, namely:

- Objectification of postoperative pain through the use of modern technologies such as fMRI
- Assessment of the influence of certain factors on the intensity of postoperative pain
- Determination of the relationship between the size of postoperative edema and the intensity of postoperative pain by examining the change in serum levels of CGRP and Procalcitonin
- Evaluation of the drugs used Placebo, Ibuprofen and Ibuprofen in combination with Gabapentin for the control of postoperative pain by reporting changes in serum levels of CGRP and Procalcitonin
- Investigation of the possibilities of using CGRP and Procalcitonin as diagnostic markers for a general inflammatory process in the body
- Assessment of the impact of anxiety and the presence of negative / positive previous experience on postoperative pain.

Pain is a complex biological phenomenon. It has a negative sign for the patient, but has a positive meaning. It is expressed in the fact that it gives a sign of disturbance in the homeostasis of the patient. It is the root cause and is the most common reason for seeking medical attention. Pain is also the basis for impaired quality of life. Of particular interest is operative and postoperative pain. It is usually short-lived and lasts an average of 5 days. If

pain is not reported and treated in time, it could become chronic and turn into a chronic pain syndrome. In these cases, its treatment is difficult, the quality of life deteriorates, and the costs of its impact increase many times over. Therefore, any study of this biological phenomenon is of great interest to medical science and practice.

The doctoral candidate demonstrated her ability to conduct research independently. She looked at different approaches to treating pain.

All of the above has enabled the doctoral candidate to define clearly and precisely the objective of her research, namely: "To study the possibilities for influencing the pain symptoms after surgical removal of impacted third mandibular molars using various drugs, using fMRI, immunological and psychological tests".

The exposition is written in good scientific language.

## **5. Research methodology**

The objective was achieved through the completion of four main tasks and two subtasks, namely:

1. Registration of pain intensity after surgical removal of impacted third mandibular molars:
  - 1.1 To study the intensity of pain using the Visual analog scale (VAS) and the factors (age, sex, smoking, difficulty and duration of surgical intervention, preemptive analgesia, postoperative complications) affecting the sensation of pain.
  - 1.2 Activation of areas in the brain after surgical removal of impacted third mandibular molars.
2. To find the relationship between the intensity of postoperative pain and reactive inflammatory process by examining Procalcitonin and CGRP.
3. To examine the serum levels of neurotransmitters and inflammatory pain mediators - Procalcitonin and CGRP (calcitonin-gene related peptide), and their response to the drugs administered.
4. To study the influence of anxiety on the intensity of postoperative pain and on the physiological parameters – blood pressure, pulse rate and saturation in young adults.

### **Study design**

The study is randomized, double-blind, placebo-controlled in order to avoid the subjective moment when including patients in a particular group, as well as to ensure that the

results of various drugs are as accurate and objective as possible. In simple randomization, the subjects are not divided according to a certain feature (eg gender, age, etc.), which includes the possibility of uneven distribution of populations in different groups.

**The clinical material examined for the dissertation tasks is as follows:**

Forty patients with impacted third mandibular molars bilaterally, with indications for extraction. At random, patients were divided into three groups, taking respectively:

- Placebo - 10 patients
- Ibuprofen (400 mg) - 15 patients
- Ibuprofen (400 mg) with Gabapentin (300 mg) - 15 patients

**Subject of observation:**

Forty patients with impacted third mandibular molars bilaterally, with indications for extraction, selected by inclusion and exclusion criteria.

**Units of observation:**

Adults who accidentally or were referred to the Department of Oral Surgery for removal of impacted third mandibular molars.

**Signs of observation:**

Age, sex, smoking, changes in saturation, pulse rate and blood pressure during surgery, postoperative pain, pain intensity, swelling - different localizations, changes in the activity of certain brain structures due to postoperative pain, study change in levels of procalcitonin and CGRP.

**Time of observation:**

The research was conducted in the period September 2017 - May 2018.

**Place of observation:**

Department of Oral Surgery, Faculty of Dental Medicine, Medical University of Plovdiv.  
Immunology Research Centre, Medical University of Plovdiv.  
Translational Neuroscience Complex, Medical University - Plovdiv.



**Surveillance authorities:**

The observations were made by the study leader in collaboration with pre-trained teachers.

The clinical material selected for the implementation of the main goal and tasks is sufficient for the development of a dissertation.

Patients participating in the study met inclusion and exclusion criteria, namely:

***Inclusion criteria:***

1. Clinically healthy patients aged between 17 and 40 years with indications for extraction of the third mandibular molar, bilateral
2. No evidence of pain associated with the extracted third mandibular molar

***Exclusion criteria:***

1. Patients not included in the studied age group
2. Pregnancy and lactation
3. Patients with aneurysmal clips and pacemakers
4. Patients with tattoos and piercings
5. Patients with a history of head trauma or seizures
6. Patients with neurological or mental illness
7. Systemic alcohol intake and drug use
8. Taking drugs that affect brain function (including aspirin) in the last two weeks before the fMRI
9. Women, 5 days before and 5 days after their menstrual cycle (in order to exclude the influence of hormonal factors on pain)
10. Anamnestic data for drug allergy
11. Acute inflammation in the area of the tooth to be extracted
12. Systemic lupus erythematosus or other disease to connective tissue
13. Diseases of the stomach or intestines, incl. Crohn's disease
14. Liver, kidney or cardiovascular diseases, incl. Hypertension
15. Chronic lung diseases
16. Intake of NSAIDs, anticoagulants, antiplatelets, digoxin, antihypertensives, phenytoin, cholestyramine, aminoglycosides, quinolones, immunosuppressants, bisphosphonates, pentoxifylline, baclofen, drugs for the treatment of diabetes and depressive drugs.

### **Statistical methods for data analysis:**

The systematization, processing and analysis of the primary data in the form of quantitative and qualitative variables was realized with the statistical package of the social science software IBM SPSS Statistics v. 25. The fMRI data were analyzed using SPM 12 (Statistics Parametric Mapping, <http://www.fil.ion.ucl.ac.uk/spm/>) on the MATLAB R2015a platform for Windows. The results of all tests are considered statistically significant at p-value <0.05. The graphical analysis was performed in an MS Office 365 environment using Excel

#### **1) Descriptive methods and methods of assessment:**

- *Analysis of variance of quantitative variables*
- *Frequency analysis of qualitative variables (nominal and rank), which includes absolute frequencies, relative frequencies (as percentages)*
- *Graphic images - histograms, bar charts, box-plot, digital images*

#### **2) Methods for hypotheses testing:**

##### *Parametric:*

- Independent and Paired Sample T-tests - check for equality of two means
- One-way ANOVA with Bonferoni correction
- Z-test
- Test of Shapiro-Wilk

##### *Non-parametric:*

- Wilcoxon signed-rank test - comparison of two related samples when the distribution cannot be assumed to be normal.

##### **Correlation analysis:**

$r_{xy}$  Pearson correlation coefficient;

$\rho$ - coefficient ( $\rho$ ) of Spearman for rank correlation

##### **Regression analysis:**

Linear regression analysis

Hierarchical multiple regression

##### **Analysis of fMRI images:**

the functional images are regrouped, co-registered with the structural images normalized in the space of the Montreal Neurological Institute (MNI) and smoothed with a 6-millimeter full width at half the maximum Gaussian function; the analysis of the state at rest at the first level is performed with the help of a general linear model applied to the time series; auxiliary covariates include the six parameters of motion of a stationary body, averaged white matter,

and cerebrospinal fluid signals in the form of time series. BOLD time series were extracted for eight predefined areas of interest from spheres with a radius of 6 mm, all of which were located in the right hemisphere; the analysis included the following regions with their MNI coordinates: PCC [0, -52, 26], mPFC [[3, 54, -2], RIPC [48, -69, 35], LIPC [-50, -63, 32] . The BOLD signal from some of the ROIs was absent in 2 patients, which led to their exclusion from further analysis.

### ***Dynamic causal modeling:***

analysis of neural processes that result from measured time series in order to evaluate the parameters of a realistic model of the neuronal system, so that the predicted depending on the level of oxygen in the blood signal (BOLD), which is obtained as a result of the transformation of the modeled neural dynamics in hemodynamic responses to correspond as much as possible to the observed BOLD time series; a fully connected model is achieved, where each node (ROI) is connected to the others in two-way pairs.

### **3) *Graphic analysis:***

- box type diagram (box)
- pie charts
- bar charts
- digital images

The presentation of the results of the conducted analyzes was performed by:

- frequency tables -
- multidimensional frequency distribution tables containing:
  - absolute frequencies - the number of units in a single group;
  - point estimates of quantitative and qualitative variables - presented with measures of average values and measures of scattering, as well as as relative frequencies - number of units in a single group relative to the total number of units in the population.

## **6. Characteristics and evaluation of the dissertation**

The dissenation was written on 175 pages, and contains 20 tables, 18 figures. 33 diagrams and 7 appendices. The bibliography includes 271 references, 5 of which are in Cyrillic and 266 in Latin. It contains all sections necessary for a dissertation.

The results are comprehensively and correctly described, analvzed and interpreted.

The dissertation finishes with conclusions based on the results, the discussion and the summaries of the study.



## **7. Contributions and significance of the dissertation for the science and practice**

As a result of the study, the following conclusions were made:

1. Postoperative pain after surgical removal of impacted third mandibular molars has the highest intensity at the 6th postoperative hour and has a significantly lower intensity after the second, compared to the first surgical intervention.
2. The difficulty of the surgical intervention is the factor that most strongly affects the postoperative pain
3. A local inflammatory reaction, most pronounced in the 24th and 48th postoperative hours, and a mild or insignificant systemic inflammatory response were found.
4. There is no association between the intensity of postoperative pain and the administered drug after surgical removal of impacted third mandibular molars
5. Preemptive analgesia reduces pain in the early postoperative period.
6. Preoperative anxiety leads to an increase in the intensity of postoperative pain and to a change in physiological cardiac parameters.
7. Familiarizing the patient with the nature of surgical manipulation leads to a reduction in anxiety and the intensity of postoperative pain.
8. The presence of previous experience in surgical intervention to remove an impacted third mandibular molar leads to a reduction in anxiety and no change in CGRP values.

The dissertation outlines the following contributions of theoretical and scientific-applied nature, as follows:

### **Theoretical contributions:**

1. For the first time in Bulgaria fMRI is applied in order to objectify the postoperative pain in Oral Surgery
2. For the first time in Bulgaria the serum levels of CGRP and Procalcitonin are examined on the occasion of operative interventions in Oral surgery.
3. The change in physiological cardiac parameters due to anxiety accompanying surgical interventions in Oral Surgery is examined
4. It has been proven that patients' awareness before surgical interventions in Oral Surgery leads to a reduction in anxiety and easier toleration of surgical manipulation.

### **Scientific and applied contributions:**

1. The intensity of postoperative pain is found to be strongest at the 6th postoperative hour
2. Difficulty is defined as a leading factor that affects the intensity of postoperative pain.
3. It was confirmed that postoperative administration of anti-inflammatory drugs is necessary in order to control the inflammatory component of postoperative pain
4. The need for pre-operative analgesia to treat postoperative pain in the early postoperative period was confirmed.
5. The reduction of anxiety after thorough acquaintance of the patient with the forthcoming procedure determines the weaker feeling of postoperative pain after surgical removal of affected third mandibular molars.

### **8. Assessment of publications related to the dissertation**

Three publications related to the dissertation are presented, as Dr. Sbirkova is the first author in two of the publications and the second in one of them, namely:

1. Sbirkova TI, Neychev DZ, Raycheva RD, Atanasov DT. Factors which Influence Postoperative Pain Intensity after Surgical Removal of Impacted Mandibular Third Molars. J of IMAB 2019 Oct-Dec;25(4):2793-9.
2. Neychev D, Sbirkova T, Ivanovska M, Raycheva R, Murdjeva M, Atanasov D. Correlation between CGRP levels and the neuropathic and inflammatory component of postoperative pain. Folia Med (Plovdiv) 2020;62(2):365-71.
3. Sbirkova T, Massaldjieva R, Neychev D, Raycheva R. Anxiety and changes in physiological parameters during surgical procedures for removal of impacted mandibular third molars in young adults 2021;14(1).

### **Participations in scientific events related to the dissertation**

1. Сбиркова Т, Нейчев Д. Съвременни аспекти на контрола на постоперативната болка чрез използване на фЯМР за отчитане на ефективността на направената аналгетична интервенция. VII Международна Конференция на Младите Учени, 15-16 Юни 2017, Дом на Учените, Пловдив.
2. Сбиркова Т, Атанасов Д. Обективизиране на контрола на постоперативната болка след екстракция на импактирани трети долночелюстни молари. Дни на медицинската наука. Проектна сесия. Пловдив 30.03.2019г.

Dr. Sbirkova's scientific articles have been published in prestigious English-language journals. The presented scientific reports presented at scientific forums are in Bulgarian. The results obtained in them satisfy quantitatively and qualitatively the legal requirements for dissertation work.

#### **9. Personal involvement of the doctoral candidate**

I consider that the research and observations of patients and the resulting conclusions and contributions of the dissertation are personal work of the author.

#### **10. Author's summary**

The author's summary contains 63 pages, illustrated with 15 figures, 26 diagrams and 20 tables. It correctly reflects the nature of the study and the results achieved in the dissertation. The conclusions are included in it.

It has been prepared in accordance with the requirements of the Act for the Development of the Academic Staff in the Republic of Bulgaria and the regulations of the Medical University of Plovdiv. It reflects the content of the dissertation.

#### **11. Critical comments and recommendations**

The set of materials related to the dissertation, which was submitted to me, is complete and is in accordance with the Act for the Development of the Academic Staff and its Implementation Rules as well as with the regulations of the Medical University of Plovdiv. I have no comments or recommendations.

#### **12. Personal impressions**

I have no personal impressions of the author of the dissertation. However, the text submitted to me shows a thorough knowledge of the problem and gives me reason to consider it a personal work.

#### **13. Recommendations for future use of dissertation contributions and results**

I recommend to Dr. Sbirkova to form and publish her dissertation as a monograph. Thus, her work will become more accessible to colleagues who work on this issue on a daily basis.

## CONCLUSION

The theme of the dissertation chosen by Dr. Tanya Sbirikova, namely “Control of postoperative pain – psychological, fMRI and immunological studies”, addresses a significant problem in the dental science and practice. In this regard, the theme is significant and well-chosen.

The literature review is comprehensive and gives a clear idea of the current state of the issue under consideration. It ends with a critical analysis, which is a good basis for the research carried out.

The clinical material and the research carried out are of interest for dental practice and science. I consider that the results obtained in the dissertation, their interpretation, and the presented publications related to it are the author's personal work.

The dissertation shows that the doctoral candidate Dr. Sbirikova **possesses** in-depth theoretical knowledge and professional skills in the specialty Oral Surgery, and **demonstrates** competences and skills for conducting independent research.

Based on the above stated, I consider that the requirements set in the Act for the Development of the Academic Staff and its Implementation Rules as well as in the regulations of the Medical University of Plovdiv are met. The presented materials and dissertation results are in **full compliance** with the specific requirements of the Medical University of Plovdiv.

**In conclusion:** Hereby, I confidently give my positive opinion of the dissertation themed “Control of postoperative pain – psychological, fMRI and immunological studies” and I will cast my positive vote for awarding doctoral degree in the scientific specialty Oral Surgery to Dr. Tanya Ivanova Sbirikova.

26.04.2021

Reviewer:.....  
(Prof. Dr. Rosen Gospodinov Kolarov, PhD)

