

## **REVIEW**

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member of scientific jury according to Order N P-109-508/ 18.11.2021 by the Rector of Medical University-Varna

for reward of the educational and scientific degree „Doctor” in doctoral program in psychiatry, educational field 7. Health and Sport and professional field 7.1 Medicine

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**Doctoral program:** full-time

**Department:** Department of Psychiatry and Medical Psychology, Medical University-Varna

**Topic:** “Digital follow-up of patients with substance use disorders”

**Scientific advisor:** Prof. Hristo Kozhuharov, MD, PhD

### **1. Overview of the procedure and the candidate**

The presented dissertation and the supplemental materials **are in accordance** with the procedure for obtaining the educational and scientific degree "Doctor" according to the Law for the Development of the Academic Staff in the Republic of Bulgaria (LDASRB) and the Regulations for the development of the academic staff at MU "Prof. Dr. Paraskev Stoyanov" - Varna (ed. January 28, 2021) and its appendices.

### **2. Brief biography of the candidate**

Dr. Samuela Krasteva graduated from the National High School for Ancient Languages and Cultures in Sofia (2011) and medicine at the Medical University of Varna in 2017. Her interest in psychiatry is early and diligent. Since 2017 she has been a full-time doctoral student and resident physician in psychiatry at the Department of Psychiatry and Medical Psychology at the Medical University of Varna. Since 2018 she has been a Lecturer at the same department. She has participated in clinical trials and has additional qualification in the application of structured clinical instruments and digital tools for clinical purposes.

### **3. Relevance of the topic and expediency of the aims and objectives**

The relevance of the topic of the dissertation stems from the introduction of digital technologies in clinical medicine and the prospects for online diagnosis, intervention, follow-up, prevention, rehabilitation and other aspects of telepsychiatry in the modern world. The coronavirus pandemic has further led to the development of new technologies and detailed recommendations of good practice in this area. The selected study population – patients with substance use disorders, is also relevant for the application of these technologies. The medical and social cost of their illness behavior is on the rise nowadays.

The formulated aim and objectives are oriented towards early recognition of the signs of

relapse in patients with substance use disorders after their discharge from the hospital, with a focus on the relationship between socio-demographic, digital and individual predictors of relapse and the time to its occurrence. The rationale for this approach is based on the inexpensive, non-invasive and easy-to-use method compared to conventional follow-up and the ability to collect different data from active and passive sources. This diversity corresponds to the multidimensionality of the process of provoking and developing "failure" (in the old-fashioned terminology) from the periods of sobriety.

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

The literature review shows a good and versatile knowledge on the topic of the study. It systematically covers the definition of relapse as a dynamic process, its conditionality in the biological paradigm of anhedonia due to dopamine depletion and in the cognitive-behavioral model, its prevalence, and risk factors for its occurrence. The comorbidity of substance use disorders with other mental disorders and somatic diseases, their relationship with metabolic and genetic factors, the role of high-risk situations for relapse and its impact on the individual, relatives, healthcare system and healthcare workers, are discussed.

The standard methods for follow-up of patients after inpatient detoxification and methods for assessing the risk of relapse – demographic, clinical and instrumental (AWARE, SRRS, A-RSAQ, C-RSAQ and ARC) are described, as well as problems in follow-up care regarding patients with substance use disorders in the period after hospital discharge. These problems are further complicated by the constraints imposed by the pandemic. The advantages and limitations of digital methods for assessment, follow-up and interventions in psychiatry are discussed: web-based tools, mobile technologies and others, including artificial intelligence. Web-based software (such as SAGE-SR, TAPS Tool and ASSITS) is comprehensively presented, together with mobile applications, ecological momentary assessments, digital phenotyping and geolocation with the ability to actively and passively collect data as well as metadata. Interesting evidence is that e-tracking increases openness compared to a clinician-led interview.

The possibilities for remote identification of patients at risk and for crisis intervention are described. Safety considerations and ethical aspects of remote follow-up are also considered. The stated sensitivity to the ethical side of remote monitoring is essential, because in an anti-utopian plot it could reach the dimensions defined in the text as a "dystopian scenario".

The brief summary of the review also highlights gaps in knowledge in this area, especially in the digital follow-up of patients with substance use disorders, which provides a foundation for the study design.

#### **5. Methodology**

The aim and the objectives are clearly formulated. The methodology and the specific evaluation tools are adequate for the study design. Relationship between potential predictors of relapse and the relapse itself and the time to its occurrence in patients with substance use disorders in conventional and digital follow-up are investigated. The study includes inpatients who are subject to discharge and outpatient follow-up for three months thereafter, looking for links between baseline levels of depression and anxiety, demographic and clinical characteristics, digital behavior and social functioning, on the one hand, and the risk of relapse and the time until its occurrence, on another. The main hypothesis of the study is that at least some of these variables have predictive value and are

informative of the risk of relapse.

The study was a prospective non-interventional follow-up of 40 patients over three months, randomized in two groups of 20 subjects each. Accurate description of the sampling method allows critical comparability of findings with samples formed in another way, or with those that are representative of larger populations.

The inclusion and exclusion criteria are formulated shortly and clearly. The set of tools used is in accordance with their practical applicability and with the study objectives. These include: the Patient Health Questionnaire-9 (PHQ-9), the Generalized Anxiety Disorder-7 (GAD-7), the Global Assessment of Functioning (GAF). In one of the groups, standard follow-up is performed by telephone calls, and in the other – digital follow-up via the mobile application mindLAMP2 installed on the participants' smartphones (Android and iOS systems). The final version of the application in Bulgarian has disabled settings for collecting so-called passive data due to ethical reasons.

Adequate technological measures to ensure the anonymity and privacy of the respondents are also described. The mobile application includes four questionnaires in Bulgarian: self-assessment versions of PHQ-9 and GAD-7, one for sleep, and one for pathological urge ("craving"). The study participants were instructed to use it whenever they wanted, as the data is reviewed regularly. In the absence of activity for more than 14 days the subject is being contacted via telephone. The follow-up continues until the 90-th day after discharge, and the presence or absence of relapse is being assessed via telephone call at the end of the study.

The statistical methods are relevant to the set objectives and include descriptive statistics and methods for testing hypotheses, mainly correlation analyzes. There is no approval of the study by the ethics committee, but the description of the methods clearly shows compliance with the ethical side of the research work.

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

The dissertation is structured according to the requirements of the Regulations for the development of the academic staff at MU "Prof. Dr. Paraskev Stoyanov" – Varna and consists of: introduction, literature review, aim and objectives of the study, hypotheses, materials and methods, results, discussion, conclusions, contributions, appendices and bibliography. The volume and the ratio between the individual parts are not optimal, as the review (47 pages) clearly exceeds the results (22 pages) and the discussion (10 pages). The work is illustrated with 5 tables and 34 figures, the clinical tools translated into Bulgarian together with some digital screens are presented as appendices, and the bibliography contains 258 sources, of which only 4 in Cyrillic and 254 in Latin (all in English).

The results are presented clearly and with a perspicuous and understandable illustration. They cover the demographic characteristics of the patients screened and included in the study, the proportion of relapses and the time to relapse in both groups and, correlation analyzes. The latter did not find a statistically significant relationship between relapse and demographic and clinical variables other than the marital status – the risk of relapse is significantly higher in divorcees and the time to onset is significantly shorter.

In the search for a connection with digital behavior, there is no statistically significant dependence of recurrence and time to recurrence on the method of follow-up and on the results of the four digital self-assessment questionnaires, although there are certain trends. There is no significant

relationship between the researcher's clinical assessment and the result of the first digital self-assessment, performed in a same day. However, a significant relationship is found between the number of completed digital questionnaires and the days of digital activity and relapse and the time to its occurrence.

In the seek for a correlation regarding digital behavior, there is no statistically significant dependence of relapse and time to its occurrence on the method of follow-up and on the results of the four digital self-assessment questionnaires, although there are certain trends. There is no significant relationship between the researcher's clinical assessment and the result of the first digital self-assessment, both performed in the same day. However, a significant relationship is found between the number of completed digital questionnaires and the days of digital activity and relapse and the time to its occurrence.

The discussion contains a descriptive interpretation of the findings with detailed references to the literature and comparisons with other studies. Both the findings and the negative results are analyzed, as they can be at least as useful as the findings, especially when they are unexpected – e.g., the lack of a significant increase in pathological cravings as a prodrome of relapse, and the strong correlation, on the other hand, with digital behavior. The possibility of predicting relapse solely on decline in digital activity, or through the so-called metadata, rather than on clinical or socio-demographic characteristics traditionally associated with higher risk, is being emphasized, as well as the practical benefits of this approach such as saving time and others.

The small sample size is correctly stated as the main limitation of the study.

## **6. Contributions and significance of the research for science and practice**

The formulated conclusions and contributions are focused on the pioneering use of a technologically advanced digital method for follow-up of patients with substance use disorders and on the findings of digital literacy and ownership in this population, and the practical applicability of the method for real prediction of relapse. The lack of a significant correlation between relapse and the time to its occurrence with a number of demographic and clinical variables (with the expected exception of marital status) is a surprising result given the research data regarding their role in the complex relapse process. The insights on digital activity open an unexpected, at the same time cheap, easy and time-saving opportunity for implementation of methods for follow-up and maintenance of therapeutic contact. A significant practical contribution is the introduction of new instruments and the demonstration of their usability in Bulgarian in clinical practice.

## **7. Personal participation of the candidate**

The presented dissertation uses international digital technology and tools in own research, which is an original product and independent work of the doctoral student.

## **8. Dissertation summary and publications**

The structure of the dissertation summary meets the requirements of the Regulations for the Development of the Academic Staff at MU "Prof. Dr. Paraskev Stoyanov" – Varna and its appendices, and represents the structure and the content of the dissertation (without the literature review). However, the overall presentation of the scales and other tools used is more appropriate for the work in extenso rather than for the dissertation summary. At the same time, it is very appropriate for a dissertation

summary to contain a short summary in Bulgarian and English at the end of the text.

One poster presentation in international congress and one accepted publication in peer-reviewed Bulgarian journal are being presented.

### **9. Critical notes and recommendations**

The small sample size ( $n = 40$ ), rightly noted by the author as a limitation of the study, requires caution in interpreting the data. The levels of statistical significance when comparing subgroups of several people can change radically in larger samples. There is no diagnostic profile of the patients. The questions in the applied instruments relate to alcohol consumption and it can be judged that this is a sample of patients with alcohol use disorder, but this is not stated anywhere, and patients are described under the broad general category of substance use disorders (F1. in ICD-10).

The results are repeated in the text, tables, figures, discussions and even conclusions. The same finding is reported in a text, presented graphically in a table or figure, it is present in the discussion and finally presented as a conclusion. Most of the conclusions are in fact statements of findings; there is no conceptual distinction between result and conclusion. The study would be more complete with a parallel objective assessment of patients through a live clinician-led interview, which could be compared to subjective digital self-assessment (especially given that the two differ and do not give similar results). The extremely scarce sources of Cyrillic (4) are a sign of one-sided coverage of the literature. Lack of knowledge on epidemiological studies on alcohol-related problems (e.g., Stankushev et al., but not only) is being demonstrated.

There are also technical and linguistic mistakes. In Table 2, the percentages in the marital status line are wrong. Under figures 21, 22, 23, 24 " $p < 0.05$ " is stated, while from the text for the presented data it is clear that the differences do not reach statistical significance. On page 88, an important exclusion criterion is the "absence of a double psychiatric diagnosis" - when in fact the existence of such is an exclusion criterion. The text abounds in unacceptable foreign words and phrases. Abstracts in Bulgarian and English for both the dissertation and the dissertation summary are missing.

### **10. Recommendations for future use of the contributions and the results**

With the sample size and the non-standard design, the study can be considered as a pilot one, so it is appropriate in the future to verify the results with a larger cohort, as well as to put efforts into the practical implementation of digital tools.

### **11. Conclusion**

The presented dissertation reflects an original study with undoubted relevance, methodological adequacy, and own contributions. The work meets the requirements for obtaining the educational and scientific degree "Doctor" according to LDASRB and the Regulations for the development of academic staff at MU-Varna, which gives grounds for a positive evaluation for awarding the scientific degree "Doctor" in medicine to Dr. Samuela Georgieva Krasteva.

Prof. Georgi Onchev

