The prevalence of insomnia in patients with psychiatric disorders

Ethic Commission of the Canton of Bern Number: 2020-01992

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Research legislation:	Ordinance on human research with the exception of clinical trials (HRO) [1]
Type of Research Project:	Research project involving human subjects
Risk Categorisation:	Risk Category A
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PROTOCOL SIGNATURE FORM

Study Title *The prevalence of insomnia in patients with psychiatric disorders*

The project leader in the UPD and the investigator at the Privatklinik Meiringen have approved the protocol version 3 (dated 09.06.2021) , and confirm hereby to conduct the project according to the protocol, the Swiss legal requirements [1, 2], current version of the World Medical Association Declaration of Helsinki [3] and the principles and procedures for integrity in scientific research involving human beings.

Project leader (lead center/site) and sponsor

Universitäre Psychiatrische Dienste UPD, Bolligenstrasse 111, CH- 3000 Bern 60

Name: Prof. Dr. med. Christoph Nissen

Date: 10.06.2021 Signature:

Local project leader at local center/site:

Privatklinik Meiringen, CH 3860 Meiringen

Name of Local Project Leader: Dr. med. Christian Mikutta

Date: 11.06.2021 Signature:

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GLOSSARY OF ABBREVATIONS

BASEC	*Business Administration System for Ethical Committees*
CRF	*Case report form*
FOPH	*Federal Office of Public Health*
HRA	*Human Research Act*
HRO	*Ordinance on Human*

1 BACKGROUND AND PROJECT RATIONALE

Mental disorders are highly prevalent, undertreated, and associated with substantial disability and reduced quality of life (Demyttenaere et al., 2004) . The 12 months prevalence of any mental disorder is 12% in Europe, whereby anxiety disorders and mood disorders are the most prevalent (Demyttenaere et al., 2004). One third of treatment-seeking outpatients with mental disorders comorbidly suffer from insomnia disorder, i.e. persistent sleep disturbances and associated daytime impairments for a duration of at least three months (Seow et al., 2018). The prevalence of acute insomnia symptoms (< 3 months) is up to 68% (Seow et al., 2018). As opposed to early lines of research aiming at the identification of disorder-specific patterns of sleep disturbance (e.g., early morning awakening as a marker of depression), recent work demonstrates that disruptions of sleep continuity (insomnia) represent a highly prevalent and trans-diagnostic problem in a wide range of mental disorders including anxiety disorders, affective disorders, schizophrenia, substance use disorders, eating disorders, borderline personality disorder and autism spectrum disorders (Baglioni et al., 2016).

Having comorbid acute or chronic insomnia is associated with significantly higher impairment compared to having a mental disorder without insomnia (Seow et al., 2018). The prevalence of insomnia in severely ill patients with psychiatric disorders treated as inpatients, however, is still under-investigated. A precise estimation of the prevalence of insomnia in this patient group is important for the implementation of disorder-specific treatment. Effective treatment of insomnia, in turn, has the potential of positive effect on the treatment outcome and potentially even the prevention of mental disorders.

Following current European and American practice guidelines for adult patients, cognitive behavioral therapy for insomnia (CBT-I) is the first line treatment (Qaseem, Kansagara, Forciea, Cooke, & Denberg, 2016) (Riemann et al., 2017). CBT-I is a treatment package including psychoeducation, restriction of time in bed, relaxation, and cognitive restructuring. The major mechanism of action of bedtime restriction is an increase of homeostatic sleep pressure, thereby shortening sleep-onset latency and increasing sleep depth

The primary aim of the proposed project is to investigate the prevalence of insomnia in patients with psychiatric disorders treated as inpatients in psychiatric hospitals in two study sites in Switzerland and nine study sites in Germany. The secondary aim is to investigate whether there are demographic or disorder specific parameters that influence the prevalence of insomnia in patients with psychiatric disorders.

The risk category according to article 7 of the HRO is A because the epidemiological study is not associated with relevant risks for participants.

2 PROJECT OBJECTIVES AND DESIGN

2.1 Hypothesis and primary objective

The primary objective of this study is to investigate the prevalence of insomnia in patients with a psychiatric disorder who are treated as acute inpatients in a psychiatric hospital. Insomnia is diagnosed according to DSM-5 criteria. It is defined as sleep onset or sleep maintenance

difficulties plus daytime impairment that occur at least three times per week. We assume a high prevalence of insomnia (>20%) in this patient group.

2.2 Primary and secondary endpoints

Primary endpoint is the prevalence of insomnia disorder.

2.3 Project design

It is a multicentre study taking place in the Universitäre Psychiatrische Dienste in Bern and in the Privatklinik Meiringen. 9 german study sites will also participate in the study (Freiburg, Ingolsatdt, Kiel, Klingenmünster, Leipzig, Mannheim, Nürnberg, Paderborn, Regensburg)

3 PROJECT POPULATION AND STUDY PROCEDURES

3.1 Project population, inclusion and exclusion criteria

We aim to include 500 participants in total in a time frame of 12 months.

The inclusion criteria are:

- patients who suffer from a psychiatric disorder according to the DSM-5 and who are currently treated as inpatients in a psychiatric hospital of the ones participating in the study mentioned under point 2.3

Exclusion criteria are:

- Age under 18 years
- involuntary stay at the clinic
- unable to give informed consent

3.2 Recruitment, screening and informed consent procedure

The recruitment of the study participants is consecutive. In all study sites, all newly admitted patients will be registered on a list each day. This list will be available for the study physicians. From this list, patients who are visibly not eligible (involuntary stay, under custody) will be deleted. Depending on the capacities of the study physicians, within three days after admission, 1-15 patients will be selected from the patients remaining on the list per day. The selected patients will be asked whether they agree to participate in the study.

3.3 Study procedures

The overall project duration will be 12 months starting the 1st of July 2021 until the end of June 2022. The patients will be screened according to the inclusion and exclusion criteria. The study investigator will then hold one session of 20 to 60 minutes with each participant filling out the following questionnaires:

- The study information and the informed consent
- The informed consent about the further use of the patient data
- Demographic data and general patient documentations
- PSQI: Pittsburgh sleep quality index
- ISI: Insomnia severity index
- The Epworth Sleepiness Scale
- SF-12: Short form 12 questionnaire about the subjective health status

- PHQ-9: Patient health questionnaire 9
- Fatigue Severity Screening

3.4 Withdrawal and discontinuation

Participants will be withdrawn from the study immediately if there are any concerns about the participants' safety. Participants can also choose to withdraw from the study at any time, and are not required to provide their reason for withdrawing from the study. Coded data acquired before withdrawal will be analyzed as described in the participant information sheet.

4.1. Statistical analysis plan

In **Table 1** the 95%- confidence intervals for prevalence in the range from 15% (p=0.15) to 25% (p=0.25) can be seen for sample sizes of n= 200, n= 250, n=300 and n= 500 patients. In consideration of the accuracy of the estimation of varying prevalence, the planned study aims to investigate 500 psychiatric inpatients. The named sample size will be sufficient to estimate prevalence rates with sufficient power.

Table 1: 95%-confidence intervals for prevalence in the range from 15% to 25% for different sample sizes

Prevalence	95%-confidence interval			
%	N = 500	N = 300	N = 250	N = 200
15	[11.9 ; 18.1]	[11.0 ; 19.0]	[10.6 ; 19.4]	[10.1 ; 19.9]
16	[12.8 ; 19.2]	[11.9 ; 20.1]	[11.5 ; 20.5]	[10.9 ; 21.1]
17	[13.7 ; 20.3]	[12.7 ; 21.3]	[12.3 ; 21.7]	[11.8 ; 22.2]
18	[14.6 ; 21.4]	[13.7 ; 22.3]	[13.2 ; 22.8]	[12.8 ; 23.5]
19	[15.6 ; 22.4]	[14.6 ; 23.4]	[11.1 ; 23.9]	[13.6 ; 24.4]
20	[17.4 ; 23.5]	[15.5 ; 24.5]	[15.0 ; 25.0]	[14.5 ; 25.5]
21	[18.3 ; 25.6]	[16.4 ; 25.6]	[16.0 ; 26.0]	[15.4 ; 26.6]
22	[18.4 ; 25.6]	[17.4 ; 26.7]	[16.9 ; 27.1]	[16.3 ; 27.7]
23	[19.3 ; 26.7]	[18.2 ; 27.8]	[17.8 ; 28.2]	[17.2 ; 28.8]
24	[20.2 ; 27.7]	[19.2 ; 28.8]	[18.7 ; 29.3]	[18.1 ; 29.9]
25	[21.2 ; 28.8]	[20.2 ; 29.9]	[19.6 ; 30.4]	[19.0 ; 31.0]

The primary analysis refers to the prevalence of insomnia in patients with mental disorders. A specific statistical analysis regarding the determination of co-variables of sleep disorders is not part of this project.

4.2. Handling of missing data

Dropouts will be replaced by recruitment of new participants until the target sample size has been achieved.

5 REGULATORY ASPECTS AND SAFETY

5.1 Local regulations / Declaration of Helsinki

This research project will be conducted in accordance with the protocol, the Declaration of Helsinki [3], the principles of Good Clinical Practice, the Human Research Act (HRA) and the Human Research Ordinance (HRO) [1] as well as other locally relevant regulations. The Project Leader acknowledges his responsibilities as both the Project Leader and the Sponsor.

5.2 Notification of safety and protective measures (HRO Art. 20)

The project leader is promptly notified (within 24 hours) if immediate safety and protective measures have to be taken during the conduct of the research project. The Ethics Committee will be notified via BASEC of these measures and of the circumstances necessitating them within 7 days.

5.3 Serious events (HRO Art. 21)

If a serious event occurs, the research project will be interrupted and the Ethics Committee notified on the circumstances via BASEC within 7 days according to HRO Art. 21[1].

5.4 Procedure for investigations involving radiation sources

not applicable

5.5 Amendments

Substantial changes to the project set-up, the protocol and relevant project documents will be submitted to the Ethics Committee for approval according to HRO Art. 18 before implementation. Exceptions are measures that have to be taken immediately in order to protect the participants.

5.6 End of project

Upon project completion or discontinuation, the Ethics Committee is notified within 90 days.

5.7 Insurance

In the event of project-related damage or injuries, the Sponsor will be liable, except for damages that are only slight and temporary; and for which the extent of the damage is no greater than would be expected in the current state of scientific knowledge (Art. 12 HRO). There is no necessity for a UNITECTRA contract. Since the study is risk category A, no insurance is needed.

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[1] A serious event is defined as any adverse event where it cannot be excluded, that the event is attributable to the sampling of biological material or the collection of health-related personal data, and which:
a. requires inpatient treatment not envisaged in the protocol or extends a current hospital stay;
b. results in permanent or significant incapacity or disability; or
c. is life-threatening or results in death.

6 FURTHER ASPECTS

6.1 Overall ethical considerations

The study has the potential to extend the knowledge about sleep disorders in patients with severe mental disorders. Indirectly, the project has the potential to contribute to the improvement of the treatment situation for patients with severe mental disorders. For participating patients, the project is not associated with any specific risks. Therefore, the value of the project outweighs the risks.

6.2 Risk-Benefit Assessment

There are no risks, but also no direct benefits for participants. There is, however, a potential benefits for other patients with mental disorders.

6.3 Rationale for the inclusion of vulnerable participants

Not applicable. Minors and patients incapable of judgement or under tutelage for health issues will be excluded from participation in the study.

7 QUALITY CONTROL AND DATA PROTECTION

7.1 Quality measures

For quality assurance the Ethics Committee may visit the research sites. Direct access to the source data and all project related files and documents must be granted on such occasions.

7.2 Data recording and source data

For each study participant, a paper based case report form (CRF) will be maintained. CRFs will be kept current to reflect subject status at each phase during the course of study. In accordance with the HFG, participants will not be identified in the CRF by name or initials and birth date, but by an anonymous participant number. Data for statistical analysis will be stored in an electronic database. Data will be transferred manually from the paper CRF to the electronic data base. As for the paper based CRF, the data stored electronically will not contain any personal information by which the participant can be identified. Only trained project personnel will be authorized for entries into the electronic database and authorized persons will be identifiable for every entry they made. Routinely collected data during daily clinical practice will be transferred to the participant CRF (e.g. diagnoses and medication).

7.3 Confidentiality and coding

Data of all subjects will be coded and data analysis will be performed using these codes only. The key to the code will stay in the responsible study site, only anonymized data will be used for data dissemination. Unblinding of subject-specific data is possible after consent has been given by the subjects and the project leader. The code will only be broken if it is necessary in order to avert an immediate risk to the health of the person concerned or to guarantee the rights of the person (e.g. in revoking the consent) or a legal basis exists for breaking the code. Data will be stored for 10 years.

Project data will be handled with uttermost discretion and only be accessible to authorized personnel who will have access to data for study purposes (e.g. data analysis) for the whole study duration. Only the investigators and Ethics Commission are allowed to have inspections

on the original data, and will be allowed direct access to source documents will be permitted for purposes of monitoring, audits or inspections.

The web application RED Cap is used as a secure database. The project leader is responsible and will ensure correct and conscientious use of the data management system, and will monitor the data management. The system is tested before the start of data collection in consultation with the institution's IT experts. Access to parts of the data will be granted only to individuals that require it to conduct the research. For instance, only individuals that need to contact or communicate with participants have access to the participant's identity and contact details. Researchers that do statistical analysis of the study cohort get only access to pseudonyms.

Biological material is not applicable.

7.4 Retention and destruction of study data and biological material

In accordance to Data Protection Directive of the UPD Bern and the SAMW-guidelines for creating biological databases, all study data will be archived for a minimum of 10 years after study termination or premature study termination. In case of paper form, data will be archived in lockable drawers at the research facility (Research Dept. of the Translational Research Center, University Hospital of Psychiatry, Bolligenstr. 111, CH-3000 Bern 60.). In case of digital data, the raw data, derived data, code, meta-data, and all history will be exported from the version control system and archived for 10 years at the University of Bern on an archival system that stores two copies of the data in two geographically distinct locations. At the end of the project, researchers are asked to remove study data from their devices and local servers. Raw data, code, and all intermediate data can be restored and/or transferred in its entirety or partially.

8 FUNDING / PUBLICATION / DECLARATION OF INTEREST

The project is funded by in house funds of the main sites. This means that there are no extra fundings. The fundings occur through already existing research funds of the investigators of the project. There is no specific budget plan for this study and it doesn't appear to be necessary. There is no exchange of fundings between the two study sites.

9 REFERENCES

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2. Human Research Act (HRA) http://www.admin.ch/opc/en/classified-compilation/20121176/201401010000/810.305.pdf
3. Declaration of Helsinki (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects)
4. STROBE statement (http://www.jclinepi.com/article/S0895-4356(07)00436-2/pdf)

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