Studentoppgave

NTNU
Norges teknisk-naturvitenskapelige universitet
Fakultet for medisin og helsevitenskap
Institutt for samfunnsmedisin og sykepleie

Bilal Hamdan
Anders Benjaminsen

Student thesis in Medicine

DO PATIENTS WITH SEIZURE DISORDERS HAVE AN INCREASED RISK OF SUICIDAL BEHAVIOR AFTER DISCHARGE FROM ACUTE PSYCHIATRIC CARE?

Studentoppgave i CMED
Veileder: Arne Vaaler
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Contents

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Bilal Hamdan, Anders Benjaminsen, Eylert Brodtkorb, Astrid Prestmo, Tuva Prestmo Kvithyld, Sverre Georg Sæther, Ole Kristian Drange, Arne Vaaler.

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Sammendrag

Bakgrunn

Flere studier har blitt gjennomført i forsøk på å finne pasientpopulasjoner med økt risiko for selvmord og selvmordsatferd. Får man til å identifisere disse høyrisikopasientene, vil man kunne komme i posisjon til å iverksette mottiltak, og forhåpentligvis redusere selvmord og selvmordsatferd.

Vi vet at personer med anfallslidelser har høyere forekomst av selvmord og selvmordsatferd sammenlignet med kontrollgrupper. Vi vet også at den standardiserte mortalitetsratioen for suicid er ca. hundre ganger høyere de to første årene etter utskrivelse hos den akuttpsykiatriske populasjonen (Prestmo et al., 2020). Hva med risikoen for selvmord og selvmordsatferd hos pasienter med en kjent anfallslidelse som utskrives fra en akuttpsykiatrisk institusjon?

Risikoen for selvmord og/eller selvmordsatferd hos pasienter med anfallslidelser i en akutt psykiatrisk populasjon har aldri tidligere blitt forsket på. Derfor var denne studiens primære formål å undersøke om pasienter diagnostisert med en anfallslidelse (epilepsi, akutt symptomatisk anfall, psykogene non-epileptiske anfall) har en høyere risiko for selvmordsatferd etter utskrivelse fra en akuttpsykiatrisk avdeling sammenlignet med de andre pasientene innlagt i akuttavdelingen. Studiens sekundære formål var å undersøke om pasienter med anfallslidelser har en økt risiko for selvmord etter utskrivelse, samt om de ulike anfallstypene var assosiert med selvmordsatferd og selvmord.

Metode

Studien ble utført ved Akuttpsykiatrisk avdeling, Østmarka, St. Olavs Hospital, Trondheim, Norge, fra september 2011 til mars 2012. Totalt 380 av 760 pasienter ga sitt skriftlige samtykke til å delta i studien.

Selvmordsatferd, definert ved ICD-10 diagnosekode X6n villet egenskade, og selvmord, ble registrert gjennom henholdsvis fire og fem års oppfølging etter utskrivelse. Anfallslidelser ble definert som epilepsi, akutt symptomatisk anfall og psykogene ikke-epileptiske anfall (PNES). Nevnte diagnoser ble satt i et konsensusmøte bestående av tre psykiatere og en epileptolog.

Binær logistisk regresjon ble brukt for å undersøke sammenhenger mellom anfallslidelser og selvmordsatferd, og anfallslidelser og selvmord.

Resultater

Trettiåtte pasienter (10%) ble diagnostisert med en anfallslidelse. Sekstiåtte pasienter (17,9%) ble diagnostisert med X6n. Syv pasienter med anfallslidelse hadde suicidal atferd og to pasienter med anfallslidelse døde av suicid under oppfølgingstiden.

I binær logistisk regresjonsanalyse forelå det ingen assosiasjon mellom anfallslidelser og selvmordsatferd (OR [95 % Cl]: 1,424 [0,525-3,862], p = 0,488). Anfallslidelser var heller ikke assosiert med suicid (OR [95 % Cl]: 0,721 [0,110-4,710], p = 0,732).

Konklusjon

Vi fant ingen statistisk signifikant sammenheng mellom anfallslidelser og selvmordsatferd eller selvmord etter utskrivelse i en akuttpsykiatrisk populasjon. Pasienter innlagt ved akuttpsykiatriske avdelinger, også pasienter med anfallslidelser, har samtidig en høy forekomst av selvmordsatferd og selvmordsforsøk. Senere studier bør ta sikte på å inkludere flere pasienter for å bedre kunne estimere risiko for selvmordsatferd og selvmord ved ulike typer anfallslidelser.

Abstract

Background

Several studies have been conducted to find groups with a higher rate of suicide and suicidal behavior. If these groups are found, countermeasures could be provided, and hopefully lowering the risk of suicide and suicidal behavior.

We know that people with seizure disorders have a higher occurrence of suicide and suicidal behavior compared to control groups. We also know that the standardized mortality ratio for suicide is approximately a hundred times higher in the first two years after discharge in the acute psychiatric population (Prestmo et al., 2020). What about the risk of suicide and suicidal behavior in patients with a known seizure disorder discharged from an acute psychiatric institution?

The risk of suicide and/or suicidal behavior in patients with seizure disorders in an acute psychiatric population has never before been studied. Therefore, the primary aim of the study was to investigate whether patients diagnosed with a seizure disorder (epilepsy, acute symptomatic seizure, psychogenic non-epileptic seizures) have a higher risk of suicidal behavior after discharge from an acute psychiatric department compared to the other patients in the psychiatric emergency department. The secondary aim of the study was to investigate whether patients with seizure disorders have an increased risk of suicide after discharge, and whether the different seizure disorders were associated with suicidal behavior and suicide.

Method

The study was conducted at the Acute Psychiatric Department, Østmarka, St. Olavs Hospital, Trondheim, Norway, from September 2011 to March 2012. A total of 380 out of 760 patients gave their written consent to participate in the study.

Suicidal behavior, defined by ICD-10 diagnosis code X6n, intentional self-harm, and suicide were registered during four and five years of follow-up, respectively, after discharge. Seizure disorders were defined as epilepsy, acute symptomatic seizures, and psychogenic non-epileptic seizures (PNES). The diagnoses were made in a consensus meeting consisting of three psychiatrists and an epileptologist.

Binary logistic regression was used to examine associations between seizure disorders and suicidal behavior, and seizure disorders and suicide.

Results

Thirty-eight patients (10%) were diagnosed with a seizure disorder. Sixty-eight patients (17.9%) were diagnosed with X6n. Seven patients with seizure disorder had suicidal behavior and two patients with seizure disorder died of suicide during the follow-up period.

In binary logistic regression analysis, there were no association between seizure disorders and suicidal behavior (OR [95% Cl]: 1.424 [0.525-3.862], p = 0.488). Seizure disorders were also not associated with suicide (OR [95% Cl]: 0.721 [0.110-4.710], p = 0.732).

Conclusion

We found no statistically significant association between seizure disorders and suicidal behavior or suicide after discharge in an acute psychiatric population. Patients admitted to acute psychiatric wards, including patients with seizure disorders, also have a high incidence of suicidal behavior and suicide attempts. Future studies should aim to include more patients to better estimate the risk of suicidal behavior and suicide in different types of seizure disorders.

Introduction

Several organizations and governments, such as the Norwegian and American, have said that suicide and suicidal behavior is a public health crisis (Prevention, 2022a; UNICEF, 2021). The Norwegian government has created a national forum to create an action plan with a zero-tolerance target for suicides in Norway. The forum slogan says: "To lose no one" (Higraff, 2020; Omsorgsdepartementet, 2020). Several studies have attempted to find groups with increased risks of suicide and suicidal behavior. If such risk factors are found, relevant patients could be prioritized for better treatment and follow-up, which potentially could lower rates of suicide and suicidal behavior.

A meta-analysis from 2019, including 53 studies, found that people with epilepsy had three times higher occurrence of suicide attempts compared to controls (pooled OR = 3.25, 95% confidence interval (CI): 2.69-3.92, $p < 0.001$) (Abraham et al., 2019). Another meta-analysis from 2018 looked at premature mortality in patients with epilepsy from high-income countries. Strong associations were found, and the cause of death pointed to drowning and suicide (Watila et al., 2018). For other seizure disorders, it also seems that mortality is elevated. A study in patients with acute symptomatic seizure disorder from 2005 found increased mortality in this patient group (Hesdorffer & D'Amelio, 2005). A more recent study from 2020 found that psychogenic non-epileptic seizure disorder had approximately the same standardized mortality ratio as epilepsy (Jennum et al., 2019; Nightscales et al., 2020). However, these studies did not specify etiology, so we do not know if suicide is related to the elevated mortality ratio.

Which definitions have we used for suicide-related terms? Suicide is death caused by injuring oneself with the intent to die (Prevention, 2022b), and a suicide attempt is when someone harms themselves with any intent to end their life, but they do not die as a result of their actions. Suicidal behavior has no clear consensus on what is included, but throughout the literature, suicide planning, thoughts, threats, and self-harm are often mentioned (Turecki & Brent, 2016).

An epileptic seizure is an impermanent state of signs and/or symptoms caused by excessive or synchronous neuronal activity in the brain (San-Juan & Rodríguez-Méndez, 2022). At the same time, epilepsy is characterized as an “enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological, and social consequences” (Fisher et al., 2014; Robert Fisher MD, 2014). An acute symptomatic seizure is defined as a clinical seizure occurring at the time of a systemic insult or in close temporal association with a documented brain insult. Psychogenic non-epileptic seizures (PNES) are defined by abrupt paroxysmal changes in behavior or consciousness that mimic epileptic seizures. The clinical presentation of PNES resembles epileptic seizures, manifesting as alterations in behavior or paroxysmal convulsive events (Nightscales et al., 2020). There are also no EEG changes or proof of the somatic cause of the seizure and evidence or suspicion of a psychogenic trigger of these seizures (Beghi et al., 2010; Bodde et al., 2009).

In summary, several studies have found increased premature mortality in people with seizure disorders due to various causes, both medical conditions and unnatural causes, particularly suicide, compared to the general population. A study of the prevalence of seizure disorders in an acute psychiatric department showed that epilepsy is five to six times as high as previous studies from the general population (Nakken et al., 2021). Furthermore, in 2020 a study was published showing that the mortality was elevated in discharged patients from an acute psychiatric department in the following 5 years (Prestmo et al., 2020). A seizure disorder could therefore be a risk factor that negatively impacts the survival of these patients. However, whether seizure disorders have an association with suicidal behavior and/or suicide after discharge from an acute psychiatric inpatient have never been studied previously.

We hypothesized that a patient history of seizure disorders increases the risk of suicidal behavior and suicide above the risk associated with being admitted to an acute psychiatric department. Therefore, the primary aim of the study was to examine whether a patient history of a seizure disorder is a risk factor for suicidal behavior after discharge from an acute psychiatric department. The secondary aims were to examine if a patient history of a seizure disorder is a risk factor for post-discharge suicide and to explore associations between each of the different seizure disorders (epilepsy, acute symptomatic seizures, and psychogenic non-epileptic seizures) and the outcomes of suicidal behavior and suicide.

Methods

Study design

This study holds a single-center observational prospective cohort design.

Setting

Study participants were patients 18 years or older admitted to the Department of acute psychiatry, St. Olavs Hospital, Trondheim, Norway from September 2011 to March 2012. In Norway acute psychiatric services are available to everyone, publicly funded, and catchment area based.

Participants

Seven hundred and sixty patients were admitted in this period. All the admitted patients were asked to participate in the study. A total of 380 out of 760 gave written informed consent to participate.

Data sources

This study builds on data from the “Agitation in the Acute Psychiatric Department study.” (ClinicalTrials.gov identifier NCT01415323). The study aimed to explore agitation as a possible risk factor for suicide in acute psychiatric inpatients.

Self-reported data, ICD-diagnostic codes from the local hospital (St. Olavs Hospital), and diagnostic codes from the National Patient Registry (NPR) were used to define seizure disorders. Data from the National Patient Registry was used to define suicidal behavior. Data from the Norwegian Institute of Public Health (FHI) and the National Cause of Death Registry were used to define suicide. Information about sociodemographic factors, medication at admission, main diagnosis at admission, and substance use disorder, were obtained during the admission.

The National Patient Registry (NPR) is a central health register in Norway which is funded and operated by the Directorate of Health and Care. NPR was established in 1997 as a governmental initiative by the Department of Health and Care. In 2007, NPR was incorporated into the health registry law, making it a person-identifiable register. Among the data collected in the NPR are all encounters with a health institution, i.e. the given clinic and specialty, date of admission and discharge, diagnosis, and all health-related procedures done on the patient. One must apply for approval from a regional committee of ethics (REK) and official approval from the Directorate of Health (e-helse) to access information from NPR.

The NPR file in our possession contains information about all the patient contact with the health service four years after discharge for this population.

The Norwegian Cause of Death Registry (DÅR) is a register where all deaths in Norway are registered. The purpose of the register is, among other things, to monitor causes of death and changes in death over time. DÅR contains information on deaths and causes of death in Norway since 1951. When a death occurs, the doctor must report to the Institute of Public Health about the cause of death. FHI is responsible for data processing and processes the data. In addition, information is obtained from the Medical Birth Register and the Cancer Register, and also from statistics on road traffic accidents and autopsies from hospitals and forensic examinations. The register includes everyone who, at the time of death, was registered as a resident in Norway, regardless of whether the death occurred in or outside the country. The cause of death register uses ICD codes to code causes of death. One must apply for approval from the Institute of Public Health (e-helse) to access information from DÅR.

The DÅR file in our possession contains information on deaths and causes of death five years after discharge for every unique patient.

Norwegian patient records have since 1997 been digitalized. If needed, and for specific purposes, paper records can be accessed from the local archive. The contact overview extends back to 1987. In the previous study conducted by Nakken et al., to which we have data access, the authors were given access to the medical records of the 380 patients included. The health record access was limited to contacts with health services in Sør-Trøndelag county.

Variables

Outcome variables, grouping variable, and covariates

The outcome variables are 1) suicidal behavior, defined as ICD-10 diagnostic code X6n, and 2) suicide. The grouping variable is seizure disorders defined as epilepsy, acute symptomatic disorder, and psychogenic non-epileptic seizure (PNES). The covariates are sociodemographic factors, medication at admission, main diagnosis at admission, and substance use disorders.

Suicidal behavior

Data on patient histories of suicidal behavior, which in this study is defined as "intentional self-harm" with ICD-10 diagnostic code "X6n", which includes poisoning, hanging, drowning, shooting, fire, sharp objects, jumping, crashing, and so on, were obtained in the following two ways by the researchers participating in the current study: 1) Information about suicidal behavior and suicide attempts four years after discharge was extracted from the NPR-file, and 2) chart review of contact with health service due to suicidal behavior and suicide attempt four years after discharge.

Suicide

Data on suicide were obtained as part of a previous study done by Prestmo et al. on the same patient population (Prestmo et al., 2020). The authors obtained the mentioned data in the following way: Information about the number and causes of deaths for the same acute psychiatric population was obtained from the Norwegian Cause of Death Registry (DÅR) at the National Institute of Public Health (FHI). Identification numbers were used for linking the patients to the DÅR. The follow-up time was set to be from the date of discharge until death within five years after discharge. The deaths were categorized as due to natural causes (defined within the ICD10 codes A00-R99) or unnatural causes (defined within the ICD-10 codes V01-Y89). Finally, the medical records of the patients who had died during the follow-up period were reviewed by two psychiatrists, independent of each other.

Seizure disorders

Data on patient histories of seizure disorders were obtained as part of a previous study done by Nakken et al. on the same patient population. They obtained the mentioned data in the following way: The 380 participants were screened for epilepsy and other seizure disorders by using four screening criteria: Screening criteria 1: Self-reported questionnaire data: "Are you or have you ever been treated for epilepsy?". Screening criteria 2: Self-reported questionnaire data: "Have you ever had seizures?". Screening criteria 3: ICD-9 (345) or ICD-10 (G40-41) diagnostic codes for epilepsy at the local hospital. Screening criteria 4: ICD-9 (345) or ICD-10 (G40-41) diagnostic codes for epilepsy in the Norwegian Patient Registry.

All patients who scored positively for one or more of the four screening criteria mentioned above underwent a string of diagnostic validation in an expert consensus meeting consisting of three psychiatrists and an epileptologist with extensive experience. The diagnostic validation entailed a review of complete psychiatric and somatic records from the local hospital. Admission reports, progression notes, discharge reports, electroencephalography (EEG) recordings, brain imaging, and medical history were reviewed in the thorough process.

The epilepsy diagnosis was set according to the newest (2017) revised International League Against Epilepsy (ILAE) criteria (Fisher et al., 2014). According to current definitions, acute symptomatic and psychogenic non-epileptic seizures were also diagnosed (Baslet et al., 2021; Beghi et al., 2010; Bodde et al., 2009).

Covariates

Data on covariates, i.e. sociodemographic factors, medications at admission, main diagnosis at admission, and substance use disorder, were gathered in various ways.

Information about sociodemographic factors was obtained from the patient record.

Information about medication at admission was collected from the admission patient record dated the same day they were included in the study, and by history taking by the doctor on call. Medication on admission was divided into anti-seizure medications, antipsychotics, antihistamines, antidepressants, lithium, stimulants, benzodiazepines, z-hypnotics, and opioids.

Information about the main diagnosis at admission was set in a consensus meeting with two specialists during the admission and categorized using ICD-10 diagnostic groups, mainly in the F-chapter and rarely outside the F-chapter.

Information about substance use disorder was extracted from the main diagnosis at admission. It was categorized into those patients with an ICD-10 diagnostic code F10-F19, “Mental and behavioral disorders due to psychoactive substance use.”

Statistics

Statistical power calculation

The grouping variable had 38 participants with seizure disorders and 342 participants without seizure disorders. Prestmo et al. found 13 suicides among the 380 participants during five years of follow-up. Given an incidence of suicide attempts is about thirty times higher than the number of suicides (Han et al., 2016), and the factum that not all suicide attempts lead to hospital contact, we conservatively assumed to find five times as many cases of suicidal behavior as suicide, i.e., 65 participants with suicidal behavior leading to hospital contact during four years of follow-up.

Based on data from a meta-analysis of people with epilepsy in general (Abraham et al., 2019), we assumed a three-fold higher prevalence of suicide attempts or suicidal behavior among participants with seizure disorders compared with those without seizure disorders in our acute psychiatric sample.

Given our assumption, we estimated to find 16 participants with suicide attempts or suicidal behavior among the 38 participants with seizure disorders (42%) and 49 suicide attempts among the 342 participants without seizure disorders (14%). This gave the study a power of 92% to detect a difference between the groups on the primary outcome at a significance level of p=0.05 (two-sided)[1].

Analysis

All the analyses were conducted in IBM SPSS, version 27.

We used binary logistic regression to investigate our primary and secondary aims, as our outcome variable was dichotomous. We built several models to investigate the hypothesis. This was done because, on the one hand, the inclusion of covariates can control for confounders, while on the other hand, the inclusion of covariates that 1) have many missing items and 2) are not confounders but, e.g., collide, can make the model less valid (Wysocki et al., 2022).

For the purpose of investigating the primary aim, we used X6n as the dependent variable and seizure disorders, age, and sex as the independent variables (model 1). We then built on this analysis by adding and removing independent variables one by one. First, we added medication (model 2), then substance use disorders (model 3), and finally, diagnostic groups (model 4). In the last binary logistic regression model (model 5), all the covariates were included except substance use disorders. This resulted in five different regression models that gave us enough results to assess the effect of different potential confounding factors. The same structure was used to investigate the secondary aim with suicide as the dependent variable and all other covariates as independent variables.

To avoid the phenomenon of multicollinearity, which occurs when two correlated independent variables are used, during the logistic regression analyses, the main diagnosis at admission and substance use disorders were not used in the same analysis. Medication on admission can be correlated, and the VIF (variation inflation factor), which identifies the correlation between independent variables or predictors and the strength of the correlation mentioned above, was therefore calculated (Frost, 2017).

We also analyzed several subgroups, comparing the subgroups with the primary and secondary aims in bivariate analyses. The explored subgroups were epilepsy, psychogenic non-epileptic seizure, and acute symptomatic seizures. All subgroups were dichotomous variables and analyzed using the Chi-Squared test. Some of the analyses had one or more expected counts under five in the cross table, and Fisher's exact test was then used instead. We used the Shapiro-

[1] http://powerandsamplesize.com/Calculators/Compare-2-Proportions/2-Sample-Equality

Wilk test to investigate age as a variable to determine that the data was not normally distributed. Therefore Mann-Whitney U, which is a non-parametric test, was used.

We used the Bonferroni multiple correction method to control the family-wise error rate (FWER). That was done because the chance of finding a false-positive result or type 1 error increases when making multiple comparisons.

Results

Sample characteristics

The sample consisted of 380 unique patients, of which 196 (51,6%) were men. The mean age for the entire sample was 39,5 years (SD ± 15).

A total of 38 patients out of 380 (10%) patients had a history of seizure disorders, of which 15 (3.9%) were classified with epilepsy, 21 (5.5%) with acute symptomatic seizures, and nine (2.4%) with psychogenic non-epileptic seizures. These numbers do not add up because some patients had more than one seizure disorder (Nakken et al., 2021).

Sixty-eight patients out of 380 (17,9%) had a history of suicidal behavior and were diagnosed with X6n in the four years following discharge from the acute psychiatric department.

Thirty-nine patients (10.3%) died within the five years following discharge, and 13 out of 17 patients who died by unnatural causes were classified as having died due to suicide.

Table 1: Table 1 presents data on sociodemographic factors (age, sex, and educational status), main diagnosis on admission, substance use disorders, and medications in patients admitted to acute psychiatric care with and without a diagnosis of seizure disorder.

	Seizure disorder (n=38)	**No seizure disorders** (n=342)	**All patients** (n=380)
Demographics			
- Age (Mean (SD))	40,4 (16,7)	39,4 (14,8)	39,5 (15,0)
- Male sex (N (%))	22 (57,9%)	174 (50.9%)	196 (51,6%)
Educational status	N (%)	N (%)	N (%)
- Secondary school	13 (34,2%)	105 (30,7%)	118 (31,1%)
- High school	13 (34,2%)	113 (33,0%)	126 (33,2%)
- Bachelor	4 (10,5%)	40 (11,7%)	44 (11,6%)
- Master	0 (0%)	7 (2,1%)	7 (1,8%)
- Ph.D	0 (0%)	2 (0,6%)	2 (0,5%)
- Not completed high school	6 (15,8%)	42 (12,3%)	48 (12,6%)
- Not completed higher education	2 (5,3%)	33 (9,7%)	35 (9,2%)
Main diagnosis on admission	N (%)	N (%)	N (%)
- F00-09 Organic psychiatric disorder	2 (5,3%)	16 (4,7%)	18 (4,7%)
- F10-19 Disorders related to psychoactive substance use	13 (34,2%)	67 (19,6%)	80 (21,1%)
- F20-29 Schizophrenia and other psychotic disorders	2 (5,8%)	49 (14,3%)	51 (13,4%)
- F30-31 Bipolar mood disorders	5 (13,2%)	51 (14,9%)	56 (14,7%)
- F32-39 Other mood disorders	5 (13,2%)	72 (21,1%)	77 (20,3%)
- F40-99 Other psychiatric disorders	9 (23,7%)	75 (21,9%)	84 (22,1%)
- Not a psychiatric main diagnosis	2 (5,3%)	12 (3,5%)	14 (3,7%)
Substance use disorders			

	N (%)	N (%)	N (%)
- F10 Alcohol-related disorders	6 (15,8%)	35 (10,2%)	41 (10,8%)
- F11 Opioid-related disorders	0 (0%)	1 (0,3%)	1 (0,3%)
- F12 Cannabis-related disorders	0 (0%)	5 (1,46%)	5 (1,3%)
- F13 Sedative, hypnotics, or anxiolytic related disorders	1 (2,6%)	3 (0,9%)	4 (1,0%)
- F14 Cocaine-related disorders	0 (0%)	0 (0%)	0 (%)
- F15 Other stimulant related disorders	1 (2,6%)	8 (2,3%)	9 (2,4%)
- F16 Hallucinogen-related disorders	0 (0%)	0 (%)	0 (%)
- F17 Nicotine dependence	0 (%)	0 (%)	0 (%)
- F18 Inhalant-related disorders	0 (%)	0 (%)	0 (%)
- F19 Other psychoactive substance related disorders	5 (13,2%)	15 (4,4%)	20 (5,3%)
Medications	N (%)	N (%)	N (%)
- Anti-seizure medications	13 (34,2%)	35 (10,2%)	48 (12,6%)
- Antipsychotics	12 (31,6%)	106 (31,0%)	118 (31,1%)
- Antihistamines	9 (23,7%)	45 (13,2%)	54 (14,2%)
- Antidepressants	14 (36,8%)	89 (26,0%)	103 (27,1%)
- Lithium	1 (2,6%)	11 (3,2%)	12 (3,2%)
- Stimulants	2 (5,3%)	6 (1,7%)	8 (2,1%)
- Benzodiazepines	14 (36,8%)	75 (21,9%)	89 (23,4%)
- Z-hypnotics	10 (26,3%)	58 (17,0%)	68 (17,9%)
- Opioids	3 (7,9%)	16 (4,7%)	19 (5,0%)

Data are presented for the whole sample and stratified on seizure disorders (n=38), no seizure disorder (n=342), and all the patients (n=380). Missing medication data in 11 patients (2,9%), except Z-hypnotics, of which there were 12 missing cases (3,2%).

Suicidal behavior among patients with seizure disorders

No statistically significant associations were found between seizure disorders and suicidal behavior in any of the five models using binary logistic regression analysis with covariates (table 2). Results model 5 (OR [95% Cl]): 1,424 [0,525-3,862], p = 0,488.

In all 5 models, the Omnibus test for model coefficients was significant (p < 0,05), and the Hosmer-Lemeshow test for goodness-of-fit was not significant (p > 0,05), which both indicates a good goodness-of-fit for the regression models. See table 2.

Table 2: Table 2 presents models for binary logistic regression done with suicidal behavior (X6n) as the dependent variable in all 5 models.

	Model 1	**Model 2**	**Model 3**	**Model 4**	**Model 5**
	OR [95% Cl]	OR [95% Cl]	OR [95% Cl]	OR [95% Cl]	OR [95% Cl]
Any seizure disorders	0,939 [0,384-2,292]	1,195 [0,456-3,130]	0,925 [0,377-2,266]	1,083 [0,431-2,724]	1,424 [0,525-3,862]
Omnibus test of model coefficients	p = < 0,001	p = 0,003	p = 0,002	p = < 0,001	p = < 0,001
Hosmer and Lemeshow test	p = 0,287	p = 0,909	p = 0,591	p = 0,907	p = 0,931
Included patient (n of 380)	376	364	376	376	364

All models have included the Omnibus test for model coefficients, the Hosmer-Lemeshow test for goodness-of-fit, and the number of cases. Suicidal behavior is set as the dependent variable. Model 1: Any seizure disorder, age, and sex (hereby referred to as the baseline model). Model 2: Baseline model and medication. Model 3: Baseline model and substance use disorders. Here we got VIF-values around 1, which indicates that there is no correlation between the medication groups. Model 4: Baseline model and diagnostic groups, included diagnostic group F10-F19. Model 5: Baseline model, medication, and diagnostic groups expect diagnostic group F10-F19.

The results of the comparisons regarding suicidal behavior can be found in table 3. In bivariate analyses (Pearson Chi-Square Tests) of subgroups, suicidal behavior was more common (5,9% vs. 4,4% and 1,6%) in the group with PNES compared with the two other subgroups of seizure disorders. However, this trend was not of statistical significance (Fisher's exact test = 0,053, Bonferroni-corrected alpha = 0,008, Phi and Cramer's V = 0,230).

Table 3: Table 3 presents data on patients with and without seizure disorder, with and without suicidal behavior, and stratification of seizure disorders in subgroups.

	Suicidal behavior (n=68)	**No suicidal behavior** (n=308)
	N (%)	N (%)
No seizure disorders (n=342)	61 (89,7%)	277 (89,9%)
Any seizure disorders (n=38)	7 (10,3%)	31 (10,1%)
	N (%)	N (%)
Epilepsy (n=15)	1 (1,6%)	14 (4,5%)
Acute symptomatic seizure (n=21)	3 (4,4%)	18 (5,8%)
PNES (n=9)	4 (5,9%)	5 (1,6%)

These numbers do not add up because some patients had more than one seizure disorder. The percentage in brackets has been obtained by taking the columns in relation to the rows.

Suicide among patients with seizure disorders

No statistically significant associations were found between seizure disorders and suicide in any models using binary logistic regression analysis with covariates (table 4). Results model 5 (OR [95% Cl]): 0,721 [0,110-4,719], p = 0,732.

In all 5 models, neither the Omnibus test for model coefficients nor the Hosmer-Lemeshow test for goodness-of-fit was significant (p > 0,05). The insignificant Omnibus test for model coefficients suggests that the current models do not outperform the null model.

Table 4: Table 4 presents models for binary logistic regression done with suicide as the dependent variable in all 5 models.

	Model 1	**Model 2**	**Model 3**	**Model 4**	**Model 5**
	OR [95% Cl]	OR [95% Cl]	OR [95% Cl]	OR [95% Cl]	OR [95% Cl]
Any seizure disorders	0,618 [0,131-2,923]	0,569 [0,110-2,957]	0,689 [0,143-3,318]	0,672 [0,137-3,298]	0,721 [0,110-4,710]
Omnibus test of model coefficients	p = 0,546	p = 0,319	p = 0,506	p = 0,367	p = 0,198
Hosmer and Lemeshow test	p = 0,859	p = 0,662	p = 0,336	p = 0,804	p = 0,999
Included patient (n of 380)	380	368	380	380	368

All models have included the Omnibus test for model coefficients, the Hosmer-Lemeshow test for goodness-of-fit, and the number of cases. Suicide is set as the dependent variable. Model 1: Any seizure disorder, age, and sex, now referred to as the baseline model. Model 2: Baseline model and medication. Model 3: Baseline model and substance use disorders. We got VIF-values around 1, which indicates that there is no correlation between the medication groups. Model 4: Baseline model and diagnostic groups, included diagnostic group F10-F19. Model 5: Baseline model, medication, and diagnostic groups, expect diagnostic group F10-F19.

The results of the comparisons can be found in table 5. In bivariate analyses (Pearson Chi-Square Tests) of subgroups, suicide was more common (15,4% vs. 7,7 and 7,7) in the group with PNES compared with the two other subgroups of seizure disorders. The association was not statistically significant after correction for multiple comparisons (Fisher's Exact Test = 0,026, Bonferroni-corrected alpha = 0,008, Phi and Cramer's V = 0,350).

Table 5: Table 5 presents data on patients with and without suicide, with and without seizure disorder, and the stratification of seizure disorders in subgroups.

	Suicide (n=13)	**No suicide** (n=367)
	N (%)	N (%)
No seizure disorders (n=342)	11 (84,6%)	331 (90,2%)
Any seizure disorders (n=38)	2 (15,4%)	36 (9,8%)
	N (%)	N (%)
Epilepsy (n=15)	1 (7,7%)	14 (3,8%)
Acute symptomatic seizure (n=21)	1 (7,7%)	20 (5,4%)
PNES (n=9)	2 (15,4%)	7 (1,9%)

These numbers do not add up because some patients had more than one seizure disorder. The percentage in brackets has been obtained by taking the columns in relation to the rows.

Discussion

Main findings

To the best of our knowledge, this is the first study examining whether a patient's history of a seizure disorder increases the risk for suicidal behavior and suicide after discharge from an acute psychiatric department when compared to the other patients in the department.

Contrary to our hypothesis, we did not find statistically significant associations between seizure disorders in general and suicidal behavior, nor between seizure disorders and suicide.

In subgroup analyses, we did find an association between psychogenic non-epileptic seizures and suicide. However, this finding was not statistically significant after correction for multiple comparisons.

Interpretation

In this study, we found no association between seizure disorder and post-discharge suicidal behavior or suicide in an acute psychiatric population.

As mentioned earlier, we know that people with epilepsy are at a higher risk of suicide (Puteikis et al., 2022; Watila et al., 2018). A systematic review and meta-analysis of previous studies have found that epilepsy is also associated with suicidal attempts (Abraham et al., 2019). Therefore, we predicted that the rate of suicidal behavior and suicide would be higher among participants with, as compared to participants without, seizure disorders.

However, why is this not the case? Our study is conducted on acute psychiatric patients, while others, such as Watila and Puteikis', are not. It is conceivable that patients admitted to an acute psychiatric ward receive a greater degree of treatment and follow-up of psychiatric comorbidity compared to people with seizure disorders who are not admitted to an institution, especially not an institution with an emergency function.

Another critical difference is the control group. The control group in this study is a group of patients with a mortality rate after discharge higher than any other patient population (Bowers et al., 2010; Chung et al., 2017; Prestmo et al., 2020; Qin & Nordentoft, 2005). Seizure disorders might not increase or decrease the risk for suicidal behavior or suicide among patients with seizure disorders relative to the known high risk among patients in acute psychiatric care. However, null-hypothesis statistical testing does not give the probability of the null-hypothesis for being true.

Another explanation is that our study population is relatively small. The study is not designed to have adequate power to detect smaller differences between the groups than indicated by previous studies or to detect differences in subgroup analyses.

There is no general international agreement or consensus on the definition of seizure disorders or suicidal behavior in either the literature or clinical practice. Puteikis used, for instance, ICD-10 diagnostic codes X60-84 for broader inclusion of suicidal behavior, giving us the third explanatory model for our findings. Different definitions can be decisive regarding the differences in findings between this study and other studies.

In subgroup analyses, we found an association between PNES and risk for suicide at follow-up. Two out of 13 patients with a history of PNES died due to suicide. The association did not survive correction for multiple testing with Bonferroni correction and must, therefore, be interpreted with caution (Fisher's Exact Test = 0,026, Bonferroni-corrected alpha = 0,008, Phi and Cramer's V = 0,350). However, these findings have also been documented before. A study published in 2022 found that PNES has a high risk of both natural and non-natural causes of death, where suicide was the cause in 18% of the deaths of patients with PNES (Nightscales et al., 2020; Zhang et al., 2022).

According to a meta-analysis that looked at psychiatric comorbidity in patients with epilepsy compared to patients with PNES, patients with PNES had an overall higher psychiatric comorbidity (RR: 1,30, 95% CI: 1,14-1,48, $p < 0,0001$), and a significantly higher risk of PTSD, personality disorders (of the borderline type) and anxiety. Comorbid depression is something both groups share (Diprose et al., 2016). The authors of the same meta-analysis also believed that PNES could be a common clinical expression of several psychiatric disorders. If this is the case, it can be thought that the underlying psychiatric disorders cause suicidal behavior and suicide in these patients. Perhaps this mainly applies to patients with comorbid depression (Hawton et al., 2013; Ribeiro et al., 2018; Walsh et al., 2018)**,** and/or borderline personality disorder (Paris, 2019; Pompili et al., 2005), where both disorders have suicidal behavior as prominent symptoms.

Limitations

Dependent variable

The study has several limitations, and interpretations must be made with caution. Perhaps the most critical limitation is in how suicidal behavior is defined. As mentioned earlier, there is no consensus on how suicidal behavior is measured. This means that our definition, ICD-10 x6n, does not contain many actions that may be natural to think are included, such as planning and suicidal ideation. Another weakness in this definition is that to get the behavior registered, the person must come to a health institution, and the doctor needs to define the behavior as X6n and then code it. As a result, the inclusion criteria are strict and, therefore, a strength, but on the downside, suicidal behavior may be under-reported.

Independent variable

As for the seizure disorder group, the strength and limitations are the same. Because of the thorough screening done on this patient group with questionnaires, a journal review for ICD diagnosis, and a journal review of an epileptologist, we are unlikely to have many false positives. On the other hand, because the different groups of seizures have small prevalence, we constructed a grouped seizure disorders variable to get more observations to analyze. Still, our grouping variable is small (n=38) and constructed by several diagnoses, such as epilepsy (15), acute symptomatic seizure (21), and PNES (9). This means that subgroups could have a different impact on the effect size and statistical significance, which one of the Chi-Square tests might indicate regarding psychological non-epileptic seizure.

There are some downsides to performing the Bonferroni correction method when doing bivariate analyses. Generally, there is a delicate balance between type 1 error, which tends to give false-positive results and type 2 error, which tends to give false-negative results. The Bonferroni correction method can rapidly reduce type 1 error by lowering the alpha level as the number of tests increases. This comes with a cost, namely increasing the type 2 error with subsequent more false-negative results (Perneger, 1998). Our bivariate analysis of the variables suicidality and PNES did not "survive" the Bonferroni correction as the significance level was reduced from 0.05 to 0.008. Furthermore, using 0.05 as a cut-off without considering other conditions, e.g., whether previous data supports an association, is also debated (Benjamin et al., 2018).

Covariates variable

A limitation in the covariate "main diagnosis", is that by including only the admission diagnosis, we also leave out other significant diagnoses that the patient may have. This could affect our ability to control for potential confounding related to psychiatric comorbidity.

A limitation in the covariate substance use is that this variable has strict inclusion criteria. We used a “substance use disorder” diagnosis from ICD-10, which means we might have fewer false positives in this covariate given the strict inclusion. However, on the other hand, we might miss patients with substance use, giving us false negatives because patients are being treated for other diseases but do not necessarily give information about their substance use for different reasons. This could affect the validity of our classification of seizure disorders subgroups (e.g., acute symptomatic seizures) and our ability to control for confounding related to substance use in general.

The medication covariate also has some limitations. Patients' medications were obtained from the patient admission journal and not at discharge. Thus, we cannot know which medications the patient used when the suicidal behavior or suicide was registered. Also, even though medications are prescribed, we cannot know the state of compliance without analyzing serum or urine.

Study size

Furthermore, there were 760 admissions during the inclusion period, where 380 patients opted to participate (50%). Three hundred eighty participants gave us adequate power to study our primary aim. However, when only fifty percent of the population consented to participate, we might have selection bias, compromising the external validity/generalizability.

There is also a weakness in the strength calculation of the study because it is calculated using results from a meta-analysis based on a different patient population than ours. Meaning that the study power will become lower if the odds ratio among participants in acute psychiatric care is lower than in other populations.

Conclusion

Our main findings are that there were no statistically significant associations between a patient's history of seizure disorders and suicidal behavior or suicide after discharge from an acute psychiatric department. Still, patients discharged from acute psychiatric care, including patients with seizure disorders, have a high risk of suicidal behavior and suicide. Further studies should include more patients to increase the ability to estimate the risk of suicidal behavior and suicide in different subgroups of seizure disorders.

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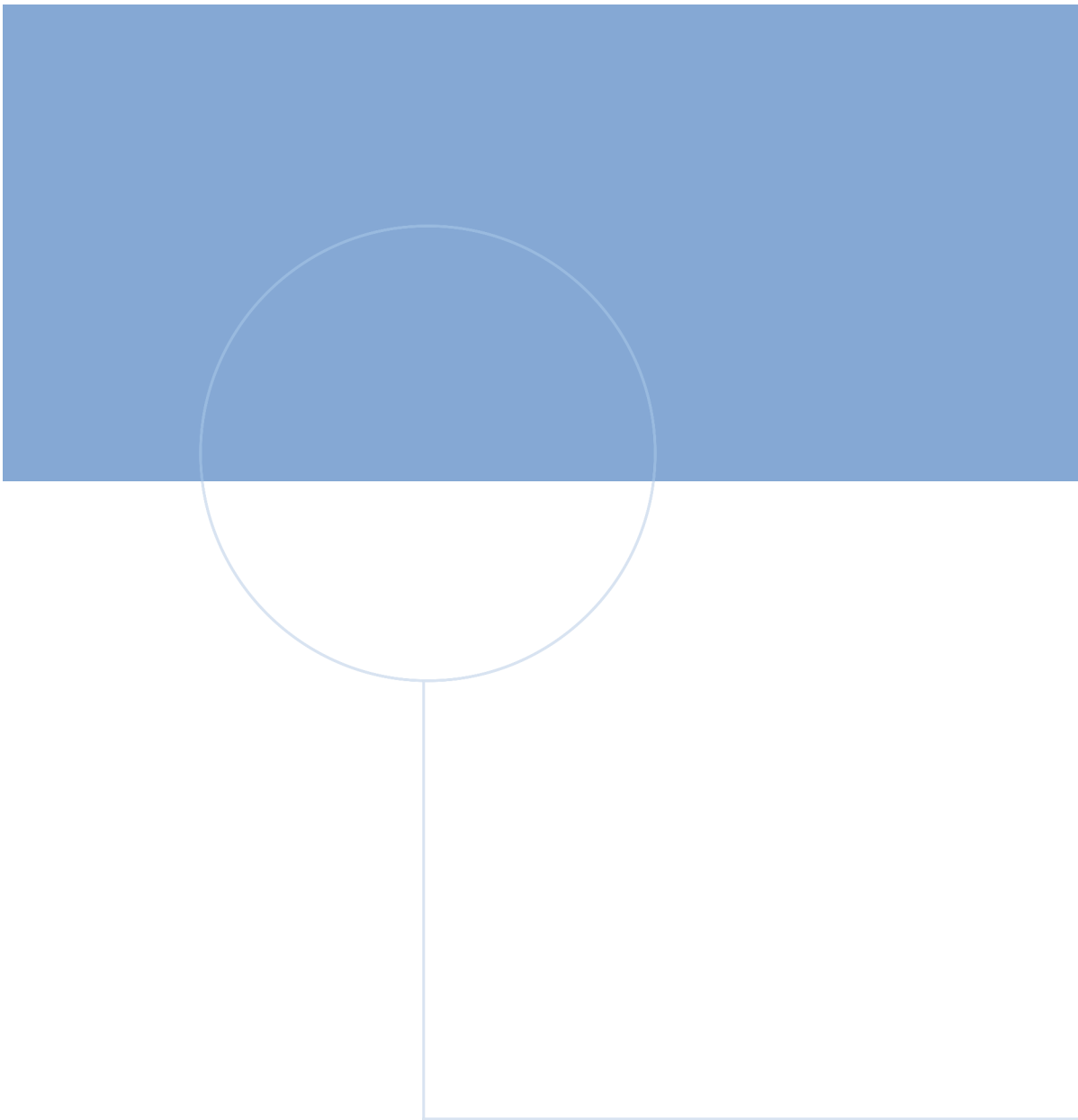

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