# Psychotic depression and suicide risk

## -a mixed method study

by

Kristin Jørstad Fredriksen

Thesis submitted in fulfilment of
the requirements for the degree of
PHILOSOPHIAE DOCTOR
(PhD)

Faculty of Health Sciences

2022

University of Stavanger

NO-4036 Stavanger

NORWAY

www.uis.no



ISBN: 978-82-8439-106-9.

ISSN: 1890-1387.

PhD: Thesis UiS No. 654.

# Foreword

Dedicated to the memory of Torstein and Stig.

A pivotal life event for me was the loss of my good friend Torstein to suicide when I was 19 years old. After this, I decided I wanted to become a psychiatrist. Further, this motivated me to want to do research on suicide. I know several close friends who have lost their next of kin in suicide, and I also personally knew several of these victims. I have to especially mention Stig, whose death made an indelible impression on me, as it taught me how incomprehensible a suicide can appear, and how difficult it was to predict that this might happen.

I have further lost patients at work and been involved in the peer support group at the hospital for clinicians who lose their patients to suicide. To be bereaved by suicide, but also as a clinician, can be one of the hardest things to experience, and leaves an emotional mark which may last for life.

I have gained knowledge from private conversations with friends and acquaintances who have died by suicide, and with those left behind whom in turn have had their own stories to tell. This opened me up to a greater understanding of motives which may form the basis of a suicidal decision. These personal experiences thus formed a part of my pre-existing knowledge base, but also influenced my interpretation and understanding of the findings in Paper 1. The same experiences also drove the development of further research questions. Few of the dead spoke explicitly of suicide ahead of their death, but most of them were severely mental ill or under severe pressure in life in general. Many of them were afraid of dying in the time before they actually died. We cannot always rationally understand what people may experience when they are irrational and in crisis or in a desperate state. I believe and hope that these thesis findings can be of comfort to those left behind by suicides which may have seemed completely incomprehensible and impulsive, maybe even accidental.

I would like to mention the critics, which sharpened my writing. Six rejections for my first paper, most of them from mainly quantitative journals, whom still gave good feedback on the paper draft and chiselled out my

understanding of what sort of knowledge qualitative findings can inform, and what might better be measured quantitatively…

I want to especially mention Ulrik Malt, the then leader of the Norwegian psychiatric association, and his comment after my presentation at a Norwegian congress in psychiatry of the findings of this thesis: “This is old knowledge, written in teaching texts in the 1800-1900s.” His statement made me think thoroughly about what research is, and about the validity of my findings.

Research in many ways is a form of innovation within a field, and a potential driver for progress within that field. The term “inventio” comes from classical rhetoric and Plato and means “to find new in that which already exists”. I have in other words sought and found connections which already existed, but which were yet unexplored or not yet uncovered by scientific methods. It is thus not a goal to always find results which seem completely contrary to clinical experience and knowledge. A lot of knowledge about psychotic depression exists both in clinicians and in teaching texts. But we need more aggregated data to be made available, including to scientific search engines. Clinical phenomena are discovered anew by each generation, and by each clinician travelling through their career. I would therefore humbly concede that the findings of this PhD dissertation may seem trivial or self-evident to the experienced clinician.

In clinical practice, many wish to have an experienced clinician, both as their supervisor or to be in charge of their mental health care. In reality, however, many clinicians are inexperienced - coming straight into practice from their studies. My goal is to convey knowledge so that it does not have to be acquired so expensively by each one of them, e.g., by losing a psychotic, depressed patient to suicide.

We have none to lose. And if this PhD dissertation builds knowledge to prevent even one or a few suicides, the 11 years of hard work and struggle have not been in vain.

# Acknowledgements

This project involves a research collaboration between the following research networks: The TIPS regional network for clinical psychosis by co-supervisor and PI Jan Olav Johannessen (MD, PhD), Wenche ten Velden Hegelstad PhD and Liss Gøril Anda PhD; Clinic of adult psychiatry at Stavanger University Hospital by main supervisor Helle Schøyen, MD PhD and co-supervisor Fredrik A. Walby, M.Sc. at "National centre for suicide research and prevention", University of Oslo, and Bergen University Hospital; Liv Mellesdal (deceased), Rolf Gjestad, Christoffer Bartz-Johannessen and Ketil J Ødegaard.

Co-Supervisor Margrethe Aase Schaufel, MD, PhD at Bergen University Hospital and co-author Larry Davidson, Yale University have supervised in the qualitative part of the project.

In paper 4, co-author Arne Vaaler at St. Olav's University Hospital, Trondheim, and collaborators Igor Galynker, Lisa Cohen at Mont Sinai University Hospital, New York have contributed.

Kristin Joerstad Fredriksen, MD, is working as a psychiatrist at the Clinic for Adult Mental Health Care at Stavanger University Hospital.

I would like to thank my eminent main supervisor Helle, whom has steadfastly and skilfully supervised this long-drawn research project. You regularly found time for me even though you were the hospital director and in charge of Norway's biggest hospital construction project – impressive!

Further, a great thanks to PI Jan Olav whom initiated this research project and was the primus motor, and ensured I was able to do research as part of my work hours. I honour Liv Mellesdal, PhD (deceased), former PI in SIPEA for her valuable input (including laughter and personal conversations) in the whole research process. We hoped for the longest time that she would live to experience the viva, but unfortunately this did not come to be.

Fredrik for always timely and valuable feedback and immense knowledge within the research field. Fredrik is responsible for my choice to research psychotic depression in particular, by pointing out that little research exists

in this field. I would further like to thank co-supervisor and friend Aase Schaufel for her help with the qualitative part of the thesis. The hospital and my leaders have allowed me to perform research at work during my spare moments since 2012.

I have otherwise had immense pleasure in my collaboration with good colleagues in TIPS: Liss Gøril Anda for very good help with writing papers and academic input, Wenche ten velden Hegelstad for great collaboration on paper 4. And Melissa Weibell for lively discussions and input along the way; our days of collaboration are in no way over neither clinically nor research wise.

Helle Schøyen, Liv Mellesdal, Fredrik Walby and I met Arne Vaaler, Igor Galynker and Lisa Cohen in Trondheim in the spring of 2019, where several of us heard about Suicide Crisis syndrome for the first time. Igor Galynker then suggested to do research related to SCS based on our qualitative findings regarding psychotic depression and suicidal behaviour. This gave rise to an exciting collaboration around paper 4.

We would like to thank all participants who contributed their valuable time and input to this study, as well as participating clinicians at the Department of Psychiatry, Bergen University Hospital, Norway who conducted the clinical assessments.

Otherwise, I have many good colleagues and leader at the Department for Security, whom make my day rewarding, fun and exciting. The group at Ombo have followed my joys and sorrows: Anja, Jeanette, Ingunn, Melissa, Elise and Pernille. My most treasured friend is however Jane, wise and funny and a supporter throughout life, as well as sharing the interest in psychiatry and suicide.

I am forever grateful to my parents and sister for their love and support. The most important ones remain my boys Filip, Noah, and David, whom I would like to thank for giving so much joy and meaning to my life, and whom have put up with this way too expansive PhD period. And Einar, with his sense of humour, patience and role of «colleague» and boyfriend in the home. You didn't get much more than a few measly trips as a companion to Lucca out of

this research project, but you never complain and a day with you is never boring. And on top of that you are handy when IT problems arise.

# Summary


## *Background*

The reasons behind suicide are multifactorial, complex, and poorly understood. Despite decades of research, suicide rates remain elevated both during hospitalization as well as shortly after discharge. Clinically relevant knowledge and tools for suicide risk assessments to guide decision-making processes in acute settings are needed.

## *Objectives*

The thesis objective was to examine and improve understanding of the complex relationship between psychotic depression and suicide behaviour. We also examined risk factors of clinical relevance in hospital settings, both during treatment, and after discharge.

## *Methods*

This research project used a sequential exploratory strategy, commencing with a qualitative part (paper 1-2), followed by a quantitative part (paper 3-4).

In paper 1 and 2, we conducted qualitative interviews with nine patients diagnosed with psychotic depression as part of uni- or bipolar disorder. Papers 3 and 4 used data from the naturalistic prospective cohort study Suicidality in Psychiatric Emergency Admissions. In paper 3, we included all patients with depression (N= 1846) in a representative sample to identify risk factors for suicide using a cox regression analysis. Paper 4 investigated a mixed diagnostic sample of 7000 acutely admitted inpatients to identify imminent- and short-term risk factors for suicide.

The findings from all four papers were combined into a secondary analysis, where we thematically synthesized the perspectives of patients' experiences

with the main findings from the prospective cohort study based on clinical assessment.

## *Results thematic summarized*

Our main finding was that psychotic symptoms in depression are associated with increased suicide risk, both short- and long-term (Paper 3). A possible mechanism to explain this association is the combination of intense emotional suffering and cognitive impairment which may motivate impulsive behaviour in psychotic depression (Papers 1 and 2). Depressed mood including overvalued ideas and delusions of self-blame and guilt predicted suicide the first following week after admission (Paper 4).

The association of intense affective states with both imminent and long-term suicide risk factors was supported by patient experiences of sleeplessness and intense anxiety as warning signs for suicidal behaviour (Paper 1 and 2). In further support of this, depression severity assessed by the Health of the Nation Scale item 7 predicted suicide the first following week after admission (Paper 4). We found higher short-term suicide rates in patients diagnosed with psychotic depression as compared to those without psychotic symptoms at all follow-up points (Paper 3). A diagnosis of psychotic depression and depression severity assessed by MADRS depression scale as independent predictors of suicide provided knowledge on the long-term perspective (median 5.5 years follow-up).

Also of clinical importance is our finding that self-report of suicidal ideation is not a good measure of imminent, short- or long-term suicide risk. Our qualitative findings indicate that shame, psychotically motivated paranoid ideation and impulsivity motivated underreporting of both suicidal ideation and psychotic symptoms in themselves. This may partly explain why, despite reporting less suicidal ideation/planning on admission, the suicide rate was higher for patients with psychotic symptoms on admission than for those without such symptoms (Paper 3). Although reported suicidal ideation was less relevant for clinical risk assessment, paper 3 and 4 identified male gender and recent suicide attempt as significant risk factors for completed suicide.

The last main finding was that patients found both security measures and a treatment approach focusing on modifying psychotic experiences, intense anxiety and sleeplessness was helpful during hospitalization. Taking the time to talk to establish good patient relations is essential for optimal treatment conditions.

## *Conclusions*

The periods of acute inpatient treatment and immediately post- discharge are associated with the highest suicide risk. High symptom load as well as a diagnosis of psychotic depression, especially the presence of overvalued ideas and delusions of self-blame and guilt, appear to indicate especially high suicide risk regardless of time horizon. Identifying delusions and other psychotic symptoms is thus of the utmost importance. Psychosis- and depression-focused interventions and treatment approaches aiming specifically to reduce both psychotic and affective symptom load may act as a suicide prevention strategy for psychotic depressed patients.

We found self-report of suicidal ideation of limited relevance when assessing suicide risk. Such assessments should thus always be combined with thorough clinical assessment by trained staff. This is especially true when assessing patients with psychotic depression, but especially given the frequent underreporting of psychotic symptoms, it remains important with any patient admitted for a depressive episode. Structured depression rating scales for clinician use may meaningfully contribute to suicide risk assessments. When assessing acute admission patients, we recommend paying particularly close attention to males, and patients with prior and recent suicide attempts.

# List of publications

1. Fredriksen, K. J., Schoeyen, H. K., Johannessen, J. O., Walby, F. A., Davidson, L., & Schaufel, M. A. (2017). Psychotic Depression and Suicidal Behavior. Psychiatry, 80(1), 17-29.

2. Fredriksen, K. J., Schaufel, M. A., Johannessen, J. O., Walby, F. A., Davidson, L., & Schoeyen, H. K. (2020). Preventing suicide among psychiatric inpatients with psychotic depression. Psychiatric Quarterly, 91(1), 223-236.

3. Fredriksen, K., Mellesdal, L., Gjestad, R., Walby, F., Anda, L., Oedegaard, K. J., & Schoeyen, H. (2022). High scores on the MADRS depression rating scale and psychotic symptoms predict suicide: -A prospective cohort study of psychiatric acute ward patients. (In press, Journal of Clinical Psychiatry)

4. Fredriksen, K., Bartz-Johannessen, C., Schoeyen, H., Vaaler, A., Walby, F. P., & Hegelstad, W. (2022). Imminent and very short-term risk of death by suicide in 7000 acutely admitted psychiatric inpatients. (Manuscript submitted).

# Table of Contents

# Table of Figures



# List of Tables

# 1 Background

## 1.1 Symptom dimensions in depression and psychosis

### 1.1.1 Depression as part of an affective disorder

Affective disorders, also called mood disorders, include severe disturbances in mood as main symptom. Both diagnostic system, the International Statistical Classification of Diseases and Related Health Problems (ICD-11)[1] and the Diagnostic and Statistical Manual of Mental Disorders (DSM-5)[2] include different types of depression (unipolar depression) and bipolar disorders. Unipolar depression involves only episodes of depression, while bipolar disorders also include one or more episodes lifetime with mania or hypomania. These symptoms do not meet criteria for schizophrenia/schizoaffective disorder. Mood disorders may arise spontaneous, or be triggered by e.g. environmental, drug use or biological factors.

In unipolar disorders, a depressive episode can be categorized as single or recurrent. In bipolar disorders, a depressive episode can be a part of the course of the disease.

The core symptoms of a depressive episode are the subjective experience of depressed mood, and loss of interest and enjoyment in normally enjoyable activities [1, 2]. Many individuals with depression also suffer from reduced energy levels, cognitive impairment, anxiety symptoms, disturbed sleep, and appetite as well as feelings and ruminations centered on guilt or low self-worth [1-3]. Both in unipolar and bipolar disorders, the severity of a depressive episode can be diagnosed as mild, moderate or severe. To fulfill diagnostic criteria in ICD-10 for a depressive episode and for a major depressive disorder in DSM, duration of depressive episode is at least two weeks.

Lifetime prevalence of bipolar 1 disorder is over 1%[4], while it is 20% major unipolar depressive disorder[5]. Depression as part of a uni- or bipolar disorder is according to WHO a leading cause of disability worldwide and is a major

contributor to the overall global burden of disease[6]. About half of all suicides have been found to suffer from affective disorders [7-9].

### 1.1.2 Psychosis

A psychotic episode entails a diverse set of severe mental symptoms that disrupt perception, cognition, emotion, and behaviour. The affected person develops inappropriate interpretations of their environment and sense of self and falls out of touch with reality. Psychotic symptoms may arise spontaneous without any environmental or identified biological trigger, or by adverse life events, psychosocial stressors, and biological factors. It may form part of a primary psychotic disorder, of which schizophrenia is considered the most severe, an affective disorder, or arise due to psychoactive substance use or somatic health issues. Symptoms associated with psychosis are often categorized as positive, negative, affective, disorganized, and cognitive [10]. Positive symptoms include delusions and/or hallucinations. Delusions are beliefs that are upheld contrary or in conflict with evidence and cannot be explained by a person's cultural or religious background. Hallucinations include perceptual disturbances, i.e., sound or visions except from external stimuli. Negative symptoms include loss of normal behaviour and motivation including social withdrawal and diminished emotional expression. Affective symptoms resemble symptoms seen in both depressive and maniform affective disorders. Disorganized symptoms include problems with organizing conversation (written or spoken) and behaviours. Cognitive symptoms include impaired cognitive function can lead to function loss in several settings as work, i.e., attention, psychomotor speed, executive function, and memory. A psychotic episode may include some or all of these dimensions, representing a clinically diverse population.

Few studies have examined the subjective experience of psychotic symptoms, with most existing studies using qualitative methodology with special emphasis on schizophrenia, in which anomalous self-experience are central [11, 12].

### 1.1.3 Psychotic depression

The diagnostic definition of psychotic depression has evolved during this PhD project. Both international diagnostic systems used during data collection in this PhD project, namely the International Statistical Classification of Diseases and Related Health Problems, 10th edition (ICD-10) and the Diagnostic and Statistical Manual of Mental Disorders, IV Edition (DSM- 4) [13, 14], define psychotic symptoms as both a subtype and a marker of severity in depressive episodes. In ICD-11[1] which have not yet been officially applied in Norway, and DSM-5[2] recently introduced in research, the psychosis specifier is independent of severity, so that depression does not have to be severe to justify a diagnosis of psychotic depression.

Psychotic symptoms during a depressive episode are characterized by the appearance of delusions and/or hallucinations in addition to symptoms that fulfil the criteria of a major depressive episode. Delusions in a major depressive episode can have themes as guilt, worthlessness, being deserved punishment, death, poverty, apocalypse, self-referential content. The same delusional content tends to reappear if the patients have repeated episodes [15, 16]. Delusions and hallucinations can be both mood congruent (i.e., reflective of a depressed mood with themes about guilt, shame punishment, disease, death) and mood incongruent (as e.g. persecutory content, delusions of thought insertion and broadcasting). Evidence suggests that there is no difference in outcome between psychotic depression with mood congruent versus mood incongruent symptoms [17]. Hallucinations may occur, predominantly auditory, but visual, olfactory and tactile hallucinations can occur both in uni- and bipolar psychotic depression[18].

Research mainly based on ICD-10 and DSM-4 criteria found that patients with psychotic depression exhibit more frequent relapses and recurrences and have increased use of services, greater disability including neuropsychological deficits [19-21] and poorer clinical course when compared with non-psychotically unipolar depressed patients [16, 22, 23]. Patients with psychotic depression are at high risk for psychosis in future depressive episodes [16]. Unipolar psychotic depression is found to increase risk of both suicide ideation and attempts [24, 25]. However, psychotic symptoms in major depression are often missed by clinicians because such symptoms may be

subtle, intermittent, or concealed [26]. In addition, few studies have systematically examined depression with psychotic depression[26].

A common estimate however is that among inpatients with major depression the rate of psychotic depression is about 25% [27]. Bipolar depression in general, and psychotic bipolar depression in particular, both remain understudied [28, 29]. However, an estimated 25% of individuals with bipolar disorder type 1 experience psychotic symptoms during at least one depressive episode [30, 31]. Also, there is an association between occurrence of chronicity, with one study finding a proportion of 8.7% to be psychotic in their first episode whilst this rose to 25% in the 15th episode[32]. The risk may also increase with age, with rates of 40% found in elderly inpatients with major depression (minimum age of 60 years) [27].

#### 1.1.3.1 Treatment for psychotic depression

Unipolar psychotic depression is described as an under-treated state [33]. Recent guidelines for treating uni- and bipolar psychotic depression suggest that the therapeutic alliance and to bring hope is of the utmost importance. Psychoeducation is also recommended [18]. However, no medication has been approved for the treatment of unipolar psychotic depression neither in Europe nor in the United States. This may be partly due to the lack of pharmaceutical industry interest in developing medications for the treatment of psychotic depression [33]. A Cochrain report conclude that evidence of optimal pharmacological treatment of psychotic depression is «heavily under-studied». Some evidence indicates that combination therapy of an antidepressant plus an antipsychotic is more effective than either treatment alone or placebo [34]. The anti-depressive effect is equal in the most common second generation antipsychotics for acute admitted inpatients with psychosis[35]. Guidelines also recommend sedation at night with antipsychotics or benzodiazepines [18]. The treatment of psychotic bipolar depressive episodes is similarly underresearched[28, 36]. The guidelines however again recommend the early introduction of antipsychotic medication to alleviate psychotic and depressive symptoms, as well as agitation and irritability. Mood stabilizers are also recommended, and stabilizing sleep is of crucial importance [18].

## 1.2 Suicide and suicidal behavior

Suicide is a leading cause of death worldwide. According to the World Health Organization, nearly 800.000 people die every year from suicide[6], which accounts for 1.5% of all deaths worldwide[37]. All ages, sexes, and regions of the world are affected[38]. Suicide is considered as a serious global public health issue, and causes great pain to those left behind[39].

The global age-standardized suicide rate was 10.5 per 100 000 person-years for 2016. The global age-standardized suicide rate was higher in males (13.7 per 100 000) than in females (7.5 per 100 000). However, the South-East Asia Region had a much higher female age-standardized suicide rate (11.5 per 100 000) compared to the global female average.

Suicide can occur throughout the lifespan. In 2019, death rates worldwide per 100.000 individuals was highest for 70+ years old (25.53), followed by 50-69 years old (14.25) and 15-49 years old (11.19) [40]. Suicide was the third leading cause of death in 15-19-year-olds for both sexes [38], which accounts for many lost life years.

Suicide rates vary considerably between countries, between genders and between population groups studied The risk is highest in populations of people with mental disorders, as up to 90% of people who died by suicide have met the criteria for a psychiatric disorder[7]. Within this heterogenic group, the risk of suicide varies according to the level of mental health care received. People receiving outpatient care had an 8 fold higher risk, and people admitted as psychiatric inpatients within the last year had a 44-fold higher risk of suicide compared to the general population[41]. High suicide rates during inpatient treatment are explained by selection; that people with severe psychiatric symptoms and assessed high suicide risk are prioritized for inpatient treatment[42].

The absolute highest suicide risk per day lived, is the first days after admission to hospital. A quarter of inpatient suicide victims if found to have died within the first week of admission, and of those, patients diagnosed with a depression have the highest risk[42]. Thus this PhD project focus upon this extreme high-risk group: Acute admitted patients with severe depressive symptoms, with follow up during hospitalization and after discharge.

This PhD project's overall aim is to identify associations between psychotic depression and suicide risk. However, paper 3-and 4 both describe suicidal behaviour at admission/baseline, and the qualitative part examined suicidal behaviour related to psychotic experiences in living patients.

Thus, international definitions of suicidal behaviour are essential. Suicidal behaviour can be categorized into suicidal thoughts, plans, suicide attempts, and completed suicides[43]. Suicidal ideation is "thoughts of killing oneself"; suicide plans entail "consideration of a specific method through which a person intends to kill oneself"; suicide attempts are the "engagement in potentially self-injurious behaviour in which there is some intent to die from the behaviour"; with suicide death resulting from intended or decisively self-injurious behaviour. Suicide attempts are up to 20 times more frequent than are completed suicides, and in contrast to the latter, attempts are most common in women [44]. The relations between suicidal ideation, suicidal attempts and later completed suicide will be described more in detail in the background section.

Suicide is to some extent preventable, but complex, and its risk and protective factors incompletely understood. The etiology is multifactorial and most likely includes both biological, genetic, psychological, social, religious/ existential and environmental factors in a multidirectional interaction. Several risk factors for suicide have been identified, I described in depth below.

## 1.3 Methodological challenges in suicide research

Suicide is among the most incomprehensive of all human behaviours because it fundamentally challenges the belief that humans and animals have a drive for self-preservation. Absurdist Philosopher Camus declared that "there is but one truly serious philosophical problem, and that is suicide" [45]. Current research in suicidology is broad and interdisciplinary, including amongst others epidemiological studies, neurobiological studies, psychological autopsy studies, clinical studies and treatment studies including also randomized controlled trials between different treatments. As establishing causality in this field is difficult, perhaps even unviable, and

suicide is a rare outcome, effective evidence-based suicide prevention strategies are difficult to design and evaluate.

Research into the effect of suicide prevention strategies is generally faced with several methodological challenges. Given the rarity of suicide, studies powered to detect risk factors must be large [9, 46], and intervention studies even larger in order to assess potential effects of these on number of completed suicides. In an ideal world, experimental research methods would be used for research for detecting suicide prevention strategies, fulfilling all requirements of falsifiability and generalization. However, ethics, time and expenses all preclude this ideal scenario, and force researchers to make design compromises.

As studies powered to detect statistically significant suicide risk factors must be very large [46], suicidal attempts as a proxy of suicide deaths are sometimes used as the main outcome in research. However, attempts correlate to varying degrees with actual death by suicide[47]. Studies of suicide deaths are needed for confirming generalizability of findings between the populations as provided e.g. in large national register studies [9].

An added complication is unfortunately that the main study objects are dead by suicide and their mental state thus cannot be explored in the aftermath. Clinical status and motive for the suicide are often unknown.

Cross-sectional studies and chart reviews can only identify what correlates with suicide, and not identify true risk factors; for this we need prospective studies. Psychological Autopsy (PA) studies [48] based on interviews with next of kin informants suffer from severe methodological biases [49], e.g. recall bias, and the fact that the bereaved try to find meaning in and explanations for the suicide in part to serve their own psychological needs. It also excludes a not insignificant minority of suicides in which there are no next of kin positioned to provide this information.

Lack of clarity and common ground in our understanding of suicide risk factors may lie in differences between populations studied, as well as the use of proxy outcome variables as described above. Some authors have called for a hierarchical classification of suicide risk factors. One classification of risk factors [50, 51] differentiates between primary (mental disorders, clinical

warning signs, previous and recent suicide attempt, recent or ongoing inpatient treatment), secondary (individual factors not directly related to mental illness, or have unclear associations to such behaviour), as opposed to tertiary (male gender, psychosocial, vulnerable periods etc.) risk factors. Alternative categorizations of risk factors may offer other perspectives, e.g., dividing them into biological, psychosocial, relational and environmental, or clinical vs. non-clinical. However, I have chosen for the purposes of this thesis to describe risk factors based on the three-part hierarchy.

This PhD project mainly focuses on clinical risk factors as depression severity and recent suicide attempt in acute admitted inpatients, supplemented with suicidal ideation and gender as predictor for completed suicide. As a diagnosis of depression is a well-established risk factor for suicide, we decided to focus mainly on patients diagnosed with a depressive episode as part of a uni- or bipolar disorder. Paper 4 include a mixed diagnostic population where we also focus on depressive symptoms on a transdiagnostic level.

## 1.4 Primary risk factors

### 1.4.1 Recent or ongoing hospital treatment

Symptoms and behaviour associated with suicide risk such as suicidal ideation or plans, non-suicidal self-injurious behaviours and suicide attempt are common reasons for admission to psychiatric hospital [52, 53], and in some health care systems, one of very few ways to secure an admission. This may partly explain why, despite significant developments in treatment and general security measures [42, 54]; suicide risk is at its highest during, and shortly after, psychiatric hospitalization [42, 53-60]. Although high suicides rates have been found extremely elevated in psychiatric inpatients compared to the background population, a review reports that only 0.14%–0.32% of all psychiatric inpatients die while admitted [42]. Even more suicides related to hospital treatment occur short term after discharge [53, 57, 61]

A recent review and meta-analysis mainly based on studies conducted in Western European and North American countries, found that 18.3% of persons who died by suicide had made contact with inpatient mental health

services the year before suicide [59]. The suicide risk associated with hospitalized patients is explained primarily by selection: people who are frequently in touch with mental health services are likely to have more severe psychiatric symptoms [42, 54].

Psychiatric emergency departments and acute wards are thus critical locations for identifying patients at risk of suicide. However, the majority of studies from psychiatric emergency departments [42] and emergency rooms [62] are based on small, non-representative samples, and thus lack statistical power and generalizability. Bolton [62] commented on the lack of research from emergency ward settings, where suicide attempters are admitted and treated, as follows : «To address this fundamental gap, research must employ methodologies that combine large sample sizes, longitudinal follow-up, population representativeness, and clinical assessment.» National register studies can provide unbiased, generalizable information on suicide rates and risk factors[9], however often lack data from clinical assessments. Research based on routinely recorded suicidal behaviour at acute wards remain alarmingly scarce. Only the prospective cohort study Suicidality In Psychiatric Emergency Admittance (SIPEA) [63-65], a cross-sectional study from Norway [66], and a Swedish register study [67] have to our knowledge recorded suicidal behaviour routinely. Thus, few studies can provide generalizable findings regarding suicide behaviour at admission and future suicide risk.

Two prospective studies of acute depressed unipolar inpatients have been published with suicide as primary outcome [68, 69], with up to 10– and 24–years follow-up respectively. Still, the potential difference between long-term static versus short-term dynamic risk means that identified long-term risk factors may be of limited clinical relevance in acutely admitted inpatients. This thesis therefore focuses on acute inpatient settings, short-term risk and have a particular diagnostic focus on depressive episodes using larger samples to ensuring better statistical power.

### 1.4.2 Depression and suicide risk related to inpatient treatment

Patients with depression are the largest diagnostic group associated with suicide both during and after inpatient stays [9, 56, 57, 59, 70, 71]. Suicide risk in

recently discharged patients also increases with the severity of their depressive episode [9, 32, 58, 68, 72] . A review of Nordic national register based studies, found 2%–8% of psychiatric inpatients with unipolar depression to have died by suicide after discharge, and 4–8% of bipolar patients having died by suicide in long term[9].

Yet very few prospective studies have examined hospitalized depressive patients. One exception is a multicenter study of patients with major depressive disorder found that neither expressed suicidal ideation nor prior attempts were associated with acute risk of suicide. [69]. Predictors were severe anxiety and agitation at admittance, global insomnia, severe anhedonia, and alcohol use problems in the 12 months prior to assessment.

Depressive symptoms are found to be associated with inpatient suicides [42, 71]. In one review [42], eight papers refer to "depressed mood" as predictors for inpatient suicide [71, 73-79]. However, these studies used clinical assessment to report diagnostic depression severity, and not standardized depression rating scales. Regarding suicide risk assessments, screening for depression is relevant [80].

Most studies of patients admitted to psychiatric departments have not used standardized rating scales for depression and suicide behaviour at admission. Depression rating scales are thus understudied as a potential tool for assessing suicide risk [81, 82]. There does not exist any research on the relationship between Montgomery–Åsberg Depression Rating Scale (MADRS) scores and suicide risk [81]. Also, the predictive validity of HoNOS item 7 "problems with depressed mood" on suicide completion remain unexplored.

To our knowledge, no existing studies have investigated a representative sample of depressed inpatients assessed with a depression rating scale, and with suicide as main outcome at follow-up. This was one of the main motivations for including two depression scales in regression analyses with suicide as main outcome in a representative sample of inpatients in this thesis.

### 1.4.3 Psychosis and suicide risk

Several studies have identified an association between psychotic symptoms and suicidal risk, including patients with affective disorders [83-85]. Systematic studies of patients with psychotic features and suicidal behaviour are however limited as these patients are often excluded from clinical studies [47, 86]. A recent review of longitudinal population studies found that individuals with psychotic experiences were at increased risk of suicidal ideation, suicide attempts, and death by suicide [87]. This review underscored that psychotic experiences were far more prevalent than psychotic disorders, and were associated with the full range of mental disorders [87].

Researchers have hypothesized that psychotic processes may transform suicidal thoughts to suicidal acts in depressed patients [26, 88]. Studies regarding psychotic depression are difficult to perform, partly because of the practical and ethical difficulties in enrolling patients with psychosis in studies [33], and because it is challenging to detect and correctly diagnose psychotic depression [26]. As psychotic depression is potentially underdiagnosed in research samples[26], this may affect estimated suicide rates.

One large Finnish prospective study of first-time hospitalized patients with unipolar depression, reported psychotic depression as an independent suicide risk factor in addition to well-established factors like male gender, previous suicide attempts and depression severity [68]. Another study from the same Finnish research group regarding discharged patients with bipolar disorder, reported that suicide risk was strongly related to bipolar depression, however psychotic depression was not examined as a risk factor during the depressive episodes[89].

A systematic review and meta-analysis of discharged patients (follow-up 3 months and one year) found that a patient with a psychotic disorder had higher suicide risk compared to a patient with affective disorder [53].

The role of psychotic symptoms in depression as risk of suicide has also been a topic of controversy [3]. A recent major register study concluded that psychotic symptoms were not an independent long-term risk factor for suicide in severe unipolar depression [70]. However, findings from studies investigating the association between psychotic symptoms and suicide risk in

unipolar depression over long-term intervals vary greatly, from insignificant to elevated [9, 25, 68, 90, 91]. The potential impact of ameliorating psychotic symptoms on suicidal behaviour thus also remains underexplored; however, one review reports the risk of suicidal behaviour to remain elevated until the remission of both depressive and psychotic symptomatology [25]. Suicide risk in bipolar disorder is primarily associated with depressed and mixed phases of illness, and risk especially high early in the course of illness [4]. Suicide risk increases among longer duration of depressive episodes, and with a longer duration of untreated illness.

Psychotic symptoms are understudied as a short-term predictor of suicide in both uni- and bipolar depression [25, 90, 92, 93]. A recent review of unipolar psychotic depression [90] reports only three dated studies with small study populations including less than one-year follow-up. [88, 94, 95]. The only study to find elevated short-time suicide risk [88] has limited generalizability due to its cross-sectional design, few participants (in total 42), retrospective assigning of diagnoses by the authors, and use of suicide as endpoint variable without predefined follow-up time-points. Comparable short-term suicide risk estimates of bipolar psychotic depression do not exist at all [92, 93].

### 1.4.4 Patients` experiences of motivations for suicide

We do not know which factors predict the transition from suicidal thoughts to completed suicides in mixed diagnostic samples [96].

Given that suicide is a personal act, understanding subjectivity is especially important in this research field. There is little qualitative research into motivation for suicide in inpatients. One qualitative study examined 30 patients in hospital after a suicide attempt. Patients described their reasons as: “to get relief from a terrible state of mind or from an unbearable situation”, “anxiety/panic and emptiness” and " loss of control" [97]. Another study described suicide attempt as a result of two different suicidal crises; as a result of loss of mental control, or as an attempt to regain control [98]. «Being in want of control» was the overall theme in relation to different aspects of oneself and overall life-situation.

Although major depression and psychotic symptoms have been identified as suicide risk factors, actual motivations for dying, as well as subjective

interpretations of symptoms in those affected, remain largely unexplained. A monograph from 2011 by Norwegian psychiatrist Arne Thorvik included qualitative interviews of patients with psychotic disorders in relation to suicide risk [99]. A subgroup of informants did not relate psychotic experiences to suicidal behaviour, and most often described the duration of the suicidal process as "months". Interestingly, another subgroup described vivid psychotic symptoms motivating the suicidal process, with the suicidal process lasting "days". Anxiety, restlessness and fear of psychotic experiences was described leading to intense suffering and suicide as a way out. In conclusion, existing research gives a very sparse understanding of motivation for suicide, and especially psychotic experiences, in relation to suicidal behaviour. To reduce suicide rates, it is important both in clinical practice and in research to understand mechanisms behind suicide, not only rely on statistically derived risk factors. No published qualitative studies, to our knowledge, have focused on inpatients with depressive psychosis. The weak knowledge base motivated the use of a hypothesis generating qualitative design to examine patients admitted for a psychotic depression in this thesis.

### 1.4.5 Previous and/or recent suicidal attempts

Previous suicide attempts are a well-established and central risk factor for later suicide completion [9, 68, 72, 96]. However, this knowledge is predominantly based on findings from longer-term follow-up studies. Suicide attempts is thus unclear as a short-term risk factor in acute and emergency psychiatry populations [55, 62, 67].

### 1.4.6 Short-term risk assessment and suggested presuicidal mental states

Although suicide risk assessments are commonly used in emergency psychiatric settings [100], clinically relevant evidence to guide decision making and precautions in these settings is scarce [62, 96]. Reviews of the predictive ability of suicide risk scales relevant to acute settings find no scales with sufficient evidence to support their use [81, 100-103], and their short-term predictive value remains untested [81, 101-103]. This is a cause for concern given

that clinicians primarily are expected to make decisions about acute risk rather than decisions about risk over years, or decades. In general, very few studies have examined clinical predictors to suicide within an immediate or short timeframe in inpatient settings [55, 62]. Glenn and Nock [96] state that "alarmingly little is known about the near-term risk factors for suicide and a review sums that "New studies with very short follow-up lengths may yield tremendous theoretical and empirical advances" [55].

Warning signs, as in symptoms or stressors observed in the final day(s) before a suicidal event [104] include anxiety and agitation [105, 106], sleep problems [106-108], psychosis [84, 109], impulsivity [110] and intense affective states [69, 84, 104, 105, 111, 112] including depressive symptoms [42, 71].

Rudd [104] refers to suggested subjective warning signs, that are observed in the final day(s) preceding suicide completion: Hopelessness, rage/anger/seeking revenge, acting recklessly or engaging in risky activities seemingly without thinking, feeling trapped (like there's no way out), increasing alcohol or drug use, withdrawing from family friends/family/society, anxiety/agitation, an inability to sleep or sleeping all the time, dramatic mood changes, and no reasons for living/no sense of purpose in life. A theoretical assumption of a "suicidal process" is important, as it often underlies the choice of endpoint in studies; with such a process starting with suicidal ideation and progressing to plans and sometimes to attempts or completed suicide [113, 114]. Under a suicidal process framework the assumption is that once a person has initiated such a process, he or she may become more vulnerable to future suicidal behaviour as a result, due to vulnerability accumulation or "scarring" [115, 116] . In turn, this would imply that effects of factors like life stress, socio-economic circumstances or mental illness on the risk of suicidal behaviour differ according to how far individuals have progressed through the suicidal process before.

However, there is considerable theoretical diversity in the suicide research field, which has been described as "still in a preparadigmatic phase» [55]. Theoretical concepts relevant for this project include entrapment theory [117] and the Suicidal Crisis Syndrome [118-120]. Suicidal Crisis Syndrome is described as a deep feeling of entrapment, affective disturbance, loss of cognitive

control, disturbance in arousal and social withdrawal, independent of reported suicidal ideation and diagnosis.

Models of warning signs and Suicidal Crisis Syndrome both describe observable signs and expressed symptoms that may indicate a high risk of suicidal behaviour in the next few minutes, hours, or days. However, as with many other theoretical constructs, their actual relationship to suicide completion remains unclear.

In short, there is a pressing need for research establishing reliable predictors associated with near-term risk for death by suicide, which such predictors are essential for clinical decision-making. There are limited relevant knowledge and tools to guide the assessment of suicide risk in emergency departments. Currently, such assessment relies heavily on patient self-report of suicidal behaviour, the predictive ability of which is underexplored in inpatient samples with an imminent/short-term perspective. Screening for suicidal ideation or behaviour is likely no more accurate than simply screening for depression [80], but the use of structured ratings of depression severity is understudied as a risk assessment method. In particular, psychotic type symptoms are underexplored as a short-term predictor of suicide.

## 1.5 Secondary risk factors

### 1.5.1 Alcohol and substance abuse

Alcohol and substance abuse can increase suicide risk [80]. In emergency rooms, concurrent psychiatric, somatic and substance use problems are extremely common [121, 122]. As for substance use, a person may be acutely intoxicated, while also suffering from abstinences due to polypharmacy problems: Half of acute admitted patients are affected by several drugs simultaneously [123]. A recent Norwegian prospective study actually found higher suicide rates in substance abuse disorders compared to affective disorders [60]. Another Swedish sample of 18.684 patients also found the highest suicide rates within one month to be in those with substance use [67]. Rates of comorbid substance use disorders are elevated in both uni- and bipolar disorders, and can also complicate the treatment of psychotic

episodes in affective disorders [18]. However, although substance disorders are relevant for suicide risk, this topic was beyond the scope of this PhD project.

### 1.5.2 Suicidal ideation

Suicidal ideation (SI) is quite common, with a lifetime prevalence of 10% in the general population [124]. It is even more common in acute settings, with our own group finding that 54% of index admissions and 60% of re-admissions were related to assessed suicide risk [52]. However, only a small minority of patients proceed to act on their thoughts. Suicidal ideation is also strongly correlated with other predictors of completed suicide, such as previous attempts[125]. It is however uncertain to what extent reported suicidal ideation independently predicts completed suicide. There is substantial variation in risk ratios between suicidal ideation in different study populations and between diagnoses [126]. One review found that risk for completed suicide was clearly higher in people who had expressed suicidal ideation compared with people who had not, with substantial variation between the different populations. Absolute risk of suicide completion was highest in the psychiatric subgroups who had expressed suicidal ideation, with 1.4% risk first year of follow-up [127]. Suicidal ideation is a less specific indicator of suicide among studies of acute admitted psychiatric patients [128] and studies with a high proportion of people with suicidal ideation as part of affective disorders [126, 127].

Existing quantitative studies from psychiatric emergency departments regarding suicidal ideation and suicide risk have also been hampered by several methodological challenges. Most studies including inpatients have been either cross-sectional or limited to chart reviews. Few studies of post-discharge suicides reported comparisons of those deceased through suicide to those still alive [53]; leaving it uncertain to what extent those still alive also had reported suicidal ideation at admission. Samples have been small and non-representative. One exception is a Swedish register study including 18,684 patients, registered suicidal ideation past month, and suicidal behaviour past 3 months in the emergency departments by Colombia Suicide Severity Rating Scale. Suicide completion was registered at 1 week, 1 month and 1 year follow-up [67], and found both suicidal ideation and behaviour to be associated with suicide within 1 week.

Other findings leave self-reported suicidal ideation of limited value as a reliable risk factor in an acute setting or close-term perspective [55, 105, 106].

Little is known about why self-reported suicidal ideation is such an unreliable predictor in acute settings. It is possible that qualitative studies may pave the way to illuminating this question. This motivated this thesis to investigate how severely depressed individuals experienced the relationship between psychotic symptoms and suicidal ideation and behavior in this thesis.

### 1.5.3 Self-harm without suicidal intent

Self-harm without suicidal intent include cutting, burning, scratching etc., and is found in mixed diagnostic samples to be associated with future suicide behaviour [129]. However, the association with completed suicide is under-investigated. The association between self-harm and actual suicide risk has to our knowledge not been studied in acute admitted depressive. Self-harm without intent to die was therefore included as a variable of interest in paper 3.

## 1.6 Tertiary risk factors

### 1.6.1 Male gender

Suicide attempts are more frequent in females[44] although paradoxically, men die by suicide 3-8 times more often than women in Western countries [130]. An exception is for the 15 to 19 age group in western countries where rates are low and women dominate[37]. Male gender stands out as a robust statistical predictor from longer-term follow-up studies [9, 55, 68, 72]. One reason why men die more often than women may be explained by the fact that perhaps men tend to use more violent and lethal suicide attempt methods [131]. Females are also more likely to report physical and psychological symptoms and to seek medical help, whereas men more often drop out of psychiatric treatment. Depression symptoms may also be less typical or clear than in women, leading to misdiagnoses i.e. of alcohol abuse and thus wrongly targeted treatment approaches [130]. Atypical symptoms of depression may also keep men from recognizing them as such, again preventing help seeking [131].

However, reasons for these gender-differences are complex and incompletely understood [130]. Testosterone has been suggested to be involved in the pathophysiology of suicidal behaviour in men. Other hypotheses are related to how socioeconomic factors including income and social status may affect men and women differently [130]

### 1.6.2 Vulnerable periods

Recent losses and legal offences are found to be risk factors, and may be stressors that can trigger a depressive episode or depressive symptoms assessed in paper 3 and 4.

### 1.6.3 Suicide prevention during and after psychiatric hospital admissions

Psychiatric inpatients as well as recent discharged patients constitute an important group for suicide preventive strategies.

Key evidence-based elements for suicide prevention strategies in hospital are individualized approaches to reduce general symptom load, and an explicit focus on suicide risk assessment [132]. Underlying psychiatric disorders must be treated, including depression and substance abuse, as well as more general symptoms / problems like insomnia[132].

These recommendations are not specific for patients with depressive and psychotic symptoms, but form part of a transdiagnostic model of risk factors including low distress tolerance, emotion dysregulation, and hopelessness[132]. Targeted psychotherapy, e.g., dialectic behaviour therapy or cognitive behaviour therapy to increase affect tolerance, may reduce these risk factors and thus be suicide preventive [132].

Medication suggested to prevent suicide include lithium treatment [4, 133, 134], and antipsychotic augmentation [135] is suggested as suicide preventive when treating a depressive episode. Antidepressants [80] appear to reduce suicide ideation and suicidal behaviour, although results are equivocal as to whether they reduce suicide rates. Some research suggest that antidepressants increase suicide risk and aggression, especially for young and not very ill individuals undergoing initial treatment [136]. In addition, this is complemented

by research which has found that antidepressants may increase suicidal behaviour, not suicide rates, in a subgroup of patients with bipolar disorder [4]. Those aspects make antidepressants difficult to choose in the emergency department where patients already may have suicidal or aggressive behaviour, and diagnosis may be unclear.

Although studies have suggested sleep problems as one modifiable risk factor and warning sign for suicidal behaviour [107, 108], acute pharmacological management of sleep as a suicide prevention strategy remains under-investigated [137]. Sleep medication and anxiolytics are however recommended based on clinical correlates of inpatients suicide [105, 132]. Benzodiazepine reduction have been related to increased suicide risk [138], and one study recommend "aggressive" pharmacological treatment of severe anxiety symptoms [105]. International guidelines recommend benzodiazepines for a broad specter of acute psychiatric states, including psychoses and agitation with or without substance abuse [123], and benzodiazepines may have a place when patients are intoxicated and agitated [121]. Both antipsychotics and benzodiazepines are recommended to treat psychomotor agitation [139]. Recently, esketamin (Ketamine) is found to reduce suicidal ideation in treatment-resistant depression [140, 141]. It is however unclear to what extent these drugs reduce long-term risk of suicide.

Electroconvulsive therapy (ECT) may reduce suicidal ideation and intent in acutely depressed patients with mood and psychotic disorders [142], however this has not been studied with suicide as a primary outcome. Reducing access to lethal means also remains relevant both in outpatient and inpatient settings [80, 132].

Existing intervention studies thus often have inadequate sample sizes and/or insufficient duration [143], and in turn suffer from limited ability to detect any effects of interventions intended to reduce suicides. There is a risk that treatment effects may thus have been overlooked (i.e., type 2 error).

As research has identified some medications as suicide preventive, thus lack of diagnoses and treatment of mood disorder may result in suicides that could have been preventable. Even though, the research base is weak regarding suicide prevention strategies for patients with psychotic

depression in hospital, largely due to methodological difficulties. We need a deeper understanding why interventions may work in a psychotic phase.

### 1.6.4 Patient experiences of suicide prevention strategies

During suicide risk assessments in clinical settings, results of controlled experiments cannot form the sole basis for clinical decision-making or guidelines for treatment. People are complicated, unique and sentient beings, and it is highly unlikely that we behave in a linear cause-and-effect way. A review of qualitative studies of how people live with or get over being suicidal [144] identified five themes: the experience of suffering, struggle, connection, turning points and of coping. However, the reviewed papers did not focus on interventions during hospital stays. Mechanisms and processes facilitating general recovery from a psychotic episode have been studied by qualitative, explorative methods [145, 146]. However, the potential impact of improvement in psychotic symptoms on suicidal behaviour remains underexplored.

There is a lack of studies exploring what patients subjectively find to be meaningful suicide prevention strategies during inpatient treatment. One qualitative study examining inpatient care experiences of recovering from suicidal crises in a mixed diagnostic sample found three overall themes: « (1) being recognized as suicidal, (2) receiving tailor-made treatment and (3) being protected by adaptive practice». Informants also described struggling to communicate suicidal ideations[147]. The same authors conducted a systematic literature review and concluded by calling for further exploration of experiences of suicidal patients from specific diagnostic groups, suggesting in particular to study patients with psychotic symptoms [148]. We have however not been unable to identify any studies heeding this call.

We have limited understanding of patient experiences during a psychotic episode and know even less of whether they experience suicide prevention strategies in hospital as helpful.

### 1.6.5 Security measures

Restriction to lethal means (e.g. pesticides, firearms, certain medications) is evidence based suicide prevention strategy [80], also recommended by WHO[6]. These general recommendations are especially relevant if the patient is going on leave or after discharge.

Providing a safe environment forms an important part of psychiatric ward interventions, including providing help to rebuild basic routines including sleep-wake cycles, set mealtimes, exercising and socializing. Safety also includes building an environment designed to preclude suicide attempts. The most frequent suicide method on psychiatric ward is by hanging/strangulation [42]. In a qualitative study interviewing suicide survivors, participants described selecting this method due to anticipating a certain, rapid and painless death with little awareness of dying. They were able to use easily accessed materials and there was little need for planning and technological knowledge [149]. Removal of ligature points from wards [150], and checklists to remove suicide hazards from inpatient mental health units [151] is found to reduce suicide rates. Suicide prevention strategies in hospital also include locked doors for security reasons, partly to reduce risk of absconding. Nevertheless, evidence regarding if locked doors is suicide preventive, is diverging [152, 153]. A review of qualitative studies evaluating patients and staff experiences of locked doors in acute inpatient psychiatry reported both advantages and disadvantages of locked doors [152]. However, the effect of psychosis on the experience of locked doors was not explored in the review.

## 1.7 Summarizing background

We desperately need more knowledge on how to prioritize inpatient admissions, how to enhance patient safety during admission and on post-discharge follow-up in order to saves lives. This has lead us in this PhD project to study high-risk groups of acute admitted inpatients and recently discharged patients with a special focus on depression, depressive symptoms and psychosis.

# 2 Aims

This PhD project's overall aim is to identify associations between psychotic depression and suicide risk associated with hospital stays. We hope to increase our understanding of the relationship between psychotic depression and suicidal behaviour both by patient descriptions of subjective experience, and by calculations of the statistical association between psychotic symptoms and suicide risk in a prospective cohort study. Outcome was different, as the qualitative part examined suicidal behaviour related to psychotic experiences in living patients, and paper 3-and 4 both describe completed suicide as main outcome at follow-up.

Overall, we hope that this mixed methods study will provide clinical meaningful data relevant for future suicide risk assessments and suicide prevention strategies.

To achieve the main aim, the study consists of four objectives:

1. To investigate how severely depressed individuals understand and describe the relationship between psychotic symptoms, and suicidal ideation and behaviour
2. To investigate which factors individuals with a psychotic depression experience as preventive of suicide during hospitalization
3. To investigate the role of depression severity in suicide risk, by studying the predictive value of psychotic symptoms and depression scale scores, controlled for suicidal behaviour and gender
4. To prospectively investigate the predictive value of diagnosis, suicidal behaviour, and subjectively experienced depressed mood for imminent risk of suicide death

# 3 Methodology

## 3.1 Mixed methods design

Qualitative research aims are ideal in the early phases of a research project where the main goal is to increase our understanding and to develop descriptions, theoretical models or new hypotheses [154]. Quantitative research on the other hand, counts and classifies features, constructing statistical models and figures to explain the observed, resulting in accepting or rejecting hypotheses.

We chose mixed methods design primarily to explore a complex phenomenon; suicide and a severe clinical status; psychotic depression. In principle, quantitative tells us "If"; qualitative tells us "How or why", and we searched for both perspectives. In the qualitative part, we thus had a clear patient- oriented perspective.

In the quantitative part, data was assessments by clinicians and due to large sample size and statistics, possible to enhance generalizability of our findings. By this design, we sought to overcome some of the limitations associated with both qualitative and quantitative design when performed separately[154]. We used a sequential exploratory strategy, a commonly accepted mixed-methods design.

The collection and analysis of qualitative data (paper 1-2) was followed by the analysis of quantitative data (paper 3-4). Equal priorities were given to the two phases. A strength is the relatively straight forward research process due to clear, distinct stages.

The qualitative part started in 2011/2012. The cooperation with SIPEA


started in 2018 making it possible to test hypotheses generated from the qualitative part the PhD project.

We integrated data during the secondary analysis, thus defining this overall project a mixed methods design.

### 3.1.1 Paper 1 and 2: Qualitative designs

Qualitative research methods are strategies for systematic collection, organization, and interpretation of textual material obtained from talk or observation [154-156]. Smaller, but focused, samples are more often used than large samples. Qualitative researchers aim to gather in-depth understanding of human behaviour and reasons that govern such behaviour. Qualitative research searches for subjective aspects and findings may contain ambiguity, ambivalence and contradictions. Philosopher Gadamer however describes medicine not only as a "science of health", but as an "art" of hermeneutic relevance, requiring the exercise of practical judgment and personal interpretation [157]. In suicide research, this means that qualitative research is crucial, in that it gives us an opportunity to gain an in-depth understanding of the patient's self-understanding and subjectively experienced factors triggering suicidal behaviour, and can contain any paradoxes and contradictions arising between individual accounts. Clinical descriptions, concepts or theoretical models may then evolve from this understanding.

Qualitative analysis was performed using systematic text condensation. This method aims for a thematic analysis across individual participant cases, and is suitable to develop knowledge about individuals' perspectives and symptom descriptions in medical research [158]. An inductive analysis was performed, with categories developed from the empirical data [159]. Data collection was by purposive sampling[160].

### 3.1.2 Paper 3 and 4: Quantitative designs

Hypotheses generated from the qualitative study:

1. Psychotic symptoms during a depressive episode predict suicide
2. Suicide ideation/plans are not a good predictor of suicide, as they are underreported by patients

Justification for choice of methods:

We chose a prospective cohort design to test our hypotheses. This design enables us to identify risk factors for suicide, not only associations which e.g., cross-sectional studies can provide. Prospective cohort are also being less prone to bias [161]. The living patients at follow up represent a statistical control group for the patients dead by suicide. To use a large representative sample from a catchment area, result is easy generalizable to other acute hospital settings where patients are not included and excluded based on criteria as economy, diagnosis and suicidal behavior.

Our goal was to identify significant predictors to suicide, using cox regression models. We aimed to identify short-term risk factors relevant for do meaningful suicide risk assessments, and prioritizing treatment.

Regarding psychotic depression, research was especially weak regarding short-term suicide risk, and the relation between this mental state and the patients self-report of suicidal ideation and plans. In general, for a mixed diagnostic sample, we didn`t have any clinical data from prospective studies of what predicted suicide first 1-2 weeks following acute admission. These research questions regarding clinical predictors of suicide with imminent and short-time follow-up can be examined by this prospective design and with a database with more clinical data than most register studies.

To address gaps in the research field, we meet this by combining a relative large sample size, longitudinal follow-up, population representativeness, and clinical assessment in the emergency rooms in line with recommendations by Bolton [62].

## 3.2 Overall setting in the Norwegian mental health care

Suicide rates in Norway have remained relative stable last ten years, constituting among 600 suicides every year, and 2/3 victims men [162].

The Norwegian psychiatric health care system is catchment area based and publicly funded independent of social background and status. There are no privately run acute inpatient facilities. A central principle for specialized

psychiatric health care in Norway is that patients are to receive treatment at the lowest effective level of care. Accordingly, patients who are admitted to psychiatric acute wards with locked doors represent a selected group, being characterized by a severe clinical condition, typically with the need of acute treatment and protection.

## 3.2.1 Research setting for paper 1 and 2

We recruited patients from a Norwegian university psychiatric hospital between September 2012 and May 2013 covering a population of 350 000 inhabitants. Acute admitted patients are first admitted to an acute ward, and the acute psychiatric ward were managing over 2500 admissions a year.

### 3.2.1.1 Participants

Inclusion process: Health care professionals on the acute ward reported potential participants to KJF. Participants were enrolled on the ward by KJF during their first week of hospital admission if they consented to. A purposive sample was sought out, aiming for diversity in age, gender, type of psychotic symptoms and religious affiliation. We suspected different pathways to suicidal behaviour especially depending on psychotic symptoms, gender and age. Several potential participants were not recruited based on their gender and age, as it was easier to recruit women and younger patients. We recruited nine individuals aged 19-55 years. We used quotations named with pseudonyms and by not specifying the name of the hospital for confidential reasons due to small sample.

Inclusion criteria: A major depressive episode with psychotic symptoms which fulfilled the diagnostic criteria of either a unipolar or bipolar disorder according to the DSM-IV, Text Revision [163, 164]. Participants were also required to be fluent in Norwegian. Exclusion criteria: Diagnoses of a primary psychotic disorder (F20-29 in ICD-10), IQ below 70.

### 3.2.1.2 Assessments and data collection

I have collected demographics and course of illness variables. For diagnostics, the Structured Clinical Interview for DSM-IV Axis I Disorders

(SCID-I) [164] was administered to participants by experienced research personnel trained at TIPS during the hospital stay. Psychotic symptoms were assessed and verified using the Positive and Negative Syndrome Scale (PANSS)[165] first week of hospital stay. Good interrater reliability for SCID-I and PANSS has been achieved within the research group [166].

When each participant was approaching his or her time of discharge, I conducted a semi-structured interview. The interview guide contained open-ended questions such as "What do you think triggered your thoughts and plans about dying?" and "What kind of feelings accompanied these unusual experiences?", "What was the turning point? Was it relief of psychotic symptoms or other factors?" and "How did your perception of yourself change?" The interview guide was revised after two pilot interviews to omit the word "suicide", as participants did not always see their life-threatening situations in the psychotic episode as a suicide attempt.

However, the complexity was rich, and not all perspectives under each category could be described in detail. Analytic themes were discussed in the group throughout the analytic process by the research team to ensure feedback and credibility of the themes.

Data were collected in a stepwise manner in paper 1, in order to adjust the interview guide and research focus according to what emerges as main important experiences by the informants. The interview guide was revised after two pilot interviews. The word "suicide" was omitted as it appeared not to comprehensively cover the nature of the life threatening situations participants reported finding themselves in. First two interviews collected and analyzed, followed by a new data collection and analysis of three interviews. The four last interviews did not alter our category classification.

The sample size was assessed to be adequate due to rich data to answer the research question. We had a narrow aim, dense specificity and a strong dialogue, and at the point of nine analyzed interviews, the developed categories were large and rich enough for thorough description of the experiences investigated.

The concept of "information power" [160] is more specific than the often used term "saturation" to describe characteristics of a sufficient data material in

qualitative research. In study two, all nine interviews were conducted before starting the analytic process. Information power was assessed to be achieved also here [160].

#### 3.2.1.3 Qualitative analysis

Before the initial coding of two interviews in paper 1. Helle Schøyen, Margrethe Aase Schaufel and I separately read the interview transcripts and met to identify themes together. Analysis proceeded through the following stages: (1) reading all of the material to obtain an overall impression, bracketing preconceptions; (2) identifying and coding units of meaning representing different aspects of the participants' psychotic experiences which were linked to suicidal behaviour; (3) abstracting and condensing meaning within each of the coded groups; and finally (4) summarizing to generalized descriptions and contents the material within each code group, to reflect the most important psychotic experiences relevant to suicidal behaviour as reported by the participants. .

In paper 2, we didn`t have a stepwise data collection and analysis, all interviews were analyzed together. We therefore could not examine in more detail perspectives that should have been illuminated more. Themes and development of categories were anyhow discussed in the team.

The original aim of this project is to explore patients' subjective experiences of hospitalization and treatment, and whether and how psychotic symptoms influenced their suicidal behaviour.

During analysis we found the aims were too wide, and the information rich. We then split the aim into two sub aims.

##### 3.2.1.3.1 Paper 1

We looked at the research question "Do depressed patients experience that psychotic symptoms influence their suicidality, and in case how?"

We conducted a stepwise analysis. The themes "directed" and "chased" were identified as a category from the first two interviews. The themes "trapped" and "deprived mental control" developed gradually throughout three successive interviews in the second analytic round.

The phenomenon of being "trapped" was first identified as a broad theme and described how patients were victims of the psychotic processes. Psychosis appeared as chaotic experiences affecting both thoughts, emotions and life situation. These descriptions were included both delusions, chaotic and irrational thoughts. Throughout the analytic process to develop categories, it was difficult to categorize those all-consuming experiences of entrapment and relation to suicidal behaviour. The "deprived of mental control"- category emerged when we divided the delusions from other thought disturbances affecting suicidal behaviour. In the "trapped" category, we still placed thoughts about death were influenced by depressive delusions and an experience of self-loss. The trapped category described more planned deaths, even though justifications based on delusions. The "deprived of mental control" category was included descriptions of thought disturbances leading to impulsive behaviour. Patients described being an "action mode" without anticipate potential consequences was a different phenomenon than being influenced by delusions. In addition, description why patients were underreporting both psychotic experiences and suicidal behaviour was better coded in "deprived mental control".

Even though, we had to accept that the content of our four categories clearly overlapped. One example is being "directed" by command hallucinations also describe phenomena of being left bereft of mental control. The four last interviews didn`t alter our category classification.

Figure 1 illustrates keywords during the development of categories, as well as the non-linearity of the analytic process. Codes are malleable and vary in the course of analysis. Analysis was performed stepwise, with new individual interviews supplementing the sample. Categories and findings were developed from the empirical data using editing analysis style.

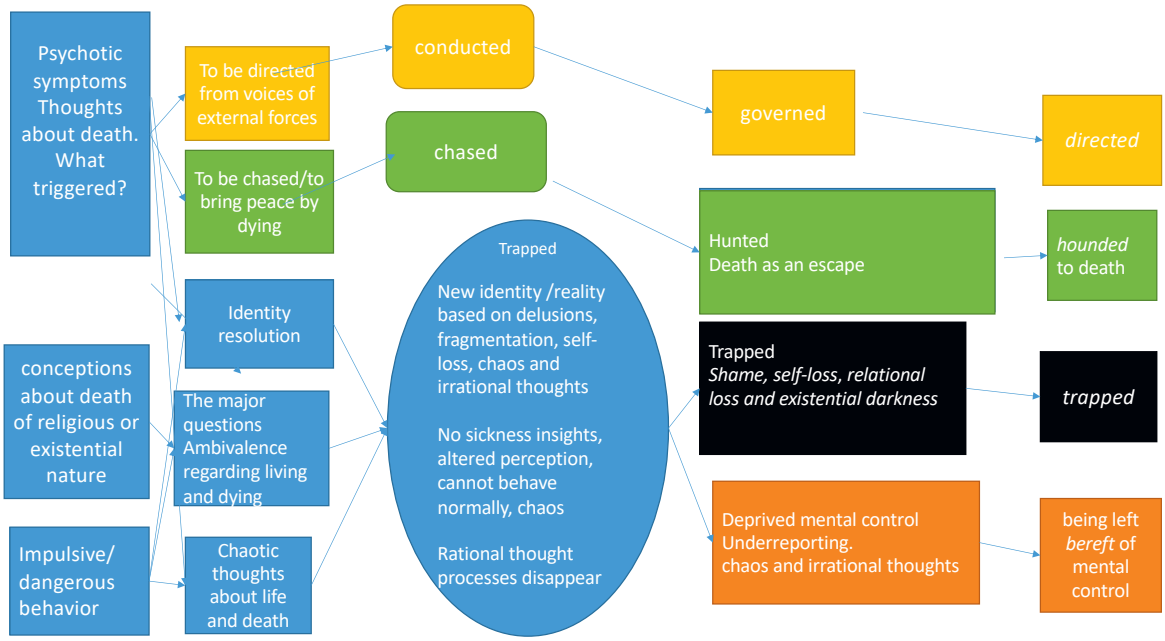


Figure 1 Overview of analysis in paper 1.

#### 3.2.1.3.2 Paper 2

In paper 2, we did not conduct a stepwise analysis. All interviews were analysed altogether. The analytic process took place over 4 years with low intensity and time spent on this project, and further 2 years before publication. It was complicated to categorize effect on suicidal behaviour regarding multiple interventions during hospital stay. Patients did not always say direct which intervention worked, and KJF not actively asked specifically about experiences regarding various interventions.

The original research question was: “What was the turning point?” meaning what contributed to turn the suicidal behaviour. Existing qualitative studies regarding psychotic depressed inpatients were totally lacking. We wanted to focus on a defined mental state, on symptoms and interventions during hospital stay.

Our preunderstanding was the importance of security measures on the ward, but also to take control in chaos by multiple treatment interventions. Our research question was narrowed to try to focus on treatment interventions during hospital stay. That included interventions that relieved symptom load, and to physical barriers that stopped or abrupt suicide attempts.

During the process, we found it difficult to distinguish interventions relieving psychotic symptoms from other suicide prevention strategies. We did not examine specific treatment interventions but allowed participants to talk freely about factors they experienced as having an impact. The themes of “protection” and “finding a hiding place” appeared early in the analytical process, while how to code and differentiate the non-medical aspects and medical treatment gradually developed throughout the analytic process. In the start of the analytic process, we had the theme “regained mental control”, that constituted experiences of both non-medical and medical interventions. At that point, we did not find it necessary to describe the interventions, but rather categorize in themes how several different interventions turned suicidal behaviour/relieved symptoms.

During the analytical process, we revised the research question to: How do psychotic depressed patients experience recovery of suicidal behaviour during inpatients treatment? The aim was to investigate the prevention of suicide in individuals with psychotic depression, based on their experience of acute hospitalization.

KJF and HKS found the medication findings of importance, and MAS emphasized empathy and talk. Discussing what this paper adds to existing knowledge, it was not previously described experiences of acute psychopharmacological treatment in hospital for patients diagnosed with psychotic depression. Although it may seem obvious, patient’s experiences of acute treatment and relation to suicide prevention add knowledge to the

field. We narrowed our focus on treatment in hospital, and not i.e., the importance of support from family members during hospital stay.

The research question was defined as "To explore whether and how hospitalization in the acute psychotic phase reduces suicidal behaviour."

Figure 2 illustrates keywords during the development of categories, as well as the non-linearity of the analytic process. Codes are malleable and vary in the course of analysis.

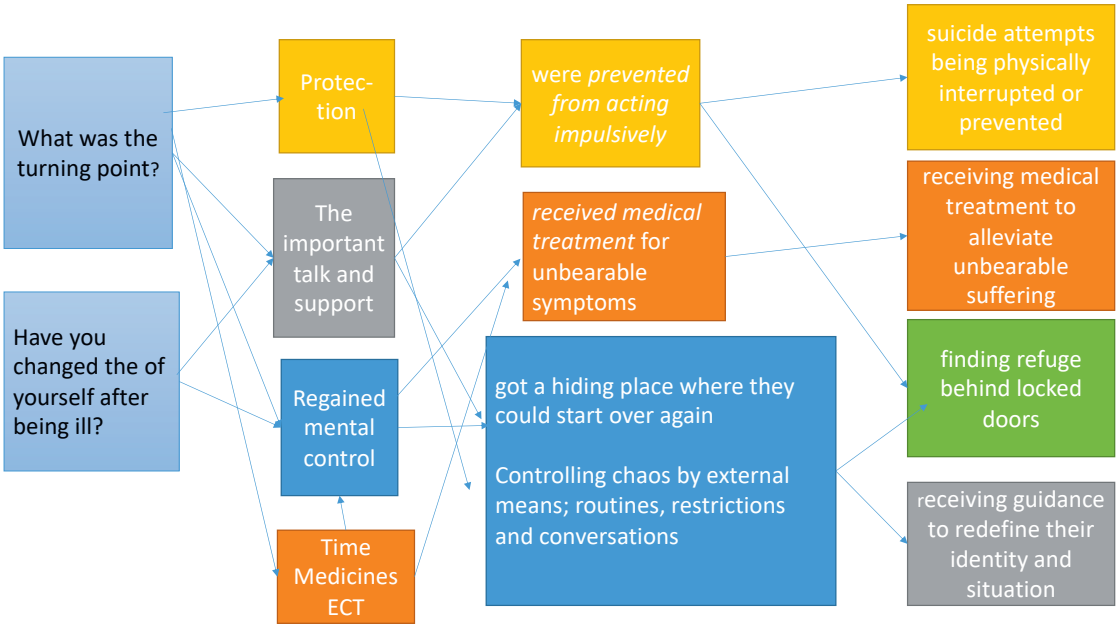


Figure 2. Overview of analysis in paper 2.

### 3.2.2 Research setting for paper 3 and 4

This work was part of the prospective cohort study Suicidality in Psychiatric Emergency Admissions (SIPEA) run by the Department of Psychiatry,

Haukeland University Hospital, Norway. The study cohort consisted of 7000 unique patients, and 18.000 admissions consecutively admitted to the Psychiatric Emergency Department at Haukeland University Hospital from May 2005 to June 2014 [52, 63, 167]. Haukeland University Hospital covers a population of approximately 400,000. The work resulted in paper 3 and 4.

## 3.2.3 Participants

In paper 3, patients were included from the SIPEA cohort if they fulfilled the ICD-10 criteria for a depressive episode as part of unipolar or bipolar disorder as a primary or secondary diagnosis. Patients with a primary or secondary diagnosis of F20–29 (Schizophrenia, schizotypal and delusional disorders), and patients with a diagnosis of F31.8 (Other bipolar disorders), which does not include a psychosis sub-specifier, were excluded from the study. In total, 1846 patients were included. In paper 4, we included a mixed diagnostic sample of 7000 patients. 38.5% were sectioned, i.e., admitted involuntarily.

### 3.2.3.1 Assessments

All raters, both clinicians and trained research assistants, were part of the staff at the hospital where the participants were admitted. They collected and coded demographic and clinical data on admission as a routine clinical evaluation. After admission and assessments in the acute ward, patients were then either moved to other hospital ward or discharged. All data used in paper 3 and 4 were collected in the acute ward.

In cases with several admissions during the study period, we used data from the most recent admission.

#### 3.2.3.1.1 Demographics

Clinicians and trained research assistants collected and coded demographic and clinical data.

#### 3.2.3.1.2 Diagnoses

In the acute admissions ward, psychiatrists, residents under supervision or clinical psychologists assess for clinical ICD-10 diagnoses and further treatment needs.

According to ICD-10[13], core symptoms of a unipolar depressive episode is depressed mood, loss of interest or pleasure and decreased energy. Accompanying symptoms are loss of confidence and self-esteem, self-reproach /inappropriate guilt, thoughts of death or suicide, diminished ability to think/concentrate, agitation or retardation, sleep disturbance of any type and change in appetite. Severe unipolar depression includes 3 core symptoms and minimum 5 accompanying symptoms. Duration at least 2 weeks, no underlying organic cause and no previous episodes of hypomania, mania or mixed symptoms. Severe depression with psychotic features (F32.3 & F33.3) meets criteria for severe unipolar depression, include presence of delusions and/or hallucinations and/or stupor, and does not meet criteria for schizophrenia /schizoaffective disorder. In a severe depressive episode with psychotic symptoms as part of a bipolar disorder (F31.5), similar diagnostic criteria for a depressive episode with psychotic symptoms as in unipolar depressive episode must be fulfilled (F32.3). In addition, diagnostic criteria include one or more episodes lifetime with mania or hypomania.

We have chosen to compile uni- and bipolar patients in the same statistical analyses, as severity criteria for a depressive episode including criteria for a depressive episode with psychotic symptoms is coincident for both uni- and bipolar disorders.

Patients with a diagnosis of F31.8 (Other bipolar disorders) were excluded from paper 3, and not included in the group of patients diagnosed with depression in paper 4 (appendix). This is because the ICD-10 diagnosis does not include a specifier whether the current episode was a hypomania or a depression, and not include a psychosis sub-specifier.

#### 3.2.3.1.3 Suicidal behaviour

Clinicians made qualitative assessments of current suicidal behaviour over the past seven days, using a standardized rating form in which only one of

the following items (the most severe) could be rated positive: no suicidal ideation, passive death wishes, suicidal ideation, suicide plans made, self-harm without suicidal intent, and suicide attempt. Suicide attempt would be considered the most severe, and no suicidal ideation would be considered the least severe. In this study, we use the following definition of self-harm in SIPEA: Self-harm without suicidal intent, excluding intention to die. This commonly involves self-poisoning with medication or self-injury by cutting. All available information was used to code this variable, including the patient's self-report, information from referring physicians, and information from any known somatic hospital admissions for suicide attempts or self-harm.

#### 3.2.3.1.4 Montgomery–Åsberg Depression Rating Scale

Intake clinicians rated symptom severity using the Montgomery–Åsberg Depression Rating Scale (MADRS), which consists of 10 items rated for severity on a Likert ordinal ranging from 0 to 6. The scale is an adaption of the Hamilton Depression Rating scale and has a greater sensitivity to change over time (APA). The total score may be seen as indicating mild (12–20), moderate (21–29), or severe depression (≥ 30). The observation time for the MADRS was the previous 72 hours. MADRS is extensively used worldwide in clinical research to assess severity of depression and have good reliability and validity [168-170].

#### 3.2.3.1.5 Health of the Nation Outcome Scales (HoNOS)

Mental health status were assessed using the Health of the Nation Outcome Scales (HoNOS) [171], a scale widely used in clinical practice and research for over 20-years [172]. A review of psychometric properties found the instruments' validity to be good, and the reliability adequate [173].

This scale covers mental health status and social functioning and was administered by clinicians on the admission day. It consists of 12 items (scales), recording information about the last 14 days including admission day: Aggression, Self-harm, Drug or alcohol use, Cognitive problems, Physical illness and disability, Hallucinations and delusions, Depression, Other mental and behavioural problems, Problems with relationships, Problems with

activities of daily living, Problems with living conditions, and Problems with occupation and activities.

Each item/scale is scored on a five-point scale representing maximum severity over the rating period (0=no problem; 1=minor problem requiring no action; 2=mild problem but definitely present; 3=moderately severe problem; 4=severe to very severe problem). Health of the Nation Outcome Scales item 7 "problems with depressed mood" was used as a measure of affective state, and a cut-off score of 3 was chosen to indicate "severely depressed mood". These scores are [174]: Score 3 Depression with inappropriate self-blame; preoccupation with feelings of guilt, and Score 4 Severe or very severe depression, with guilt or self-accusation. Symptoms are rated at scale 7 irrespective of diagnosis. Rating instructions focus on the cognitive, affective or behavioural aspects of depressed mood (e.g., loss of interest or pleasure; lack of energy; loss of self-esteem; feelings of guilt).

HoNOS item 7 has been evaluated in one German study investigating 132 adults with depressive disorder, finding that HoNOS differentiated significantly between patients with moderate versus severe depression at baseline ($p<0,05$) [175].

#### 3.2.3.2 Statistical Analyses

##### 3.2.3.2.1 Outcome

We obtained suicide data by linking each patient's 11-digit birth number to the Norwegian Cause of Death Registry (CDR) up to December 31, 2015, representing a mean follow-up time of 5.5 years. The CDR contains information about Norwegian residents death, both in Norway and abroad, and has a completeness rate of > 98% [176].

Suicide was primary outcome for both paper 3 and 4. At follow up in Dec 2015, median 5.5 years, 988 patients (14%) were dead, all causes, including 152 patients (2.2%) dead by suicide (unpublished). At one-year follow up, 101 patients were dead by suicide (paper 4, in review).

#### 3.2.3.2.2 Paper 3

As a rule of thumb, the number of outcome events per predictor variable should be 10 or more in Cox regression models [177]. We used 6 predictor variables in the main analysis, and the number of outcome events (deaths) was 48. This resulted in 8 deaths per variable, which is not ideal from a statistical point of view. However, Vittinghoff et al. [177] concluded that 5–9 outcome events per variable are usually sufficient. Cox regression analyses were used to investigate six predictor variables (depression with psychosis vs. non-psychotic depression, reporting suicide ideation/plan, non-suicidal self-harm, suicide attempt, men vs. women, and MADRS sum score). There were included in the first step based on a priori hypotheses. In a second step the variable measuring passive death wishes was entered. This failed to statistically significantly improve the model, thus we the results from the first step are reported. Correlation analyses of predictor variables indicated that multicollinearity was not present. In a sub-analysis including only patients diagnosed with a severe depressive episode as part of a unipolar or bipolar disorder, we used the Kaplan-Meier Wilcoxon test to compare those with psychosis to those without psychosis.

All tests were two-tailed and a P-value < .05 was considered statistically significant. SPSS software (v. 24; IBM SPSS, Armonk, NY, USA) was used in all analyses.

#### 3.2.3.2.3 Paper 4

Descriptive analyses were used to describe clinical and demographic characteristics of the participants at admission. SI and SA were categorical variables: present or not. 4175/7000 had score 0 on both variables. Time to suicide was analysed with the Kaplan–Meier method to provide survival probability within the first year following admission. We censored patients if they died of other reasons than suicide. Cox Regression Models (missing data on 177 subjects; N= 6823) were fitted with time to suicide as outcome. There is no consensus regarding a definition of “Imminent” suicide risk. We defined one-week follow up as imminent, and up to 1 year as short-term timeframe.

Predictors chosen were based on hypotheses from our qualitative study and clinical experience that near-delusions would predict imminent suicide risk,

and reported suicidal ideation would not. In addition, in line with the Suicidal crisis syndrome model, we assumed high depressive symptom severity to predict imminent suicide risk. Predictors in the first model were a diagnosis of depressive disorder within the F30-39 chapter of the ICD-10 (see appendix), suicidal ideation and attempts. Because of the low base rate of the outcome variable (completed suicide, i.e., 10 suicides after 7 days), the number of predictors per model had to be limited to three. The second model included the predictor from our second research aim; severely depressed mood, suicide ideation and attempt. A diagnosis of depressive disorder was excluded, as it did not contribute to model 1. To conclude we conducted a new Cox regression with only diagnosis of depression and Health of the Nation Outcome Scales item 7 (model 3).

Analyses were repeated for the imminent (within one week) and short-term (two weeks, one month, six months and up to one year post admission) follow-ups. At the one-year follow up, we added gender as predictor variable. This was in order to adjust for gender, as male gender is a well-established risk factor for suicide during inpatient stay and shortly after discharge [9, 42, 56, 57, 64, 70]. All tests were two-tailed and a P-value < .05 was considered statistically significant. We used the statistical software R [178] for all analyses.

## 3.3 Secondary analysis

The objective in this PhD project was to examine the complexity of the overall research question of relationship of psychotic depression and suicide behaviour. The original data consisted of three samples (1 sample with two sub-studies), and 2 different samples from the same prospective cohort study). We collected main thematic findings from all four studies with a mixed methods approach.

I used some elements from “Integrative review” to synthesize both qualitative and quantitative findings [179]. The four categories were constructed by finding common themes and subthemes across all four sub-studies.

Table 1 Overview of samples in the secondary analysis

| **Sample** | **1 (Paper 1 and 2)** | **2 (Paper 3)** | **3 (Paper 3)** |
|---|---|---|---|
| Unit of analysis | Patient experience | Clinical assessment and registration | |
| Participants | 9 patients | 1846 patients | 7000 patients |
| Data collection methods | - Individual interviews<br>- Demographics<br>- SCID-1<br>- PANSS | - Demographic variables (education level, income, marital status, housing, gender, age)<br>- Assessment of suicidal behaviour<br>- Linkage to the Cause of Death Registry<br>- ICD-10 diagnosis | |
| | | MADRS | HoNOS |

Importantly, paper 1 and 2 draw upon the perspectives of patients' experiences, and paper 3-and 4 incorporate clinical data from a prospective cohort study. Outcome was different, as the qualitative part examined suicidal behaviour related to psychotic experiences in living patients, whereas paper 3-and 4 have completed suicide as main outcome at follow-up.

# 4 Ethics

## 4.1 Research as an ethical imperative and an ethical problem

Despite the body of research published on psychotic depression, depression and suicide risk in the last decade, no findings have been ground-breaking in the sense of effecting changed practices in emergency rooms, psychiatric inpatient treatment, or meaningfully reduced suicide rates for this group. How to identify potential victims and prevent suicide is of clear importance. However, suicide research including suicidal inpatients poses multiple philosophical and ethical questions and dilemmas. Ethical challenges have resulted in a reluctance among some researchers to engage directly with patients who may be suicidal [180, 181] with suicidal patients often excluded e.g. from clinical intervention studies [47]. Intervention studies about suicide prevention for patients with depressive psychosis are thus doubly difficult, for both ethical and practical reasons [86, 182, 183]. In suicide-specific clinical trials, psychotic patients are often excluded [86].

One reason that persons at high risk for suicide are excluded from treatment or intervention trials is that the use of “placebo”, waitlist, or minimal-care groups is ethically problematic given the potential risk that a person might complete suicide. Furthermore, determining the competency of suicidal people to provide informed consent to participation in research is problematic.

Although basic moral principles in medical ethics including respect for autonomy, non-maleficence, beneficence, and justice [184] is difficult to fully comply with when planning research projects involving participants with elevated risk of suicide. Our qualitative study was approved by the Regional Committee for Medical Research Ethics, West Norway (number 2012/740). Even though, the study arises many ethical questions of autonomy and written informed consent in patients with psychotic depression and doing in-depths interviews on a vulnerable patient group.

However, this is a case where moral good principles to protect participants may become the enemy of the good, because this might mean that some

groups i.e., diagnosed with psychosis do not get investigated at all. Basic moral principles may conflict with each other, and we need to weigh them against each other. Our quantitative study raised i.e., questions if it is ethically justifiable to conduct research without informed consent.

## 4.2 Ethical positions and narrative ethics

Normative ethics examines standards for the rightness and wrongness of actions. In the case of psychiatry assuming that we should base our decisions on medical moral principles like respect for autonomy, non-maleficence, beneficence, and justice[184]. However, I will limit this current discussion to describing the key aspects of consequentialism and narrative ethics.

Consequentialism is a normative, ethical theory describing that a morally right action is one that produces a good outcome. Consequences of an action can outweigh other considerations[184]. The goal is the "greatest good for the greatest number" or avoid misfortune for as many people as possible (negative utilitarianism). With a consequence-ethical justification for recruiting a representative sample of inpatients, we hope to provide clinical meaningful data relevant for future prevention strategies.

Narrative ethics is an approach that focuses on personal identity through the life story of the individual, assuming that "Humans are narrative beings who make sense of themselves, others, and the world in and through narrative" [185]. In suicide research, this supports the necessity of applying qualitative research to gather in-depth understanding of the patient's self-understanding and factors triggering suicidal behaviour, as every patient have their unique story.

# 5 Results

## 5.1 Paper 1: Psychotic depression and suicidal behaviour [186]

The aim was to investigate how severely depressed individuals experienced the relationship between psychotic symptoms and suicidal ideation and behaviour. Main outcomes were accounts of participants' psychotic experiences related to suicidal ideation, plans and attempts.

Four main themes described their experiences during the acute, psychotic phase. Participants experienced 1) being directed to perform impulsive potentially fatal actions, 2) feeling hounded to death, 3) becoming trapped in an inescapable darkness, and 4) being left bereft of mental control. They described how impulsivity directed by delusions and hallucinations resulted in unpredictable actions with only moments from decision to conduct. This paper demonstrated that individuals with severe depression might view suicide both as a strategy to escape from and as a consequence of psychotic experiences. Suicide was seen as an escape not only from life problems, but also from psychotic experiences and intense anxiety. Participants reported being in a chaotic state, unable to think rationally or anticipate the consequences of their actions. Their ability to identify and communicate psychotic symptoms and suicidal ideation and behaviour was compromised, leaving them to struggle alone with these terrifying experiences. Participants experienced intense shame due to mood-congruent delusions, in combination with negatively grandiose delusions about their impact on those around them. The accompanying anxiety linked to potential exposure of this shame, or delusions of being exposed, was associated with withdrawal and avoidance rather than with communication and help-seeking behaviour.

The findings imply that psychotic experiences override mental control. Impulsive suicidal behaviour and under communication towards health-personnel illustrate why suicide risk assessments is challenging. Shame and paranoid ideas towards hospital staff are possible hindrances for self-report.

## 5.2 Paper 2: Preventing suicide among psychiatric inpatients with psychotic depression [187]

This paper involves the same interview material as in paper 1. The aim was to investigate which factors individuals with a psychotic depression experience as preventive of suicide while being hospitalized. Four main themes emerged in accounts of participants' experiences of suicide prevention measures and treatment, and how these affected suicidal ideation, plans, and attempts. Participants experienced (1) suicide attempts being physically interrupted or prevented; (2) receiving medical treatment to alleviate unbearable suffering; (3) finding refuge behind locked doors; (4) receiving guidance to redefine their identity and situation. At time of discharge, participants reported no psychotically motivated suicidal thoughts. They described a new, insightful self-view and acknowledged having been severely mentally ill. Empathic and caring attitudes in hospital staff are crucial in order to gain patients' trust and for patients to accept help. Patients emphasize that having time to talk is crucial to this process.

Participants in our study described psychosis as stripping them of their autonomy for as long as it lasted, leaving them unable to make rational choices or take care of their own basic needs.

This study demonstrates how several individuals hospitalized for psychotic depression experienced pharmacological management of anxiety, psychosis and insomnia, ward security measures and time to talk as necessary to prevent suicidal behaviour in an acute, psychotic phase. These interventions helped alleviate their intense suffering as well as reducing suicidal ideation and behaviour.

## 5.3 Paper 3: High scores on the MADRS depression rating scale and psychotic symptoms predict suicide: -A prospective cohort study of psychiatric acute ward patients [64]

In this paper, we wanted to investigate the role of depression severity in suicide risk, by studying the predictive value of psychotic symptoms and depression scale scores, controlled for suicidal behaviour and gender.

Data was collected from the prospective cohort study SIPEA (Suicidality in Psychiatric Emergency Admissions). Inclusion criteria were an ICD-10 diagnosis of unipolar or bipolar depression with a current depressive episode (N= 1846), with depression severity measured by the Montgomery–Åsberg Depression Rating Scale. Patients were assessed for suicidal ideation/planning, self-harm, and recent suicide attempts on admission. 46 patients died by suicide during the follow-up period, 30 (65%) within the year following admission. Psychotic depression (P = .014), admission Montgomery–Åsberg Depression Rating Scale score (P = .006), suicide attempts (P = .021), and male gender (P = .043) significantly predicted suicide. Suicidal ideation and self-harm did not predict suicide. The cumulative suicide risk in psychotic depression was 1.7% after 12 weeks, and 3.0% after 52 weeks.

We revealed a dose-response effect of baseline ICD-10 severity criteria for depression on risk of suicide: Mild to moderate depression entailed 1.7% suicide risk. A severe depressive episode was associated with 3.3% risk, while a severe depressive episode with psychosis had a higher risk of 4.7%. We found no significant differences in suicide risk between unipolar and bipolar groups (P = .77). Admission Montgomery–Åsberg Depression Rating Scale score predicted suicide (P = .006). We compared MADRS sum scores between patients who died by suicide to the scores of those who did not. Group level sum scores differed significantly groups (P = .003), with the baseline mean sum score of suicide victims exceeding that of suicide survivors by nearly 4 points in the sample.

## 5.4 Paper 4: Imminent and very short-term risk of death by suicide in 7000 acutely admitted psychiatric inpatients [188]

The aim of this study was to identify factors conveying imminent suicide risk in acutely admitted inpatients. We conducted a naturalistic prospective cohort study covering consecutive psychiatric acute ward admissions between 2005 and 2014 from a Norwegian catchment area. In total, 7000 patients were included.

Data indicated that severely depressed mood was the only significant predictor the following first week after admission in analyses including a diagnosis of depressive disorder, suicidal ideation or recent suicide attempt.

A diagnosis of depressive disorder, including both mild, moderate and severe depressive episodes, did not indicate increased neither imminent nor longer-term risk of suicide.

Suicidal ideation predicted suicide throughout the follow-up period; however, when adjusted for severely depressed mood, it did not predict suicide within the first week. Suicide attempts the last week prior admission predicted suicide at, and after, one month when adjusted for severely depressed mood.

After one year, 101 (1.44%) participants had died by suicide. Almost 70% decedents were men.

We believe that these results may have clinical implications for guiding decision-making in the assessment and treatment of imminent suicide risk. We argue that suicide risk assessments in acute settings should be based on clinical examination rather than interview-based assessments of suicidal behaviour.

## 5.5 Synthesizing the main findings across sub-studies

Through synthesizing the perspectives of patients' experiences with findings from the prospective study based on assessments of clinicians, four main themes emerged.

Summary: Psychosis and intense affective states increase suicide risk in both an immediate, short-term and long-term time frame. Patients self-report of suicidal behaviour has neither in qualitative nor in quantitative studies been easy to rely on when assessing suicide risk. Findings suggest a psychosis- and depression focused treatment approach to prevent suicide both during hospitalization and after discharge.

The table below gives an overview of the synthesis with common themes and respective paper findings.

Table 2 Overview of the synthesis

| Main theme | Psychosis and intense affective states increase suicide risk in both immediate, short-term, and long-term | | | |
|---|---|---|---|---|
| Sub theme | Psychotic symptoms increase suicide risk | Intense affective states increase suicide risk | Self-report of suicidal ideation is not a good measure of imminent, short- or long-term suicide risk | Psychosis- and depression focused treatment approach to prevent suicide |
| Patients' perspective Paper 1 and 2 | Psychotic experiences override mental control<br><br>Autonomy compromised by intense suffering and chaos, impulsive behaviour. | Severe depressed symptoms, intense anxiety, entrapment, sleeplessness, shame, guilt, cognitive chaos,<br><br>Remission of psychotic symptoms reduced suicidal behaviour | Suicidal behaviour was underreported | Medical treatment, talk with staff and routines to regain mental control and reduce symptom load |
| Statistical analyses Paper 3 | Psychotic depression significant predict suicide. | Psychotic depression has increased suicide risk after 1- and 4-weeks follow-up | Suicidal ideation does not predict suicide for the whole depression group Patients with psychotic depression are significantly less likely to report SI, however higher suicide rates. | Treatment approach focusing on modifying psychotic and severe depressive symptoms. |
| Statistical analyses Paper 4 | Severe depressive symptoms (including psychosis-like ideas of self-blame) predict imminent suicide | Severe depressive symptoms predict imminent suicide risk | Suicidal ideation doesn't predict imminent suicide risk | Severely depressed mood should be assessed and treated carefully |

# 6 Discussion of main findings

## 6.1 Psychotic symptoms increase suicide risk

Psychotic depression significantly predicted suicide (P = .014). Those with psychotic depression had a suicide risk of 1.7% after 3 months following admission, 3% at one-year follow up, and almost 5% after 5.5 years follow-up [64]. Our findings are in line with two existing reviews, which have already established that unipolar psychotic depression predicts long-term suicide risk[25, 90]. However, these reviews did not include any prospective or retrospectively defined time points/intervals to determine the imminent- or short-term suicide risk of psychotic depression and found very limited data for evaluating short-term suicide risk. Short-term suicide risk of psychotic depression was not either calculated in the huge prospective study by Aaltonen [68] The important new finding of the current thesis is that a higher proportion of patients with psychotic depression compared to non-psychotic died by suicide at every time-points following admission, including short-term (1, 4, 12 and 26 weeks) following admission. Our findings may thus inform clinical practice for inpatient treatment, with particular attention paid to this group, as well as how we prioritize outpatient treatment after discharge because of the high risk for relapse of psychosis in future depressive episodes [16].

The qualitative studies in this thesis also provide another conflicting hypothesis of short-term risk: The statistical association between psychotic depression and suicide risk may be even stronger than it appears, given that participants reported significant difficulties in acknowledging, interpreting, and talking about psychotic experiences when they occurred. Underreporting of such symptoms may lead some to be wrongfully diagnosed as non-psychotic. Two of the participants in fact described psychotic symptoms as coinciding in time with their suicide attempt. Had the outcomes of their attempts been fatal, their psychotic symptoms before death would never have come to light. Findings are in line with Rotschild describing the psychosis to be subtle, intermittent, or concealed [26]. Clinicians or researchers may sometimes fail to detect psychotic symptoms present

immediately preceding a suicide, thereby risking underdiagnosing, which might again bias studies examining clinical risk factors for suicide.

Our qualitative findings also highlight how psychotic symptoms may trigger impulsive suicidal behaviour [186, 187]. Psychotic experiences and intense suffering may combine to override perceived mental control, leading to impulsive suicidal behaviour as well as potentially life-threatening situations and accidents. Our findings indicating that a wide range of psychosis symptoms affected suicidal behaviour in the imminent/acute phase may help us understand the reason behind increased suicide rates in the acute psychotic phase and why it is higher than for non-psychotic depressed.

The overall symptom complex described in papers 1 and 2 was one of chaos, stress, anxiety, and experience self-loss without an awareness of prevailing severe mental illness. Existing neuroimaging and neuropsychological research have found a stress-responsive hypothalamic–pituitary–adrenal (HPA) axis and a cortico-limbic dysfunction in psychosis, depression and in suicide attempters [189-193] and leading to hypofrontality and impulsive behaviour. These completely different research approaches, qualitative studies and neuroimaging and neuropsychological research provide findings not strictly comparable, but interestingly describe the same phenomena of loss of control over emotional regulation, planning, problem solving and regulation of impulses. Our findings illuminating impulsivity as central for suicidal behaviour are in accordance with research proposing impulsivity as a risk factor for suicidal attempts across diagnostic boundaries [110, 194]

Participants in our study described an intense feeling of shame in combination with delusions about their negative impact on those around them. This motivated them to want to die. They also described deep inner ambivalence with a fear of dying coinciding with suicidal behaviour. The diagnostic criteria of psychotic depression, with its emphasis on positive symptoms over cognitive and disorganized ones, do not seem to cover the wide range of symptoms described by the participants in the study. This may lead the clinicians not to search for and validate these symptoms as a part of the psychotic state.

The subjective descriptions of the psychotic state included in this thesis may also increase understanding of why this state is difficult both to diagnose and

the risk of suicidal behaviour. Paranoid ideas prevent both help seeking and connecting with staff. Psychosis affects both the brain- and core emotional experiences, preventing self-insight and resulting in an entrapped state. Suicide in the mind of a psychotic person can thus make remarkably good sense as a way to escape this inner prison. Our findings thus support hypotheses that delusional processes may transform suicidal thoughts to completed suicide [26, 88].

Our qualitative findings of residual psychotic symptoms at discharge may also explain both increased short-term risk and post-discharge suicide. Findings of increased length of stay in paper 3 in psychotic depression compared to non-psychotic depressed, also show that patients with psychotic depression have a poorer clinical course when compared with non-psychotically unipolar depressed patients [16, 22, 23], indicating more time spent in this high suicide risk state.

Findings of cognitive symptoms in the acute psychotic state are in line with results from quantitative research of poorer daily functioning and neuropsychological deficits [19-21]. Neuropsychological deficits are not described in detail diagnostic criteria in ICD-11 beyond that "psychomotor retardation, or stupor so severe that ordinary social activities are impossible"[1]. This may lead clinicians to overlook that these symptoms and psychomotor agitation that may follow a psychotic depression, and lead to impulsive behaviour and compromised autonomy. In DSM-11 [2], the psychotic symptoms are described as delusions and/or hallucinations that are frequently consistent with depressive themes of guilt and worthlessness. Our findings complement neuropsychological research and provides an ethical imperative to protect this patient group with psychotic depression in the acute, psychotic phase when their cognitive autonomy is impaired.

Our findings challenge our view of suicide as an individual choice. Participants describe intense anxiety and fear of death at the same time as they may engage in "unconscious" suicidal behaviour. These findings have implications for clinicians when assessing criteria for involuntary hospitalization for patients with psychotic symptoms.

Paper four found that severe depressive symptoms including feelings of guilt or self-accusation predicted suicide at one-week follow-up. Even if scores 3

and 4 on HoNOS measure (inappropriate self-blame; preoccupation with feelings of guilt) are not defined as psychosis specific in HoNOS, firmly held overvalued and unrealistic ideas are per definition a delusion.

Our qualitative study illuminated interesting aspects of the association between self-understanding/awareness and shame experiences during depressive psychosis. Participants described believing they were subject to the incredibly negative attention of others, which I understand as «negative grandiosity». Grandiosity is thus not the total opposite of a depressive state/position: Dying can be a kind of sacrifice made in the name of love. «Negative grandiosity» thus may be a warning sign for suicide risk, since law-abiding and conscientious people do not want to harm loved ones, even if they believe avoiding this can only be achieved by suicide. The transdiagnostic phenomenon of severe depressed symptoms with (near) delusional content, highlights the importance of identifying and treating delusional thought content, including shame and self-blame, in acute settings. Major mood and psychotic disorders are not static, sharply defined illnesses with separate etiologies and courses, but rather syndromes that overlap and develop in stages [195, 196]. A clinical staging model, with stages determined by severity of symptoms in several dimensions, as well as distress and disturbances in functioning, may bring us closer to more transdiagnostic clinical tools for assessing imminent suicide risk.

In line with diagnostic criteria in ICD-11 and DSM-5, we found no correlation between severity of depressive symptoms and psychotic symptoms [197-200], suggesting an individual variation in susceptibility to psychosis during mood episodes, which is at least in part divested from severity.

## 6.2 Intense affective states increase suicide risk

Our studies revealed a variety of symptoms in time-near relation to suicidal behaviour and suicide. Paper 1 and 2 found descriptions of intense anxiety, panic attacks, insomnia, bodily pain, loss of mental control and severe depressive symptoms including thoughts of shame and guilt, leading to intense suffering. This supports results from quantitative research finding anxiety and agitation [105, 106], psychosis [84, 109], impulsivity [110] and intense

affective states [84, 104, 105, 111, 112] including depressive symptoms [42, 71] and sleep problems [106-108] as clinical warning signs for suicidality.

We also found the experience of relational and existential isolation to be reported as immediately preceding a suicide attempt. The narratives of entrapment and isolation may increase our understanding of how death may seem like the only way out. These experiences of being entrapped have similarities with theoretical perspectives of suicide as an escape from an entrapped state [201] and Suicide Crisis Syndrome, where entrapment is a central criterion in the presuicidal state [119, 120, 202].

High scores on depression rating scales (Both HoNOS item 7 and MARDS) are compatible with elements as including ruminative flooding and emotional pain and entrapment Suicide Crisis Syndrome (SCS) [119, 120], suggested suicide warning signs by Rudd [104] and "intense affective states" [112]. Our project adds the first test of these variables with suicide as main outcome. Severe depressive symptoms including inappropriate self-blame and guilt may a factor in the transition from suicidal ideation to behaviour, as HoNOS item 7 was found as a significant predictor for suicide first following week after clinical evaluation at admission. Intense affective states like that assessed by HoNOS item 7 may be modifiable by treatment over the course of an admission and after discharge. As such, item 7 by HoNOS may be relevant for future suicide risk assessment tools. Madsen et al [42] proposed for future studies of large study samples focusing on modifiable predictors over the course of an admission, such as hopelessness, depressive symptoms to develop future risk assessment tools, and with this project, our studies may expand the evidence base.

In Paper 3, the severity of depressive symptoms as measured by MADRS sum score predicted suicide. We also found a dose-response effect of both baseline ICD-10 severity criteria for depression and suicide risk. High scores on MADRS both with or without psychotic symptoms may be viewed as an intensive affective state; [112]. The finding of dose-response effect of baseline ICD-10 severity criteria on risk of suicide are otherwise in line with other studies following previous hospitalized patients with a depressive episode [9, 32, 68].

Contrary to our expectations, we found in paper 4 that samples of patients with affective disorders did not have a particularly high suicide rate compared to other diagnostic groups. Results are however in line with findings in a major systematic review of patients discharged from inpatients treatment [53]. Findings that 24.7 % of total suicides occurred in the group of substance abuse (table 1, paper 4), constituting a suicide rate of 2% after one year, supports a recent Norwegian prospective study of discharged inpatients which also found higher suicide rates in substance abuse disorders compared to affective disorders [60]. Another Swedish sample of 18684 individuals, similarly found the highest suicide rates among substance use disorders after one month [67]. Severe symptom load and intensive affective states assessed by HoNOS 7 is not present only in patients diagnosed with affective disorders. Table 1 in paper 4, illuminate that 35.6% of suicide victims score >2 on HoNOS item 7, however only 15.8% of suicide victims also received a diagnosis of depression. In other words, 20% of suicide victims had severe depressive mood as assessed by HoNOS 7 but were not diagnosed with a depression. Substance abuse may be a comorbid disorder, not excluding depressive disorders, and especially in male substance abuse patients, depression may be underdiagnosed and undertreated. Men are generally thought to be underdiagnosed for depression, which may again can be a reason for their increased suicide rates [130]. The diagnostic practice and a clinical snapshot in the acute ward may have profound impact for both the right to treatment, and your likelihood of receiving the right symptomatic treatment for i.e., depression which may in turn reduce symptom load and suicide risk [80, 132]. If your main diagnosis is substance use, you may not get the lifesaving depression treatment and symptomatic treatment of i.e., anxiety and sleeplessness, regardless of depression scores.

Our findings should be taken in favour of considering a more transdiagnostic view of the phenomenon of intensely negative affective states. Severely depressed mood may not exclusively be part of a diagnosed affective disorder. In emergency rooms and when assessing suicide risk for inpatients, we need to focus on clinical states. Depression scales as MADRS and HoNOS item 7, may be relevant tools for assessing depression severity, and a component in suicide risk assessment for both imminent, short- and long-term suicide risk. Our findings support a review suggesting screening for depression is relevant in suicide risk assessments regardless of previous

diagnoses [80]. Our paper 4 identified severe depressive mood as predictor of imminent suicide risk, while reported suicidal ideation and a diagnosis of depression didn`t predict imminent suicide risk. This further support the theory of suicide crisis syndrome that is described independent of diagnoses and self-report of suicidal ideation [119, 120, 202]. As no previous studies have found depression scale relevant for use in suicide risk assessments of inpatients [81, 82], our finding may add knowledge to the field and warrant further research.

Our results of increased suicide risk for the mixed diagnostic study population in SIPEA (1.4 % after one year) support existing research that highlights the overall increased suicide risk after discharge[53]. In paper 4, we found increased suicide rates in diagnostic groups as substance abuse, psychotic disorders, and mood disorders at one-year follow-up. Variables other than intensive affective states at admission thus potentially and likely play a role but were not explored in this thesis. Symptoms identified at admission are not static. They are more like snapshots, and fluctuate for the whole study population, regardless of admission HoNOS scores. Further studies should assess symptom development over time to obtain measurements leading up to the time of any suicide attempts, rather than relying on a single measurement at admission at last admission before suicide.

## 6.3 Self-report of suicidal ideation is not a good measure of imminent, short- or long-term suicide risk

### 6.3.1 Acute admitted inpatients

Systematically assessment of suicidal ideation and behaviour at admission in all consecutively admitted acute psychiatric ward patients, combined with clinical data, have to our knowledge never previously been conducted in a prospective cohort study. The Colombia-Suicide Severity Rating Scale (C-SSRS) which is currently being tested [67], covers suicidal ideation in the past month, whereas SIPEA only covers suicidal ideation and plans last week, admission day included. SIPEA thus presents data on more immediately

present suicidal ideation/plans, over chronic suicidal ideation/plans. Both SIPEA findings and Bjureberg's register study [67] find self-report of suicidal ideation of limited relevance alone, indicating that it must be combined with a more thorough clinical assessment.

Patients' self-report of suicidal ideation in Paper 4 was a less significant predictor than were severe depressive symptoms in an imminent follow-up perspective. Even if suicidal ideation is a suicide risk factor in population studies [55, 127], this factor appears to be of less importance in hospitalized patients [128]. Suicidal ideation still predicted death by suicide at two weeks and all follow-up time points after. These findings alone however provide limited clinical implications for suicide risk assessments, given that as many as 30.9% of patients reported suicide ideation/plans at admission. Our significant findings that suicidal ideation predicts suicide support existing research that suicidal ideation/plans predicted suicide in mixed diagnostic samples [55, 127], and our study adds significant findings that this is also true after only 14 days follow-up as well as later.

Our findings and existing knowledge call into question the entire practice of suicide risk assessments in acute settings based on patients' self-report of suicidal ideation/plans. Special attention when assessing suicide risk should however be made when recent suicide attempts and male gender. Despite promising findings of clinical predictors of suicide risk, recent suicide attempts have the highest hazard ratio in paper 3 and most significant results after one-month follow-up in paper 4 when adjusted for severely depressed mood. This support a wide range of existing research of different study populations [9, 42, 59, 203], and support recommendations of asking patients about prior suicide attempts also when patients are acute admitted. Our findings also replicate male gender as robust risk factors in relation to inpatient treatment [9, 42, 56, 57, 70], as almost 70% of patients dead by suicide after one year were men (paper 4), and male gender significant predict suicide in paper 3.

### 6.3.2 Depression group

In paper 3, we found that suicidal ideation/plans did not predict suicide in the depression group as a whole (median 5.5 years follow-up). Suicidal ideation is found to be a less important suicide risk factor in affective disorders [126, 127]. Many clinical studies lack a control group presenting self-reports of suicide survivors [53, 109]. Our results thus support existing research regarding affective disorders, however with a strength of its prospective design.

### 6.3.3 Psychotic depression group

Patients with psychotic depression reported less extent suicidal behaviour at admission, however had a two-fold suicide risk at follow-up compared to the non-psychotic counterparts. Findings are in line with our qualitative findings of patients with psychotic depression indicating that they may underreport suicidal behaviour during the actively psychotic phase of their illness [186, 187]. Participants in paper 1 described underreporting of suicidal behaviour due to paranoia towards health personnel, shame and impulsive behaviour. Shame has previously been highlighted as a significant dynamic factor in suicidal behaviour [204]. Psychoanalyst Leon Wurmser [205] describes "shame anxiety" as the fear of dishonour: the fear of being looked upon with contempt for something we have done, or something we are, and shameful experiences may be described as "secrets too terrible for words" [206]. This is illustrated by certain participants in our paper 1 who experienced intense shame due to mood-congruent delusions in combination with delusions about their impact on those around them. The accompanying anxiety linked to potential exposure of this shame, or delusions of being exposed, was associated with withdrawal and avoidance rather than with communication and help-seeking behaviour.

The phenomenon of not cognitive understanding their own suicidal process, and therefore being unable to communicate this, was also described. The psychotic world made them not see experiences as symptoms that needed to be reported, and motivations for dying had an inner logic. An important clinical consequence is that questions about "suicide" in suicide risk assessments may be easy to deny especially by individuals with psychosis.

Both underreporting of suicidal ideation and psychotic symptoms may mislead the clinicians to assess risk as low, and hinder the right treatment, security measures and follow-up after discharge. Self-reports include several biases, both as severe mental illnesses affect brain functions, patients may not have insight in their mental illness. Reporting inner thoughts and identifying semiconscious processes requires a great deal of mental control.

Our findings of less reporting of suicidal behaviour in psychotic depression compared to non-psychotic depressed, is in contrast to a review reporting increased suicidal ideation in hospitalized patients of unipolar psychotic depression contrary to non-psychotic depressed [25]. However, studies referred in this review were small, dated and did not include representative samples [95, 207-209]. In total, studies in the review included 255 patients (Nelson: 25 patients, Miller: 45 patients, Hori: 93 patients and Woldersdorf: 92 patients), whilst our study of 1846 patients in contrast have higher power to say something certain about psychotic depression and reporting of suicidal ideation at admission.

## 6.4 Psychosis- and depression focused treatment approach to prevent suicide

All papers lead us to conclude that focus upon identification and treatment of severe affective states is the most tangible way to prevent suicide during hospital and after discharge. Intensive treatment and care will potentially reduce inpatients and post-discharge suicides. Depressive symptoms and psychotic symptoms may be modifiable factors over the course of an admission and after discharge. This may contribute to a more optimistic view of suicide prevention strategies related to hospital treatment.

Paper 1 illuminated that lack of insight into their severe mental illness and underreporting of psychotic symptoms may hinder help seeking, may lead to misdiagnosis after admission, and may not prioritize for inpatient treatment including providing security measures and hinder psychosis-focused treatment approach. The study suggested a need for intervening with intensive treatment and security measures.

In paper 2, hospital treatment was experienced to have great impact on suicide risk. The participants underlined the need for both security measures and a treatment approach focusing on modifying psychotic experiences and intense anxiety. Patients were helped to control chaos by external means as routines (sleep-wake cycles, set mealtimes) and conversations. In addition, by stay on a locked ward, they were shielded from too many sensory impressions. Several participants in paper 2 reported being protected from suicidal impulses and imagined persecutors in a secure environment included locked doors with staff present.

Suicidal behaviour can arise as an impulsive response to perceived acute stress and suffering [98, 110, 194]. One study found that in nearly half of cases, the period between first current suicidal ideation and actual attempt was only 10 minutes or less [210]. This requires staff to intervene quickly and decisively to prevent lethal incidents. Even if evidence regarding if locked doors is suicide preventive is diverging [152, 153], qualitative studies of psychotic motivations for inpatients to find locked doors comforting or distressing is lacking [152]. As many suicide prevention studies are conducted on mixed diagnostic samples, this may be one reason outcomes and results diverge. One review suggest reducing accessibility to the means and possibilities for absconding while hospitalized [42], whereas a recent large scale observational study comparing completed suicide rates in hospitals or wards with or without locked doors failed to find a difference between the two [153]. The latter by Huber and co-workers finding no suicide prevention effect of locked doors was performed as a large naturalistic observational study comparing open and locked wards, including patients with all types of diagnoses [153]. This may have overshadowed that some patient groups have had the effect of locked doors as an intervention, while another groups may have had opposite effect. Increased understanding of why/how some interventions may be suicide preventive for some patients, and maybe not effective or even harmful for other patients seems clinically relevant.

Another hypothesis our study may suggest, is that an intervention may have suicide prevention effect in an acute phase, while existing studies i.e., focusing on locked doors do not divide interventions effect in short and long terms- effect in reducing suicide risk. Phase-specific suicide prevention strategies during inpatient treatment seems warranted.

People experiencing psychosis may need to be protected from themselves, but the qualitative study emphasize their equally pressing need for compassion, understanding, containment and empathy even, or especially, when most ill. Dialogue can also break pathological shame. Being in want of control is a key issue in the experience of being suicidal is supported by several interview studies [98]. The theme in paper 1 «Bereft mental control» also illuminates this, as they were in different ways out of mental control, also because of psychosis, anxiety and sleeplessness. Treatment thus can be a way of regarding control, both talking, medicines and routines at the wards etc.

Medical treatment was described to alleviate psychosis, sleeplessness and intense anxiety (paper 2). Our results are also in line with Bjørnestad et al, whose participants with non-affective psychoses described antipsychotic treatment as helpful in reducing mental chaos and stress during the acute phase, thus increasing subjective experience of control [145].

This is in line with guidelines and recommendations treating underlying psychiatric disorders as psychoses, including substance abuse and insomnia [18, 132]. Even though not described as explicitly connected by the patients in paper 2, improved sleep due to medication was experienced as crucial in reducing the overall symptom load, including anxiety, agitation, and somatic pain as well as psychotic and depressive symptoms. This is In line with researchers suggesting sleep problems as warning signs [106-108]. As intervention studies are difficult to conduct because of i.e., ethical reasons and the very large study population to identify eventual suicide reduction effects, qualitative studies can provide knowledge regarding effect on suicide prevention not easily accessible by other research methods.

Paper 2 described that antipsychotic treatment reduced suicidal behaviour, even if depressive symptoms still were present. At time of discharge, participants reported no psychotic motivations for suicide, i.e., wanting to pre-empt imagined certain death, saving those around them from further destruction, or wanting to obey commanding hallucinations. Our qualitative findings may complement a review of quantitative data that conclude that the risk of suicide remains increased until the patient has had remission of their depressive and psychotic symptomatology [25].

In paper 3 and 4, we found high suicide rates both first three months, and first year following admission related to patients with severe depressive symptoms, in line with a major review[53] and a large national cohort study [57]. Findings support prioritizing follow-up first year and a particular concern the first months after discharge.

# 7 Discussion of methods

## 7.1 Paper 1 and 2

### 7.1.1 Reflexivity

It is of utmost importance to avoid a framework that sticks to the researchers' preconceptions [185] Preconceptions can be defined as researcher experiences, hypotheses, perspectives, prejudices, and frames of reference that can influence any part of the research process [154-156]. The role of the researchers' preconceptions is important to acknowledge, as it clearly affects the data collection phase and how to follow-up questions, and how to interpret findings in the analytic phase. Our first paper describes how we dealt with this issue. Categories were be developed from the empirical data while at the same time acknowledging that the theoretical and clinical understanding by me (KJF) and Helle K. Schøyen (HKS) may have influenced the patterns identified. HKS and I are specialists in psychiatry, and our clinical experience was that patients with psychotic depression were at particular risk of suicide. However, by the inclusion of a third supervisor Margrethe Aase Schaefer (MAS) whose clinical training was in cardiology, findings were assessed and interpreted not only from a psychiatric point of view. This broadened perspectives and brought about critical discussions of traditional psychiatric views.

In paper 2, our preconception was that patient would say that medicines helped and that security measures were important. This was based on KJF and HKS's clinical experience and knowledge of, for example, lithium as an effective symptom-reducing drug. An example of different preconception and weighting of which findings that provide new knowledge in paper 2, is i.e., that KJF and HKS found the medication findings of importance, but MAS found the empathy and talk more important. Also, other co-authors brought in perspectives from their clinical and research in the fields of psychosis, recovery processes and suicide research. This broadened perspectives and brought about critical discussions of our findings and the transferability to other settings.

## 7.1.2 Validity

There is a great responsibility resting on the researcher when doing analysis and extracting meaning from narrative interviews in such a complex research field. Validity and credibility in qualitative studies largely determined by the skills of the researchers' [211], and guidelines to address validity of the findings have been made [155]

### 7.1.2.1 Internal validity

The interview guide was developed based on our preconceptions as we didn`t find much research to substantiate the questions in the interview guide. We had a clinical experience leading to a special concern regarding command hallucinations when they consist of suicide-related commands. We suspected existential thought content was instrumental in a death wish arising, and therefore included a question regarding this theme in the interview guide. We also suspected different pathways to suicidal behaviour to be highly individual in nature, and especially depending on age, gender, type of psychotic symptoms, and religious affiliation, criteria we had as a basis for the purposive sample strategy.

The interview guide contains several closed questions. Even if questions were conducted in a flexible manner, some aspects may have disappeared, as there was no opening to answer. On the other side, KJF experienced that without some closed questions, participants find it hard and chaotic to describe their psychotic experiences. An important way to open up questions in this project, was to ask the patient to give a descriptive example if the participant only answered i.e., "yes" or "no". Then the genuine psychosis experience emerged well in the patient's own words.

I conducted interviews during my specialist training in psychiatry and had extensive clinical experience and personal knowledge of each patient from the time of enrolment in the study. This may have made it easier to select relevant follow-up questions during interviews and strengthened the internal validity of the study.

Rather than basing categories on predefined theoretical concepts, an inductive analysis was performed, with categories developed from the

empirical data [159]. This helped us to free ourselves from the theory of suicidal process starting with suicidal ideation and progressing to plans and sometimes to attempts or completed suicide [113], and the somewhat one-sided focus on psychotropic drugs as a suicide prevention strategy in psychiatric research.

In paper 1, the validity of this study is strengthened by findings that were not consistent with our presumptions: unexpected findings were the participants did not seem to complete a rational thought and planning process prior to a suicide attempt, and that some denied suicidal ideation in suicide assessments, but reported suicidal thoughts after symptom improvement. Our findings also surprisingly revealed how some of the participants had motivations and explanations for dying that differed significant from what they associate with the word "suicide". The perspective of suicide as an accident were also not in our presumption, and their preparations on a "subconscious" level, even we know that patients with psychosis have thought disturbances. Suicide as a possible accident caused by psychotic experiences was also a surprising finding.

In paper 2, the interview guide had open-ended questions to avoid leading questions about medicines and security measures as lifesaving confirming our preconceptions. We could have had advantage of asked more in detail and focused about factors that were perceived as effective during inpatient treatment. Patients in this study also talked of factors outside hospital treatment, i.e., talk to relatives, friends, employer that we did not include in the paper, as it was outside the research question.

Validity was strengthened by findings that were not consistent with our presumptions: The paradox of fearing death at the same time as being in a suicidal process, some time on a sub-conscious level, may help us understand the ambivalence and chaos patients may experience when receiving treatment and protective measures in hospital. Another example is where participants describe how psychotic motivations for locked doors comforting. Hospital became a safe refuge from the outside world, both physically and psychologically, where the hospital became a hiding place, and the psychotic motivation for dying disappeared. This was an unexpected finding not earlier described in existing literature. Qualitative interviews may

be a tool to highlighting and understanding diverging research findings. i.e., how we found that locked doors at the hospital may prevent suicide, when most studies conclude that locked doors fail to reduce suicide rates [152, 153]. Our findings suggest that locked doors may be experienced as a helpful intervention for certain patients, and the "counter story" of locked doors not preventing suicide, needs to be challenged and nuanced. Our "counter stories" within the study illuminate that everyone experienced the hospital as a safe haven during the acute phase. Patients themselves pointed specifically to sleep as the major factor that reduced suicidal behaviour, an unexpected finding that strengthened the validity.

The use of narratives in qualitative research rises several ethical and methodological considerations. The characterization of others in the analysis based on the written material can give the researcher power to define a reality that is not shared by the research participant.

Another issue is that participants might not however provide truthful responses, thereby undermining the integrity of the research [180]. One could assume i.e., they would report that hospitalization was more helpful than it was, maybe to please KJF who was an "insider", a member of the hospital staff as well as a researcher. We tried to overcome this by not recruiting participants that had ever been in contact with KJF. What strengthen credibility, was that several participants described negative circumstances at the ward they were admitted to, and especially the fact that the treating doctor did not have enough time to talk to them.

#### 7.1.2.2 External validity

Validity and credibility in qualitative studies are to a large extent determined by the skills of the researchers' [212], and guidelines to address validity of the findings have been made [155].

The qualitative study involved a small inpatient sample and cannot predict the distribution or prevalence of these phenomena in inpatients with psychotic depression. Generalizability in qualitative methodology is on a theory level only and may provide new hypotheses.

Our study involved a small sample of hospitalized individuals, for whom the content of some delusions was contextual and culturally influenced. One should avoid overemphasis on one or few stories. In a way, the systematic nature of the qualitative analysis performed using systematic text condensation [158] helped us in this regard. This method aims for a thematic analysis across individual participant cases, and is suitable to develop knowledge about individuals' perspectives and symptom descriptions in medical research [158]. The diversity of ages, genders, psychotic symptoms and religious background represented among participants increases the transferability of our findings to other clinical inpatient settings in western health care systems. In e.g., China, where more women than men die by suicide, they use other suicide methods as pesticides, and there may be other cultural reasons for suicide not related to mental illness. The enrolment process and the need to obtain written informed consent during the first week of hospitalization made it impossible to include some of the most severely depressed patients for practical and ethical reasons. Thus, findings are maybe not transferable to most severe ill patients, where their severe symptoms may have a different and unknown relationship to suicide risk.

Without thinking about diagnostic criteria for psychosis, in a way we categorized psychotic symptoms the same way by dividing delusions from thought disturbances. The transferability is achieved if the reader becomes familiar with the rich symptoms descriptions and finds some findings recognizable in his own clinical work. Then the reader can decide whether the findings are transferable to their context. Symptom descriptions in the two papers relevant for suicidal behaviour may help e.g., clinicians in psychiatric outpatient clinics to justify hospitalization of patients with psychotic depression.

Qualitative studies can support and challenge experimental studies in natural sciences paradigms [154] and vice versa. Our study illuminates that professional conduct and relation building in inpatient treatment were not only therapeutic in their own right but could facilitate administration of such biological treatments. Findings can be relevant when evaluating medical treatment and electroconvulsive therapy (ECT) in psychotic depression [29, 34, 213] as suicide preventive. The transferability of the findings is strengthened in

this PhD project, as some findings are tested by quantitative methods, and thus can generalize findings. The claim from the qualitative study that psychotic symptoms may constitute a key factor triggering suicidal ideation and behaviour is confirmed by increased suicide rates of patients diagnosed with psychotic depression as described in paper 3. And the conclusion in the qualitative paper 1 that "Suicide risk assessments based on verbal reports from individuals with psychotic depression may not always be valid due to potential impulsivity and underreporting of suicidal ideation", have a quantitative follow-up that can generalize findings. Despite reporting less suicidal ideation/planning on admission, patients with psychotic depression were at increased risk of suicide (paper 3).

## 7.2 Paper 3 and 4

### 7.2.1 Strengths

#### 7.2.1.1 Health care system

In Norway, contact rates with mental health services have been found to be above 45% in the year before suicide [59]. We thus have clinical data on a relatively large proportion of suicide victims in our catchment area the year before suicide. The completeness of the Norwegian Cause of Death Registry is a strength and made it possible to identify and follow every patient after discharge. Other unnatural death causes as accidents and intoxes; events of undetermined intent to die, i.e., are not included in the suicide data. Including only well-defines suicides makes our data more precise.

The SIPEA study provide data on a clinically representative high-risk population of acutely admitted patients without any exclusion criteria. The SIPEA study recruited patients at a single hospital and had one project manager (Liv Mellesdal) for several years in the data collection period. It may thus have a more unidirectional way of coding. Both the SIPEA study and our statistical analyses included all patients above 18 years. This is regarded as a strength as most studies regarding unipolar psychotic depression and suicide risk have exclude patients above 60 years [15].

#### 7.2.1.2 Design and statistics

To produce clinically useful research findings, we need prospective cohort studies with short-time follow-up time to identify significant clinical predictors of suicide.

Prospective cohort studies have been described as more appropriate than retrospective studies for identifying suicide risk factors, while also being less prone to bias [161]. The SIPEA prospective study include large sample sizes, longitudinal follow-up, population representativeness, and clinical assessments from the emergency room. Patients with psychosis, increased suicide risk and with involuntary admissions were not excluded, which is often the case in clinical trials [47, 86].

Existing studies regarding short-term risk for psychotic depression have small sizes [88, 94, 95]. Only one study with 42 participants has found an short-term association between psychotic depression and suicide [88]. Our follow-up points of psychotic symptoms on suicide risk in the first year after a depressive episode as part of a unipolar or bipolar disorder is a strength, and to our knowledge, this has not been studied before in a prospective study.

#### 7.2.1.3 Acute time perspective

A one-year prospective cohort study with completed suicides at one and two weeks, and one, six and twelve months to our knowledge has never been conducted before.

Studies with shorter timeframes are necessary to inform clinical practice, both during inpatient treatment, but also of discharged patients. The acute perspective is a strength- both regarding assessing only acute symptoms, and the short follow-up, thus we can assess some clinical “states” and not only “traits” regarding suicide risk. We have data on the acute state including more accurate measurement of severity of depressive symptoms (HoNOS and MADRS last week, admission day included), and suicidal behaviour last week. Thus, we do not collect historical data of suicide attempt and clinical history that may have recall bias.

Our clinical data of diagnostics, suicidal behaviour, and HoNOS represent the psychiatric acute population at admission; “real world” data generalizable to

other acute settings. Relation between diagnosis, HoNOS, suicidal behaviour and completed suicide have the most exact data at the first follow up point of 1 week, even if CI is broader. Clinical state (HoNOS item 7, diagnostics and suicidal behaviour) may shift over time after first assessment in the acute ward. The later follow up points have narrower CI and p-values, though results are associated with greater uncertainty regarding clinical utility. This is the case with all research with long follow-up time, which impede clinical utility of the findings. I find the greatest strength of the SIPEA material is the symptom-assessments by HoNOS and MADRS that no register study so far has not been able to provide.

#### 7.2.1.4 Assessments

Systematically assessment of suicidal behaviour at admission (both suicidal/ideation/plans, passive death wishes, self-harm and suicide attempt) in all consecutively admitted acute ward patients has to our knowledge never previously been conducted in a prospective cohort study combined with clinical data. However, systematic assessment is done in a smaller cross-sectional study in Norway [66], and in a Swedish register study of 18684 patients [67]. The Swedish register study however have 20.9% missing on rating of suicidal ideation/behaviour, compared to SIPEA with very low missing rates of registered suicidal behaviour (177 of 7000, 2.5%). Whereas SIPEA register suicidal behaviour with an acute term perspective of presence only last week, the Swedish recorded suicidal ideation past month and behaviour past 3 months before admission [67]. SIPEA thus provide data on acute suicidal behaviour and acute severe depressive mood (by HoNOS) before admission, constituting data to our knowledge not provided before.

It should be noted that the high percentage reporting suicidal ideation in this SIPEA (30.9% of patients reported suicide ideation/plans) might reflect the criteria required for admission to acute wards in Norway.
Deinstitutionalization have resulted in more strict criteria for admission in Norway than a few decades ago, like in many countries in the western world, leading to increased illness severity among those who are prioritized for admission [60, 214]. In addition, elevated suicide risk combined with identified or suspected severe mental illness meets legal conditions for involuntary hospitalization, and patients reporting suicidal behaviour may thus be

prioritized for hospitalization over those reporting only depression severity. When psychotic depression is identified however, patients can more easily be admitted due to their severe mental state, also under the Norwegian Mental Health Act mental act, without additional criteria of identified suicide risk. This selection bias in inpatients may be a factor in explaining our findings.

## 7.2.2 Limitations

### 7.2.2.1 Design/setting and statistics

The SIPEA study is from one Norwegian hospital. A limitation may be some local traditions i.e., for diagnostics, and which patients the hospital prioritizes for acute hospitalization affecting generalizability.

One main limitation is a low base rate of suicides, resulting in wide confidence-intervals in paper 4 especially regarding one and two week follow up. This prevented inclusion of potential confounders and other candidate predictors, or interaction effects. We fully agree that other factors, included unmeasured factors may be associated with suicide risk. Ideally, the SIPEA cohort should have been even larger. Large, real-world prospective studies, i.e., multi-site studies ought to be the definitive methodology for validating instruments as depression ratings scales and identify clinical high-risk symptoms predicting imminent/short-term suicide risk.

The cohort in paper 3 cohort is smaller and number of events fewer than register-based studies regarding psychotic depression [68, 70]. This also meant we were unable to explore several potential risk factors or protective factors for suicide which may be pertinent, including age, socioeconomic status measured by educational level, paid employment, and being married/cohabitant. A larger study sample may have allowed us to combine identified predictors of suicide in this study to identify and study a potentially ultra-high-risk group. We found no difference in death by suicide when comparing those with and without psychosis from the group with a severe depressive episode only. This is contrary to a recent review and meta-analysis which found increased risk of suicide in psychotic depression. [90] Our finding may be due to type two error given the small size of the sample.

Considering our attempts to assess whether suicidal ideation and depression severity predicts suicide, it is in fact possible that successful interventions affected our findings. Assuming this was the case, this would limit the predictive value of our findings. This limitation is shared with the majority of international research into suicide risk factors. E.g. research using register data often includes less in-depth clinical data than did the SIPEA project.

#### 7.2.2.2 Acute time perspective

When hospitalized, patients are in a protected period for which they are at reduced risk of suicide. This may understate imminent risk of variables chosen in paper 4.

In the SIPEA Study, we cannot know whether patients died by suicide on the day they were discharged, or during their hospitalization. In paper 4 about imminent suicide risk, we are thus unable to assess whether these patients were discharged prematurely.

#### 7.2.2.3 Assessments

##### 7.2.2.3.1 Diagnostics

Using clinical diagnoses assessment may suffer from a limited diagnostic validity. Inter-rater reliability for diagnosis and HoNOS was not established. However, three studies validating clinical diagnoses in register data in the affective spectrum found the highest validity for cases in the severe end of the spectrum [215, 216]. This, psychotic disorders, an exclusion criterion in paper 3, is hopefully in a large extent high diagnostic validity, and the right psychotic patients excluded from the participant group and patients with depression and affective disorders as main psychiatric disorder.

Because our sample included both bipolar and unipolar patients, and both inpatient and outpatient suicides, suicide rates are not directly comparable to those of other studies.

Diagnostic instability is a common weakness in longitudinal studies including ours, as we used the diagnoses at last admission in the inclusion period. Such instability makes it difficult to examine the specific ways in which psychotic symptoms induce suicidal behaviour, especially given that we don't know the clinical state at the time of suicide. However, clinical examination at point of suicide is missing in almost all studies.

#### 7.2.2.3.2 MADRS and HoNOS

In our study, test-retest stability and interrater reliability was not tested. In SIPEA, we only have available MADRS sum score. For future studies, single items of each symptom are of outermost importance to study warning signs with suicide as main outcome. Sleeplessness, item four in MADRS, is to my opinion one item of great research interest.

Score of HoNOS and MADRS would have been interesting to have available at discharge. Then we could have investigated if it were patients without treatment response during hospital that died by suicide.

In HoNOS item 7, score 3 and 4, we don't know what kind of content of delusions increase suicide risk, and if near-delusions are mood congruent or mood incongruent. The assessment gives a relatively superficial measure of the symptom load, and thus our findings are complemented by the qualitative part (paper 1 and 2) that provide in-depth knowledge about how delusions may appear during a depressive episode.

#### 7.2.2.3.3 Suicidal behaviour

Our study evaluated suicidal behaviour at admission, and patients may have reported more suicidal thoughts/behaviours at a later stage during their admission. Caution generalizing findings to other none-acute, longer-term settings.

#### 7.2.2.3.4 Statistics

Today, most suicide research do many of the same regression analysis, or even more simple descriptions of their material as we also did, including diagnostic distribution of the included patients' material and of suicide

victims. It is also possible to do more advanced statistic, sequence analyses, to estimate symptom progress over time before suicide. This is possible for patients that have been admitted several times in the inclusion period. In this project, we have relied on one single assessments during the last admission before an eventual suicide. Statistical sequence analysis of symptom progression before suicide could have been done, if several admissions in the inclusion period, and would definitively had added knowledge to the research field.

## 7.3 Mixed methods

Most research in suicidology rely on the paradigm of modern natural science providing empirical knowledge characterized by "objectivity" and "universality" [157]. Many existing studies in suicide research use hypothesis-deductive or experimental methodology originating from the natural sciences and the biomedical illness model. Researchers are looking for statistical associations based on numerical materials. It has been argued that suicide research would benefit from incorporating elements of the hermeneutic approach to understand the complexity of human nature and behaviour [217]. Clinical knowledge in medicine incorporates facts, skills, and experience -the latter should thus also include knowledge of patients' subjective experiences as uncovered by qualitative studies. The patient's narrative and behaviour including clinical signs are essential for decision-making by health personnel.

Although major depression and psychotic symptoms have been identified to be statistical risk factors for suicide in several studies, the specific ways in which these factors may induce the suicidal behaviour remains largely unexplained. A deeper understanding may contribute to improve suicide prevention strategies for affected individuals. Mixed methods research may provide a better understanding of complex issues and incorporate both perspectives of "objective" ratings of clinicians in the quantitative part and "subjective" experiences told by living patients in the qualitative part.

Mixed methods design when investigating the complex association between psychotic depression and suicidal behaviour thus is seen as a strength.

It is possible that e.g. a diagnosis of depression and reported suicidal thoughts and plans would have been even more predictive of suicide in the quantitative papers if the study participants had not been receiving psychiatric treatment. Potentially interfering factors may have happened both during and after hospitalization, and include medical and psychological treatment, security measures as well general post-discharge care. Results of quantitative research are to a certain extent outcomes of treatment interventions and interpretations of the clinicians who coded symptom and diagnostic variables[154]. In this regard, our paper 2[187] may fill a gap in a method limitation in our quantitative research by increasing our understanding of how treatment during hospitalization may reduce symptom load assessed by variables (e.g. psychotic symptoms) at admission, and then reduce suicide risk.

A strength with the sequential exploratory strategy, is the relatively straight forward due to clear, distinct stages. Weakness is i.e., very time consuming especially as both phases were given equal consideration and priority.

## 7.4 Generalizability of the findings after secondary analysis of the findings

The qualitative studies provide empirical descriptions of how the unbearable suffering during the psychotic depression torments the participants both physically, mentally, and relationally. Our use of rigorous, qualitative methods has ensured the voice and language of the patients to be heard and taken seriously and has obtained new knowledge that cannot be detected through quantitative approaches. The quantitative part reveals the increased suicide risk by several findings assessing the severity of depressive symptoms and psychotic symptoms. Even though we can assume some factors that are associated with increased suicide risk at an aggregate level, it should be interpreted cautiously and are not necessarily applicable to individual patient.

Some of the psychotic experiences described in paper 1 and 2 may not only be relevant for psychotic depression, but also present in other psychotic disorders. Research suggest a transdiagnostic psychosis phenotype that

overlaps affective and non-affective psychotic syndromes [218, 219] both in inpatient- and population-based samples.

# 8 Discussion of ethical issues

Even if we have an ethical imperative to do suicide research, still, this project also involves ethical dilemmas. I will discuss the ethical dilemmas pertaining to the planning-, implementation- and analysis-phase.

Overall, I have identified three themes, (1) Autonomy and written informed consent in patients with psychotic symptoms. (2) Research without informed consent and (3) Is it ethically justified to undertake narrative interviews on vulnerable patient populations?

## 8.1 Autonomy and written informed consent

One commonly accepted principle of health care ethics is respect for autonomy. This principle is founded in cognitivist ethics, based on the view that humans have the capacity to make decision based on reason. Philosopher Hacker describes humans as beings with consciousness, intentionality, imagination, memory, senses and perceptions [220]. A philosophical question is whether autonomy presupposes a healthy brain. In a psychotic depression, neuropsychological deficits are common [19-21], personality traits can temporarily change, and especially in the case of psychosis, severe conflict between reason and emotions appears evident. Participants in our study described psychosis as stripping them of their autonomy and insight into their severe mental illness for the duration of their episode, leaving them unable to make rational choices or take care of their own basic needs [187]. Psychotic experiences by definition override mental control. Illogical thought processes dominated, with arguments for and against suicide at times partly or completely based on delusional ideation. Psychotic symptoms effectively deprived patients of both autonomy and insight into potential consequences of their actions. Autonomy as a prerequisite for research thus have had major consequences for patients with severe mental illnesses. Patients with psychotic depression as part of a uni- or bipolar disorder are admitted to hospital, but evidence base is very weak to guide clinicians in decision making. Thus, the research

field is not making sufficient progress in developing suicide prevention strategies affecting a large number of patients worldwide.

While informed consent is a crucial aspect in all medical research, impaired brain functions as well as psychotic symptoms and lack of insight presents particular challenges. These impairments can affect patients' abilities both to understand and to make fully informed decisions about care and research participation. Ensuring that consent for treatment is informed, voluntary, and genuine can thus become difficult. Being suicidal might in itself be considered as an indicator of inability to give informed consent, as the inherent devaluation of their own health and safety indicates they are unable to make a sound judgement about any risks or drawbacks to participation [180].

As representatives of biomedicine, researchers and institutions are charged with the responsibility of protecting the welfare of currently suicidal subjects [181]. The interest of scientific advance in order to help future patients may be seen as conflicting with this. Researchers can thus be seen as generally biased to favour societal utility over individual subjects' rights. However, an example how this was resolved, was that included patients could withdraw from the study at any point without consequence, and two included patients did so, and therefore weren`t interviewed at discharge.

In some cases, in clinical practice, upholding the ethical medical principles of beneficence and non-maleficence means failing to respect a person's autonomy to die by suicide. This was illustrated by our inpatient participants being subjected to hospital security measures, e.g., locked doors and tamper proof windows. In practical terms, the participants were denied the choice to perform a suicide, even if they had strong impulses to do so. A moral conflict thus exists between the respect for autonomy and the staff mandate of saving lives, and their choice to override the respect for autonomy for a limited period. The patient's autonomy and right to self-determination must always be weighed against his or her safety during hospital stay and during the research process. This is in line with general psychiatric practice and the law in Norway, where patients are not regarded as genuinely free to select death by suicide if they have a severe mental illness, e.g., psychosis.

The question still remains however whether patients under strict protective measures simultaneously may be deemed able to give truly informed consent to participate in research. Given that suicide is a personal act, we argue that subjectivity is especially important to explore in this research field. In qualitative paper 1 and 2 [186, 187], patients were included in the study after having been fully informed written and oral about the study procedure. Written informed consent was obtained from all participants and they could withdraw their consent at any point. In this thesis, we thus assumed that active psychosis did not automatically preclude meaningful informed consent on the part of the patient, but that any potential vulnerabilities had to be considered realistically on an individual basis. This meant, for instance, that some of the most severely depressed patients were unable to be enrolled given that recruitment happened during the first week of. These challenges in the recruiting process are consistent with Rothschild [182], who notes that systematic studies of depression with psychotic features are inherently limited by the difficulty of enrolling patients with this disorder.

In interviews at the time of discharge, participants reported no psychotically motivated suicidal thoughts, and a new, insightful self-view which included acknowledging they had been severely mentally ill. They described their autonomy as having been compromised by intense suffering and chaos in the psychotic phase, which left them unable to make rational choices or take care of their own basic needs. Ability to provide informed consent was individually assessed in each case, a highly complex ethical decision-making process given that psychotic symptoms and suicidal behaviour often were still present at inclusion. We also had to carefully consider ethical dilemmas around performing interviews with participants who had recently gone through a severe mental state associated with suicidal behaviour. To illustrate, one patient cried when planning the interview, and did not want to talk about the terrible experiences she had in the psychosis. We therefore agreed to make the interview as short as possible. However, themes raised by the interviews did differ greatly from questions asked of patients during routine treatment in hospital. Using a skilled clinician, experienced in talking to this patient group, as the interviewer was also intended to minimize any patient distress. Attention was constantly paid to the interviewee's well-being and state-of-mind, and although we were ready to terminate any interview, if necessary, we did not find this was required. Procedures to

protect participants included follow-up on their ward t if they felt mental unrest after the interview and alerting the treating physician if the participants were considered to still be in danger of dying by suicide.

Participant's ability to provide truly informed consent at inclusion could of course be debated. However, at the time of discharge, consent competence was clearly regained by all participants, and the principle of autonomy were safeguarded.

## 8.2 Research without informed consent

The Regional Committee for Medical Research Ethics (REK 2009/1057) and the Norwegian Social Science Data Service approved the study (NSD 11237). The Norwegian Directorate of Health Care authorized the use of patient information (SHDIR 07/2558). The SIPEA study was exempted by these boards from requiring written or oral informed consent, because the collected data were part of standard assessments on admission to inpatient psychiatric care. All data were stored and analysed anonymously. All data were stored and analysed anonymously.

Consequentialism can be used to justify doing research on vulnerable, high-risk groups like patients with psychotic depression. The project is of significant importance to society. At best, SIPEA may contribute new and significant hypotheses for the prevention of suicidal behaviour when designing both future research and clinical services, which in turn would benefit individual patients and society at large. Research about this life-threatening condition is sorely needed [221].

Paper 4 included all 7000 SIPEA patients, many without consent competence because of i.e., mental retardation, psychosis, dementia and mania. For instance, 38.5% were committed under the Norwegian Mental Health Act, and a high proportion of them are not assessed as consent competent due to psychosis. The lack of exclusion criteria means findings have greater ecological validity and are more generalizable to other acute settings, nationally and internationally. Requiring informed consent would mean these vulnerable groups could not be studied at all, which would make findings less clinically relevant.

## 8.3 Can we justify performing narrative interviews with vulnerable patients?

Psychiatric patients in general are a vulnerable participant group [222], and suicide research in particular requires procedures to protect participants and an ongoing process of ethical considerations [180]. When encountering any ethical dilemma, we may need to determine which moral concerns outweigh the others, with the purpose of applying the best moral judgement to a difficult medical situation. An example of an ethical dilemma is having to juggle multiple possible costs/harm dilemmas for each individual participant: Patients for papers I were contacted and recruited in a vulnerable period of hospital stay. It may be difficult to refuse participation and patients may be especially prone to either feeling or actually being manipulated into participation. Suicidality or severe symptoms may be exacerbated by bringing their attention to their recent psychotic episode. Several patients described it as upsetting to talk about their experiences when recovered, some cried during the interview and reported unease, which on one hand may be ethically problematic. On the other hand, the inconvenience and risk they were exposed to was limited to a single open-ended interview. Such interviews are quite similar with regular individual consultations on the ward. In our case we believe that allowing a small amount of discomfort to interviewees is justified for the greater moral concern of preventing future suicides. Previous studies have also shown that it is not dangerous to talk about suicide [223-225], and we believe that performing this type of research helps deconstruct stigma and misunderstandings that asking about suicide somehow increases suicide risk. It can however be ethically valuable to discuss to what extent we should expect people to tolerate having to revisit difficult experiences and existential questions in the name of research.

In light of narrative ethics, what happens in the face of the individual during the interview is central and not easy to measure objectively. The researcher's competency is essential to not harm the participant. Handling a situation inappropriately, being over-intrusive, insensitive, or saying something offensive that may cause distress and at worst, encourage suicidal behaviour [180]. An example of how narrative ethics applies to suicide research is the importance of maintaining focus on the wellbeing of each participant during the dynamic interview situation.

However, participants in our qualitative study often reported that the interviews were beneficial, and for some, they increased well-being. They appreciated the time to talk, gained self-understanding, felt that it was an altruistic thing to do, and found comfort in learning that they were not alone and that others suffer similarly, in other words, experiencing a kind of utilitarianism from a participant perspective. It is almost impossible to say upfront which participants will have a more positive experience and who will find the experience harder to bear. In addition, excluding the perspectives of the latter group would mean missing very important patient voices and narratives. Last, feeling that something is challenging and finding reward in altruistic activities are by no means exclusive.

# 9 Conclusion

In psychiatry and regarding suicide prevention, it is of utmost importance to understand both the patients and the disease. We will probably never be able to predict with 100% certainty which patients will die by suicide. Our patients are too complex, they are impulsive, and factors outside hospital treatment play a substantial role that health care personnel are unable to control. A substantial part of suicides is in fact out of the hands of both hospital staff and next of kin.

Findings of this thesis support that severe depressive symptom, including guild and self-blame as revealed by thorough clinical examination in acute psychiatric emergencies, is indicative of imminent risk of death by suicide, and should be followed by careful further measures. The identification of severely depressed mood might aid prioritizing in hospital intake processes, ensuring adequate treatment and security measures are applied where needed.

Depression rating scale MADRS sum score and HoNOS item 7 may be useful tools in assessing depression severity, and for prioritizing treatment which may also have suicide preventive outcomes. Identified warning signs including sleeplessness, thought disturbances, psychosis and intense anxiety should become a guiding focus for symptomatic treatment. Patients with severe depressive symptoms and psychotic symptoms should receive treatment aimed at alleviating psychotic symptoms as this may reduce their risk of suicide.

Based on findings from 7000 acute admitted patients, findings regarding suicide risk of hospitalized patients also give an optimistic view of hospital treatment and security measures. In total, 30.9 % of patients reported suicidal ideation/plans, and 7.1% reported a recent suicide attempt. However, the 10 suicides, which happened during the first week of admission, makes up only 0.1% of the patients. Even if every such loss is immensely tragic, hospital treatment has likely saved and provided adequate safeguards for a much high number of very high-risk individuals. We cannot report patients saved, but we study patients lost and predictors for those. In a way, we find predictors of our unwanted outcomes in statistical methods,

but to a much lesser extent do we have data of what we did right during a hospital stay. In this regard, qualitative findings from suicidal patients who lived through their hospital stays may better identify better how suicide preventive strategies might be further improved for future clinical practice. Sleeping aids, sedatives, and medicines for uni- and bipolar disorder should also not be disregarded. Relations and staff actually seeing the patients and having time for the patients is very important. If we want people to live, we cannot cut costs and staff. Gaining anxious and paranoid patients' trust is also essential to build motivation for medical treatment. Suicide prevention may be a positive side effect of more intensive care.

## 9.1 Implications for clinical practice

There are many paths to suicide, and for each path, the risk factors and decision-making processes differ. Some diagnostic states may have some distinct risk profiles, as psychotic depression that can be characterized by underreporting of suicidal behaviour and impulsivity. As suicide is a subjective act, even if not always self-chosen and may be directed by psychotic impulses, the uncovering of subjective distress and the mental chaos is of crucial importance. On another side, there seem to be to be aware of some transdiagnostic phenomenon regarding depressive and psychotic symptoms. Feelings of shame, guilt, remorse, and entrapment especially should thus be thoroughly assessed when caring for depressed inpatients. Depression scales can be a helpful tool as part of the suicide risk assessment, and for evaluating symptoms development during inpatient stay and after discharge. Self-report of suicidal ideation of limited relevance as it is so unspecific and must be combined with thorough clinical assessment. Our data support previous research identifying suicide attempts and male gender as predictors of suicide, and particular care should thus be paid to these subgroups of patients.

Suicide can be seen as a symptom and end-stage of a serious mental illness or an adverse event, not a specific target for intervention. Many risk factors studies, including this PhD project, support the notion that the general clinical load, and treatment aiming to alleviate this, is the best place to start if we want to prevent suicides. Intense treatment of depressive- and psychotic symptoms, including anxiety and sleeplessness is therefore also

suggested as this is our best chance at alleviating intolerable subjective states. Ideally, all patients with psychotic depression should be offered individualized follow-up in the first year following admission to hospital, as they should not be considered cured at the time of discharge. That would probably be suicide preventive, because any relapse of psychotic episodes would likely be discovered, so that appropriate measures like readmission and medication interventions for sleep deprivation may be provided in a timely manner. This is however not feasible even in Norway, the world's richest country, both for economic reasons and for lack of available professionals. However, more could be done to increase knowledge and awareness about psychotic depression, e.g., through more detailed descriptions of symptoms in formal diagnostic criteria texts and in textbooks for health care staff. Our qualitative research indicates that the psychotic symptoms are more vivid and complex that described in diagnostic criteria, and we must work to close this gap.

Patients described not feeling in control of their own actions during the psychotic phase. They were not rational nor able to organize themselves to seek help. This indicates a need for locked doors and involuntary admissions in the most severe phase of illness for this group. Patients reported being thankful for the hospital treatment, and in several instances described such security measures as lifesaving. Such experiences should thus form part of our knowledge base when discussing use of involuntary hospitalization and security measures in hospitals. A deeper understanding of how suicide preventative interventions are experienced while in a state of psychotic depression may provide avenues for improved suicide prevention strategies during inpatient treatment.

## 9.2 Implications for further research

Research on suicide prevention strategies remains scarce and we recommend further studies identifying suicide prevention strategies for high-risk clinical states. Lack of knowledge of suicide prevention strategies especially in psychotic depression is striking, despite more research focusing on this high-risk state over the past decade. Both systematic studies of pharmacological treatment and other suicide prevention strategies are

needed for psychotic depressed inpatients and acute admitted inpatients in general.

We also generally need more focus on isolated clinical states, not “mixed diagnostic samples» which have been used in many research studies. We need more prospective studies of short-term (1 week or less) suicide rates in psychotic depression with large samples. We also need more research regarding both subjective experiences of clinical states and how suicidal ideation in e.g., psychotic states may increase in the risk of transition from suicidal ideation to actual attempt/suicide. Shame or shameful delusions (and delusional guilt) have not been extensively studied as a potential predictor of suicidal behaviour in psychotic depression specifically, and our findings warrant further investigation of how apparent or expressed feelings of shame might provide an important indicator of unreported suicidal intent or potential for impulsive suicidal actions in this disorder.

We also of course need more research focusing on predictors of imminent suicide risk in high-risk samples which are from mixed diagnostic and acute hospitalized patient groups. Prediction windows should ideally resemble clinical practice with timeframes of minutes, hours, days, and weeks. Longitudinal, multicenter studies of acute admitted inpatients are essential to achieve the statistical power needed for such important research.

Our results of the three first papers were collected and analysed before we met Galynker and Cohen talking about Suicide Crisis Syndrome. As this theoretical model make sense to clinical practice and our research findings, I hope this model will be tested more with suicide as main outcome.

And finally, more advanced research into symptom development over time before suicide for both depressive and psychotic symptoms is needed, not only statistical analyses of one single assessment of each patient as was the case in this prospective study.

# 10 References


1. World Health Organization. International classification of diseases for mortality and morbidity statistics (11th Revision). 2018.
2. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. American Psychiatric Publishing; 2013.
3. Goodwin FK, Jamison KR, Ghaemi SN. *Manic-depressive illness: bipolar disorders and recurrent depression*. vol p 267. Oxford University Press; 2007.
4. Miller JN, Black DW. Bipolar Disorder and Suicide: a Review. *Current psychiatry reports*. 2020/01/18 2020;22(2):6. doi:10.1007/s11920-020-1130-0
5. Hasin DS, Sarvet AL, Meyers JL, et al. Epidemiology of Adult DSM-5 Major Depressive Disorder and Its Specifiers in the United States. *JAMA Psychiatry*. Apr 1 2018;75(4):336-346. doi:10.1001/jamapsychiatry.2017.4602
6. World Health Organization. https://www.who.int/news-room/fact-sheets/detail/depression. 2021;
7. Cavanagh J, Carson A, Sharpe M, Lawrie S. Psychological autopsy studies of suicide: a systematic review. *Psychological Medicine*. 2003;33(3):395-405.
8. Mann JJ, Apter A, Bertolote J, et al. Suicide Prevention Strategies. *JAMA: The Journal of the American Medical Association*. October 26, 2005 2005;294(16):2064-2074. doi:10.1001/jama.294.16.2064
9. Isometsä ET. Suicides in Mood Disorders in Psychiatric Settings in Nordic National Register-Based Studies. *Frontiers in psychiatry*. 2020;11:721. doi:10.3389/fpsyt.2020.00721
10. Shevlin M, McElroy E, Bentall RP, Reininghaus U, Murphy J. The Psychosis Continuum: Testing a Bifactor Model of Psychosis in a General Population Sample. *Schizophr Bull*. Jan 2017;43(1):133-141. doi:10.1093/schbul/sbw067
11. Møller P, Husby R. The initial prodrome in schizophrenia: Searching for naturalistic core dimensions of experience and behavior. *Schizophrenia bulletin*. 2000;26(1):217.
12. Parnas J, Handest P. Phenomenology of anomalous self-experience in early schizophrenia. *Comprehensive psychiatry*. 2003;44(2):121-134.
13. World Health Organization. *The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines*. World Health Organization; 1992.
14. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders: DSM-IV-TR®*. Washington, DC: American Psychiatric Publishing; 2000.

15. Gournellis R, Efstathiou V, Yotsidi V, et al. Guilt delusional beliefs increase the risk of suicidal attempt in elderly unipolar psychotic depressives. *The Journal of nervous and mental disease*. 2019;207(1):29-33.
16. Nelson JC, Bickford D, Delucchi K, Fiedorowicz JG, Coryell WH. Risk of Psychosis in Recurrent Episodes of Psychotic and Nonpsychotic Major Depressive Disorder: A Systematic Review and Meta-Analysis. *Am J Psychiatry*. Sep 1 2018;175(9):897-904. doi:10.1176/appi.ajp.2018.17101138
17. Dubovsky SL, Ghosh BM, Serotte JC, Cranwell V. Psychotic Depression: Diagnosis, Differential Diagnosis, and Treatment. *Psychotherapy and psychosomatics*. 2021;90(3):160-177. doi:10.1159/000511348
18. Bassett D, Boyce P, Lyndon B, et al. Guidelines for the management of psychosis in the context of mood disorders. *Schizophrenia Research*. 2022/03/01/ 2022;241:187-196. doi:https://doi.org/10.1016/j.schres.2022.01.047
19. Lefteris L, Rossetos G. Psychotic (Delusional) Major Depression: New Vistas. *Current Psychiatry Reviews*. 2009;5(1):1-28. doi:http://dx.doi.org/10.2174/157340009787315271
20. Zaninotto L, Guglielmo R, Calati R, et al. Cognitive markers of psychotic unipolar depression: a meta-analytic study. *J Affect Disord*. Mar 15 2015;174:580-8. doi:10.1016/j.jad.2014.11.027
21. Fleming SK, Blasey C, Schatzberg AF. Neuropsychological correlates of psychotic features in major depressive disorders: a review and meta-analysis. *Journal of Psychiatric Research*. Jan 2004;38(1):27-35.
22. Coryell W, Leon A, Winokur G, et al. Importance of psychotic features to long-term course in major depressive disorder. *The American journal of psychiatry*. 1996;
23. Vythilingam M, Chen J, Bremner JD, Mazure CM, Maciejewski PK, Nelson JC. Psychotic depression and mortality. *American Journal of Psychiatry*. 2003;160(3):574-576.
24. Gournellis R, Tournikioti K, Touloumi G, et al. Psychotic (delusional) depression and suicidal attempts: a systematic review and meta-analysis. *Acta Psychiatr Scand*. Nov 26 2017;doi:10.1111/acps.12826
25. Zalpuri I, Rothschild AJ. Does psychosis increase the risk of suicide in patients with major depression? A systematic review. *J Affect Disord*. Jul 01 2016;198:23-31. doi:10.1016/j.jad.2016.03.035
26. Rothschild AJ, Winer J, Flint AJ, et al. Missed diagnosis of psychotic depression at 4 academic medical centers. *J Clin Psychiatry*. Aug 2008;69(8):1293-6.
27. Rothschild AJ. *Clinical manual for diagnosis and treatment of psychotic depression*. American Psychiatric Publishing, Inc.; 2009.

28. Caldieraro MA, Dufour S, Sylvia LG, et al. Treatment outcomes of acute bipolar depressive episode with psychosis. *Depression and anxiety*. 2018;35(5):402-410.
29. Fountoulakis KN, Yatham L, Grunze H, et al. The International College of Neuro-Psychopharmacology (CINP) Treatment Guidelines for Bipolar Disorder in Adults (CINP-BD-2017), Part 2: Review, Grading of the Evidence, and a Precise Algorithm. *The international journal of neuropsychopharmacology*. Feb 1 2017;20(2):121-179. doi:10.1093/ijnp/pyw100
30. Frankland A, Cerrillo E, Hadzi-Pavlovic D, et al. Comparing the phenomenology of depressive episodes in bipolar I and II disorder and major depressive disorder within bipolar disorder pedigrees. *J Clin Psychiatry*. Jan 2015;76(1):32-8; quiz 39. doi:10.4088/JCP.14m09293
31. Goes FS, Sadler B, Toolan J, et al. Psychotic features in bipolar and unipolar depression. *Bipolar Disord*. Dec 2007;9(8):901-6. doi:10.1111/j.1399-5618.2007.00460.x
32. Kessing LV. Severity of depressive episodes during the course of depressive disorder. *The British Journal of Psychiatry*. 2008;192(4):290-293.
33. Rothschild AJ. Psychotic depression and suicide. *Acta Psychiatr Scand*. Apr 2018;137(4):364-365. doi:10.1111/acps.12864
34. Kruizinga J, Liemburg E, Burger H, et al. Pharmacological treatment for psychotic depression. *Cochrane Database of Systematic Reviews*. 2021;(12)
35. Kjelby E, Jørgensen HA, Kroken RA, Løberg E-M, Johnsen E. Anti-depressive effectiveness of olanzapine, quetiapine, risperidone and ziprasidone: a pragmatic, randomized trial. *BMC Psychiatry*. 2011/08/31 2011;11(1):145. doi:10.1186/1471-244X-11-145
36. Yatham LN, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013. *Bipolar disorders*. 2013;15(1):1-44.
37. Naghavi M. Global burden of disease self-harm collaborators: global, regional, and national burden of suicide mortality 1990 to 2016: systematic analysis for the global burden of disease study 2016. *BMJ*. 2019;364(l94)
38. World Health Organization. Suicide in the world. *https://appswhoint/iris/bitstream/handle/10665/326948/WHO-MSD-MER-193-engpdf*. 2019;
39. World Health Organisation. *https://wwwwhoint/news-room/fact-sheets/detail/suicide*. 2019;
40. Global Change Data Lab. Our world in data. *https://ourworldindataorg/grapher/suicide-death-rate-by-age?country=~OWID_WRL*.

41. Hjorthoj CR, Madsen T, Agerbo E, Nordentoft M. Risk of suicide according to level of psychiatric treatment: a nationwide nested case-control study. *Soc Psychiatry Psychiatr Epidemiol*. Sep 2014;49(9):1357-65. doi:10.1007/s00127-014-0860-x
42. Madsen T, Erlangsen A, Nordentoft M. Risk Estimates and Risk Factors Related to Psychiatric Inpatient Suicide-An Overview. *International journal of environmental research and public health*. Mar 2 2017;14(3)doi:10.3390/ijerph14030253
43. Nock M. Self-Injury. *Annual review of clinical psychology*. 03/01 2010;6:342. doi:10.1146/annurev.clinpsy.121208.131258
44. World Health Organization. Suicide prevention (SUPRE). http://www.who.int/mental_health/prevention/suicide/suicideprevent/en/#
45. Camus A. *Sisyfos-myten*. Gyldendal A/S; 2018.
46. Gunnell D, Frankel S. Prevention of suicide: aspirations and evidence. *Bmj*. 1994;308(6938):1227-1233.
47. Sisti DA, Joffe S. Implications of Zero Suicide for Suicide Prevention Research. *JAMA*. 2018;320(16):1633-1634. doi:10.1001/jama.2018.13083 %J JAMA
48. Shneidman ES. *Suicide as psychache: A clinical approach to self-destructive behavior*. Jason Aronson; 1993.
49. Rasmussen ML, Dieserud G, Dyregrov K, Haavind H. Warning signs of suicide among young men. *Nordic Psychology*. 2014/07/03 2014;66(3):153-167. doi:10.1080/19012276.2014.921576
50. Voros V, Tenyi T, Nagy A, Fekete S, Osvath P. Crisis Concept Re-loaded?—The Recently Described Suicide-Specific Syndromes May Help to Better Understand Suicidal Behavior and Assess Imminent Suicide Risk More Effectively. Conceptual Analysis. *Frontiers in psychiatry*. 2021-March-24 2021;12(312)doi:10.3389/fpsyt.2021.598923
51. Rihmer Z. Strategies of suicide prevention: Focus on health care. *Journal of Affective Disorders*. 1996/07/08/ 1996;39(2):83-91. doi:https://doi.org/10.1016/0165-0327(96)00007-9
52. Mellesdal L, Mehlum L, Wentzel-Larsen T, Kroken R, Jorgensen HA. Suicide risk and acute psychiatric readmissions: a prospective cohort study. *Psychiatric services (Washington, DC)*. Jan 2010;61(1):25-31. doi:10.1176/appi.ps.61.1.25
53. Chung DT, Ryan CJ, Hadzi-Pavlovic D, Singh SP, Stanton C, Large MM. Suicide Rates After Discharge From Psychiatric Facilities: A Systematic Review and Meta-analysis. *JAMA Psychiatry*. Jul 1 2017;74(7):694-702. doi:10.1001/jamapsychiatry.2017.1044
54. Walsh G, Sara G, Ryan CJ, Large M. Meta-analysis of suicide rates among psychiatric in-patients. *Acta Psychiatr Scand*. Mar 2015;131(3):174-84. doi:10.1111/acps.12383

55. Franklin JC, Ribeiro JD, Fox KR, et al. Risk factors for suicidal thoughts and behaviors: A meta-analysis of 50 years of research. *Psychol Bull*. Feb 2017;143(2):187-232. doi:10.1037/bul0000084
56. Madsen T, Erlangsen A, Hjorthøj C, Nordentoft M. High suicide rates during psychiatric inpatient stay and shortly after discharge. *Acta Psychiatr Scand*. Jul 26 2020;doi:10.1111/acps.13221
57. Olfson M, Wall M, Wang S, et al. Short-term Suicide Risk After Psychiatric Hospital Discharge. *JAMA Psychiatry*. 2016;73(11):1119-1126. doi:10.1001/jamapsychiatry.2016.2035 %J JAMA Psychiatry
58. Deisenhammer EA, Behrndt E-M, Kemmler G, Haring C, Miller C. Suicide Risk Factors in Patients Recently Discharged From a Psychiatric Hospital: A Case-Control Study. *J Clin Psychiatry*. 2019;80(5). doi:10.4088/jcp.18m12702 Accessed 2019/09//.
59. Walby FA, Myhre MO, Kildahl AT. Contact With Mental Health Services Prior to Suicide: A Systematic Review and Meta-Analysis. *Psychiatric services (Washington, DC)*. Jul 1 2018;69(7):751-759. doi:10.1176/appi.ps.201700475
60. Prestmo A, Høyen K, Vaaler AE, Torgersen T, Drange OK. Mortality Among Patients Discharged From an Acute Psychiatric Department: A 5-Year Prospective Study. *Frontiers in psychiatry*. 2020;11:816. doi:10.3389/fpsyt.2020.00816
61. Nordentoft M, Erlangsen A, Madsen T. Postdischarge suicides: nightmare and disgrace. *JAMA psychiatry*. 2016;73(11):1113-1114.
62. Bolton JM. Suicide risk assessment in the emergency department: out of the darkness. *Depress Anxiety*. Feb 2015;32(2):73-5. doi:10.1002/da.22320
63. Strømme MF, Mellesdal LS, Bartz-Johannesen C, et al. Mortality and non-use of antipsychotic drugs after acute admission in schizophrenia: A prospective total-cohort study. *Schizophr Res*. Jul 21 2021;235:29-35. doi:10.1016/j.schres.2021.07.009
64. Fredriksen K, Mellesdal L, Gjestad R, et al. High scores on the MADRS depression rating scale and psychotic symptoms predict suicide: -A prospective cohort study of psychiatric acute ward patients. *manuscript accepted J Clin Psychiatry*. 2022;
65. Kroken RA, Kjelby E, Wentzel-Larsen T, Mellesdal LS, Jørgensen HA, Johnsen E. Time to discontinuation of antipsychotic drugs in a schizophrenia cohort: influence of current treatment strategies. *J Therapeutic advances in psychopharmacology*. 2014;4(6):228-239.
66. Fosse R, Ryberg W, Carlsson MK, Hammer J. Predictors of suicide in the patient population admitted to a locked-door psychiatric acute ward. *PloS one*. 2017;12(3):e0173958. doi:10.1371/journal.pone.0173958
67. Bjureberg J, Dahlin M, Carlborg A, Edberg H, Haglund A, Runeson B. Columbia-Suicide Severity Rating Scale Screen Version: initial screening for suicide risk in a psychiatric emergency department. *Psychol Med*. Mar 26 2021:1-9. doi:10.1017/s0033291721000751

68. Aaltonen KI, Isometsa E, Sund R, Pirkola S. Risk factors for suicide in depression in Finland: first-hospitalized patients followed up to 24 years. *Acta Psychiatr Scand*. Nov 27 2018;doi:10.1111/acps.12990
69. Fawcett J, Scheftner WA, Fogg L, et al. Time-related predictors of suicide in major affective disorder. *The American Journal of Psychiatry*. 1990;147(9):1189-1194.
70. Leadholm AK, Rothschild AJ, Nielsen J, Bech P, Ostergaard SD. Risk factors for suicide among 34,671 patients with psychotic and non-psychotic severe depression. *Journal of Affective Disorders*. Mar 2014;156:119-25. doi:10.1016/j.jad.2013.12.003
71. Large M, Smith G, Sharma S, Nielssen O, Singh SP. Systematic review and meta-analysis of the clinical factors associated with the suicide of psychiatric in-patients. *Acta Psychiatr Scand*. Jul 2011;124(1):18-29. doi:10.1111/j.1600-0447.2010.01672.x
72. Hawton K, i Comabella CC, Haw C, Saunders KJJoad. Risk factors for suicide in individuals with depression: a systematic review. *Journal of Affective Disorders*. 2013;147(1-3):17-28.
73. Lin S-K, Hung T-M, Liao Y-T, et al. Protective and risk factors for inpatient suicides: A nested case–control study. *Psychiatry Research*. 2014/06/30/ 2014;217(1):54-59. doi:https://doi.org/10.1016/j.psychres.2014.03.008
74. Steblaj A, Tavcar R, Dernovsek MZ. Predictors of suicide in psychiatric hospital. *Acta Psychiatr Scand*. Nov 1999;100(5):383-8. doi:10.1111/j.1600-0447.1999.tb10882.x
75. King EA, Baldwin DS, Sinclair JM, Campbell MJ. The Wessex Recent In-Patient Suicide Study, 2. Case-control study of 59 in-patient suicides. *The British journal of psychiatry : the journal of mental science*. Jun 2001;178:537-42. doi:10.1192/bjp.178.6.537
76. Hunt IM, Kapur N, Webb R, et al. Suicide in current psychiatric in-patients: a case-control study The National Confidential Inquiry into Suicide and Homicide. *Psychol Med*. Jun 2007;37(6):831-7. doi:10.1017/s0033291707000104
77. Dong JY, Ho TP, Kan CK. A case-control study of 92 cases of in-patient suicides. *J Affect Disord*. Jul 2005;87(1):91-9. doi:10.1016/j.jad.2005.03.015
78. Taiminen TJ, Kujari H. Antipsychotic medication and suicide risk among schizophrenic and paranoid inpatients. A controlled retrospective study. *Acta Psychiatr Scand*. Oct 1994;90(4):247-51. doi:10.1111/j.1600-0447.1994.tb01588.x
79. Powell J, Geddes J, Deeks J, Goldacre M, Hawton K. Suicide in psychiatric hospital in-patients. Risk factors and their predictive power. *The British journal of psychiatry : the journal of mental science*. Mar 2000;176:266-72. doi:10.1192/bjp.176.3.266

80. Mann J, Michel C, Auerbach R. Improving Suicide Prevention Through Evidence-Based Strategies: A Systematic Review. *Am J Psychiatry* 2021;178(7):611-624. doi:10.1176/appi.ajp.2020.20060864
81. Runeson B, Odeberg J, Pettersson A, Edbom T, Adamsson IJ, Waern M. Instruments for the assessment of suicide risk: A systematic review evaluating the certainty of the evidence. *PloS one*. 2017;12(7):e0180292.
82. Roos L, Sareen J, Bolton JM. Suicide risk assessment tools, predictive validity findings and utility today: time for a revamp? *Neuropsychiatry*. 2013;3(5):483.
83. Radomsky ED, Haas GL, Mann JJ, Sweeney JA. Suicidal behavior in patients with schizophrenia and other psychotic disorders. *American journal of psychiatry*. 1999;156(10):1590-1595.
84. Sani G, Tondo L, Koukopoulos A, et al. Suicide in a large population of former psychiatric inpatients. *Psychiatry and clinical neurosciences*. 2011;65(3):286-295.
85. DeVylder JE, Lukens EP, Link BG, Lieberman JA. Suicidal ideation and suicide attempts among adults with psychotic experiences: data from the Collaborative Psychiatric Epidemiology Surveys. *JAMA psychiatry*. 2015;72(3):219-225.
86. Villa J, Ehret BC, Depp CA. Systematic Review of the Inclusion of People With Psychosis in Suicide-Specific Clinical Trials. *Crisis*. May 2020;41(3):233-236. doi:10.1027/0227-5910/a000628
87. Yates K, Lång U, Cederlöf M, et al. Association of Psychotic Experiences With Subsequent Risk of Suicidal Ideation, Suicide Attempts, and Suicide Deaths: A Systematic Review and Meta-analysis of Longitudinal Population Studies. *JAMA Psychiatry*. Feb 1 2019;76(2):180-189. doi:10.1001/jamapsychiatry.2018.3514
88. Roose SP. Depression, delusions, and suicide. *The American journal of psychiatry*. 1983;
89. Isometsa E, Sund R, Pirkola S. Post-discharge suicides of inpatients with bipolar disorder in Finland. *Bipolar Disord*. Dec 2014;16(8):867-74. doi:10.1111/bdi.12237
90. Gournellis R, Tournikioti K, Touloumi G, et al. Psychotic (delusional) depression and completed suicide: a systematic review and meta-analysis. journal article. *Annals of General Psychiatry*. September 21 2018;17(1):39. doi:10.1186/s12991-018-0207-1
91. Suominen K, Haukka J, Valtonen HM, Lonnqvist J. Outcome of patients with major depressive disorder after serious suicide attempt. *J Clin Psychiatry*. Oct 2009;70(10):1372-8. doi:10.4088/JCP.09m05110blu
92. Kuperberg M, Katz D, Greenebaum SLA, et al. Psychotic symptoms during bipolar depressive episodes and suicidal ideation. *Journal of Affective Disorders*. 2021/03/01/ 2021;282:1241-1246. doi:https://doi.org/10.1016/j.jad.2020.12.184

93. Maina G, Quarato F, Bramante S. Risk factors for suicide in bipolar disorder. *Further exploration of suicidal behavior*. 2019;25:149-154.
94. Robinson DG, Spiker DG. Delusional depression. A one year follow-up. *J Affect Disord*. Jul 1985;9(1):79-83. doi:10.1016/0165-0327(85)90013-8
95. Wolfersdorf M, Keller F, Steiner B, Hole GJAPS. Delusional depression and suicide. 1987;76(4):359-363.
96. Glenn CR, Nock MK. Improving the short-term prediction of suicidal behavior. *American journal of preventive medicine*. Sep 2014;47(3 Suppl 2):S176-80. doi:10.1016/j.amepre.2014.06.004
97. Schnyder U, Valach L, Bichsel K, Michel K. Attempted suicide. Do we understand the patients' reasons? *Gen Hosp Psychiatry*. Jan-Feb 1999;21(1):62-9.
98. Pavulans KS, Bolmsjo I, Edberg AK, Ojehagen A. Being in want of control: Experiences of being on the road to, and making, a suicide attempt. *International journal of qualitative studies on health and well-being*. 2012;7doi:10.3402/qhw.v7i0.16228
99. Thorvik A. Suicid som etisk fenomen: teoretiske og empiriske perspektiver. 2011;
100. Bolton JM, Gunnell D, Turecki G. Suicide risk assessment and intervention in people with mental illness. *BMJ*. 2015;351:h4978.
101. Large M, Kaneson M, Myles N, Myles H, Gunaratne P, Ryan C. Meta-Analysis of Longitudinal Cohort Studies of Suicide Risk Assessment among Psychiatric Patients: Heterogeneity in Results and Lack of Improvement over Time. *PloS one*. 2016;11(6):e0156322. doi:10.1371/journal.pone.0156322
102. Chan MK, Bhatti H, Meader N, et al. Predicting suicide following self-harm: systematic review of risk factors and risk scales. *The British journal of psychiatry : the journal of mental science*. Oct 2016;209(4):277-283. doi:10.1192/bjp.bp.115.170050
103. Lindh AU, Dahlin M, Beckman K, et al. A Comparison of Suicide Risk Scales in Predicting Repeat Suicide Attempt and Suicide: A Clinical Cohort Study. *J Clin Psychiatry*. Nov 19 2019;80(6)doi:10.4088/JCP.18m12707
104. Rudd MD. Suicide warning signs in clinical practice. *Current Psychiatry Reports* Feb 2008;10(1):87-90.
105. Busch KA, Fawcett J, Jacobs DG. Clinical correlates of inpatient suicide. *J Clin Psychiatry*. 2003;64(1):14-19. doi:10.4088/JCP.v64n0105
106. Berman AL. Risk Factors Proximate to Suicide and Suicide Risk Assessment in the Context of Denied Suicide Ideation. *Suicide Life Threat Behav*. Jun 2018;48(3):340-352. doi:10.1111/sltb.12351
107. Pigeon WR, Pinquart M, Conner K. Meta-analysis of sleep disturbance and suicidal thoughts and behaviors. *J Clin Psychiatry*. Sep 2012;73(9):e1160-7. doi:10.4088/JCP.11r07586

108. Bernert RA, Kim JS, Iwata NG, Perlis ML. Sleep disturbances as an evidence-based suicide risk factor. *Current psychiatry reports*. Mar 2015;17(3):554. doi:10.1007/s11920-015-0554-4
109. Britton PC, Ilgen MA, Rudd MD, Conner KR. Warning signs for suicide within a week of healthcare contact in Veteran decedents. *J Psychiatry Research*. 2012;200(2-3):395-399.
110. Gvion Y, Apter A. Aggression, impulsivity, and suicide behavior: a review of the literature. *Archives of Suicide Research*. 2011;15(2):93-112. doi:10.1080/13811118.2011.565265
111. Fawcett J, Scheftner WA, Fogg L, Clark DC. Time-related predictors of suicide in major affective disorder. *The American Journal of Psychiatry*. 1990;
112. Hendin H, Maltsberger JT, Szanto K. The role of intense affective states in signaling a suicide crisis. *J Nerv Ment Dis*. May 2007;195(5):363-8. doi:10.1097/NMD.0b013e318052264d
113. Runeson BS, Beskow J, Waern M. The suicidal process in suicides among young people. *Acta Psychiatrica Scandinavica*. 1996;93(1):35-42. doi:10.1111/j.1600-0447.1996.tb10616.x
114. van Heeringen K, Hawton K, Williams G, Mark J. Pathways to suicide: an integrative approach. *The international handbook of suicide and attempted suicide*. 2008:223-234.
115. Post RM. Transduction of Psychosocial Stress Into the Neurobiology. *Am J Psychiatry*. 1992;149:999-1010.
116. Segal ZV, Williams J, Teasdale J, Gemar M. A cognitive science perspective on kindling and episode sensitization in recurrent affective disorder. *Psychological Medicine*. 1996;26(2):371-380.
117. Williams JMG, Williams M. *Suicide and attempted suicide: Understanding the cry of pain*. Mark Williams; 2001.
118. Bloch-Elkouby S, Barzilay S, Gorman B, et al. The Revised Suicide Crisis Inventory (SCI-2): Validation and Assessment of Prospective Suicidal Outcomes at One Month Follow-Up. *J Affect Disord*. 2021/08/27/ 2021;doi:https://doi.org/10.1016/j.jad.2021.08.048
119. Galynker I. *The suicidal crisis: clinical guide to the assessment of imminent suicide risk*. Oxford University Press; 2017.
120. Schuck A, Calati R, Barzilay S, Bloch-Elkouby S, Galynker I. Suicide Crisis Syndrome: A review of supporting evidence for a new suicide-specific diagnosis. *Behavioral sciences & the law*. May 2019;37(3):223-239. doi:10.1002/bsl.2397
121. Vaaler AE. Benzodiazepines in emergency psychiatric treatment. *Tidsskrift for den Norske laegeforening : tidsskrift for praktisk medicin, ny raekke*. May 7

2019;139(8)Benzodiazepiner i akuttpsykiatrisk behandling. doi:10.4045/tidsskr.19.0228
122. Zealberg JJ, Brady KT. Substance abuse and emergency psychiatry. *Psychiatr Clin North Am*. Dec 1999;22(4):803-17. doi:10.1016/s0193-953x(05)70127-1
123. Allen MH, Currier GW, Hughes DH, Docherty JP, Carpenter D, Ross R. Treatment of behavioral emergencies: a summary of the expert consensus guidelines. *J Psychiatr Pract*. Jan 2003;9(1):16-38. doi:10.1097/00131746-200301000-00004
124. Nock MK, Borges G, Bromet EJ, et al. Cross-national prevalence and risk factors for suicidal ideation, plans and attempts. *The British journal of psychiatry : the journal of mental science*. Feb 2008;192(2):98-105. doi:10.1192/bjp.bp.107.040113
125. Klonsky ED, May AM, Saffer BY. Suicide, Suicide Attempts, and Suicidal Ideation. *Annual Review of Clinical Psychology*. 2016;12(1):307-330. doi:10.1146/annurev-clinpsy-021815-093204
126. Chapman CL, Mullin K, Ryan CJ, Kuffel A, Nielssen O, Large MM. Meta-analysis of the association between suicidal ideation and later suicide among patients with either a schizophrenia spectrum psychosis or a mood disorder. *Acta Psychiatr Scand*. Mar 2015;131(3):162-73. doi:10.1111/acps.12359
127. Hubers AAM, Moaddine S, Peersmann SHM, et al. Suicidal ideation and subsequent completed suicide in both psychiatric and non-psychiatric populations: a meta-analysis. *Epidemiology and psychiatric sciences*. Apr 2018;27(2):186-198. doi:10.1017/s2045796016001049
128. McHugh CM, Corderoy A, Ryan CJ, Hickie IB, Large MM. Association between suicidal ideation and suicide: meta-analyses of odds ratios, sensitivity, specificity and positive predictive value. *BJPsych open*. Mar 2019;5(2):e18. doi:10.1192/bjo.2018.88
129. Klonsky ED, Victor SE, Saffer BY. Nonsuicidal self-injury: what we know, and what we need to know. *Canadian journal of psychiatry Revue canadienne de psychiatrie*. 2014;59(11):565-568. doi:10.1177/070674371405901101
130. Sher L. Suicide in men: the time is ripe for active scientific investigations. *Acta Psychiatrica Scandinavica*. 2018;137(4):275-276. doi:10.1111/acps.12861
131. Rutz W, Rihmer Z. Suicidality in men – practical issues, challenges, solutions. *The Journal of Men's Health & Gender*. 2007;4(4):393-401. doi:10.1016/j.jmhg.2007.07.046
132. Brent DA, Oquendo MA, Reynolds CF, 3rd. Caring for Suicidal Patients. *JAMA Psychiatry*. Aug 1 2019;76(8):862-863. doi:10.1001/jamapsychiatry.2019.0927
133. Baldessarini RJ, Tondo L, Davis P, Pompili M, Goodwin FK, Hennen J. Decreased risk of suicides and attempts during long term lithium treatment: a meta analytic review. *Bipolar disorders*. 2006;8(5p2):625-639.

134. Cipriani A, Pretty H, Hawton K, Geddes JR. Lithium in the prevention of suicidal behavior and all-cause mortality in patients with mood disorders: a systematic review of randomized trials. *American Journal of Psychiatry*. 2005;162(10):1805-1819.
135. Reeves H, Batra S, May RS, Zhang R, Dahl DC, Li X. Efficacy of risperidone augmentation to antidepressants in the management of suicidality in major depressive disorder: a randomized, double-blind, placebo-controlled pilot study. *J Clin Psychiatry*. Aug 2008;69(8):1228-336.
136. Sharma T, Guski LS, Freund N, Gøtzsche PC. Suicidality and aggression during antidepressant treatment: systematic review and meta-analyses based on clinical study reports. *BMJ*. 2016;352:i65. doi:10.1136/bmj.i65
137. DiazGranados N, Ibrahim L, Brutsche N, et al. Rapid Resolution of Suicidal Ideation after a Single Infusion of an NMDA Antagonist in Patients with Treatment-Resistant Major Depressive Disorder. *The Journal of clinical psychiatry*. 07/13 2010;71(12):1605-1611. doi:10.4088/JCP.09m05327blu
138. Gaertner I, Gilot C, Heidrich P, Gaertner HJ. A case control study on psychopharmacotherapy before suicide committed by 61 psychiatric inpatients. *Pharmacopsychiatry*. Mar 2002;35(2):37-43. doi:10.1055/s-2002-25027
139. Garriga M, Pacchiarotti I, Kasper S, et al. Assessment and management of agitation in psychiatry: Expert consensus. *The World Journal of Biological Psychiatry*. 2016/02/17 2016;17(2):86-128. doi:10.3109/15622975.2015.1132007
140. Wilkinson ST, Ballard ED, Bloch MH, et al. The Effect of a Single Dose of Intravenous Ketamine on Suicidal Ideation: A Systematic Review and Individual Participant Data Meta-Analysis. *Am J Psychiatry*. Feb 1 2018;175(2):150-158. doi:10.1176/appi.ajp.2017.17040472
141. Witt K, Potts J, Hubers A, et al. Ketamine for suicidal ideation in adults with psychiatric disorders: A systematic review and meta-analysis of treatment trials. *The Australian and New Zealand journal of psychiatry*. Jan 2020;54(1):29-45. doi:10.1177/0004867419883341
142. Kellner CH, Li EH, Farber KG, Geduldig ET, Ahle GM. Electroconvulsive Therapy (ECT) and Suicide Prevention. *Current Treatment Options in Psychiatry*. 2016// 2016;3(1):73-81. doi:10.1007/s40501-016-0067-8
143. Hawton K, Heeringen K. *The International Handbook of Suicide and Attempted Suicide, pp.585-595*. Wiley Online Library; 2000.
144. Lakeman R, FitzGerald M. How people live with or get over being suicidal: a review of qualitative studies. *Journal of advanced nursing*. 2008;64(2):114-126.
145. Bjornestad J, Davidson L, Joa I, et al. Antipsychotic treatment: experiences of fully recovered service users. *Journal of mental health (Abingdon, England)*. Jun 2017;26(3):264-270. doi:10.1080/09638237.2017.1294735

146. Bjornestad J, Hegelstad WTV, Joa I, et al. "With a little help from my friends" social predictors of clinical recovery in first-episode psychosis. *Psychiatry Res*. May 30 2017;255:209-214. doi:10.1016/j.psychres.2017.05.041
147. Berg SH, Rortveit K, Walby FA, Aase K. Safe clinical practice for patients hospitalised in a suicidal crisis: a study protocol for a qualitative case study. *BMJ open*. Jan 27 2020;7(1):e012874. doi:10.1136/bmjopen-2016-012874
148. Berg SH, Rortveit K, Aase K. Suicidal patients' experiences regarding their safety during psychiatric in-patient care: a systematic review of qualitative studies. *BMC health services research*. Jan 23 2017;17(1):73. doi:10.1186/s12913-017-2023-8
149. Biddle L, Donovan J, Owen-Smith A, et al. Factors influencing the decision to use hanging as a method of suicide: qualitative study. *The British journal of psychiatry : the journal of mental science*. Oct 2010;197(4):320-5. doi:10.1192/bjp.bp.109.076349
150. University of Manchester. The National Confidential Inquiry into Suicide and Homicide by People with Mental Illness 2016;
151. Watts BV, Young-Xu Y, Mills PD, et al. Examination of the effectiveness of the Mental Health Environment of Care Checklist in reducing suicide on inpatient mental health units. *Arch Gen Psychiatry*. Jun 2012;69(6):588-92. doi:10.1001/archgenpsychiatry.2011.1514
152. van der Merwe M, Bowers L, Jones J, Simpson A, Haglund K. Locked doors in acute inpatient psychiatry: a literature review. *Journal of psychiatric and mental health nursing*. 2009;16(3):293-299.
153. Huber CG, Schneeberger AR, Kowalinski E, et al. Suicide risk and absconding in psychiatric hospitals with and without open door policies: a 15 year, observational study. *The lancet Psychiatry*. Sep 2016;3(9):842-9. doi:10.1016/s2215-0366(16)30168-7
154. Malterud K. The art and science of clinical knowledge: evidence beyond measures and numbers. *Lancet*. Aug 4 2001;358(9279):397-400.
155. Malterud K. Qualitative research: standards, challenges, and guidelines. *The Lancet*. 2001;358(9280):483-488.
156. Malterud K. *Kvalitative metoder i medisinsk forskning: en innføring*. Universitetsforlaget; 2011.
157. Gadamer H-G. *The enigma of health: The art of healing in a scientific age*. John Wiley & Sons; 2018.
158. Malterud K. Systematic text condensation: A strategy for qualitative analysis. *Scandinavian Journal of Public Health*. 2012;40(8):795-805.
159. Miller WL, Crabtree BF. *Doing qualitative research*. vol 3. Thousand Oaks, California: Sage publications Inc; 1999.

160. Malterud K, Siersma VD, Guassora AD. Sample Size in Qualitative Interview Studies: Guided by Information Power. *Qualitative Health Research*. Nov 27 2015;Vol. 26(13):1753–1760. doi:10.1177/1049732315617444
161. Mann C. Observational research methods. Research design II: cohort, cross sectional, and case-control studies. *Emergency medicine journal*. 2003;20(1):54-60.
162. FHI. *https://wwwfhino/nettpub/hin/psykisk-helse/selvmord-i-norge*. 2021;
163. American Psychiatric Association. *Diagnostic criteria from DSM-IV*. Amer Psychiatric Pub Inc; 1994.
164. First M, Spitzer R, Gibbon M, Williams J. Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition (SCID-P). New York, NY, New York State Psychiatric Institute, Biometrics Research Department. 1996;
165. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia bulletin*. 1987;13(2):261-276.
166. Weibell MA, Joa I, Bramness J, et al. Treated incidence and baseline characteristics of substance induced psychosis in a Norwegian catchment area. *BMC Psychiatry*. 2013;13:319. doi:10.1186/1471-244x-13-319
167. Mellesdal L, Kroken RA, Lutro O, et al. Self-harm induced somatic admission after discharge from psychiatric hospital - a prospective cohort study. *European psychiatry : the journal of the Association of European Psychiatrists*. May 2014;29(4):246-52. doi:10.1016/j.eurpsy.2013.06.006
168. Müller MJ, Himmerich H, Kienzle B, Szegedi A. Differentiating moderate and severe depression using the Montgomery–Åsberg depression rating scale (MADRS). *Journal of Affective Disorders*. 2003/12/01/ 2003;77(3):255-260. doi:https://doi.org/10.1016/S0165-0327(02)00120-9
169. Williams JBW, Kobak KA. Development and reliability of a structured interview guide for the Montgomery-Åsberg Depression Rating Scale (SIGMA). *British Journal of Psychiatry*. 2008;192(1):52-58. doi:10.1192/bjp.bp.106.032532
170. Svanborg P, Asberg M. A comparison between the Beck Depression Inventory (BDI) and the self-rating version of the Montgomery Asberg Depression Rating Scale (MADRS). *J Affect Disord*. May 2001;64(2-3):203-16. doi:10.1016/s0165-0327(00)00242-1
171. Wing J, Curtis R, Beevor A. 'Health of the Nation': measuring mental health outcomes. *Psychiatric Bulletin*. 1994;18(11):690-691.
172. James M, Painter J, Buckingham B, Stewart MW. A review and update of the Health of the Nation Outcome Scales (HoNOS). *BJPsych Bull*. 2018;42(2):63-68. doi:10.1192/bjb.2017.17
173. Pirkis JE, Burgess PM, Kirk PK, Dodson S, Coombs TJ, Williamson MK. A review of the psychometric properties of the Health of the Nation Outcome Scales (HoNOS)

family of measures. *Health Qual Life Outcomes*. Nov 28 2005;3:76. doi:10.1186/1477-7525-3-76
174. Wing J, Curtis RH, Beevor A. Health of the Nation Outcome Scales (HoNOS). Glossary for HoNOS score sheet. *The British journal of psychiatry : the journal of mental science*. May 1999;174:432-4. doi:10.1192/bjp.174.5.432
175. Fankhauser S, Hochstrasser B, Sievers M, Soyka M. [Assessing Change of Depressive Symptoms and Severity of Depression in an Inpatient Setting : Performance of the HoNOS (Health of the Nation Outcome Scales)]. *Psychother Psychosom Med Psychol*. Sep 2017;67(9-10):391-400. Die Eignung der HoNOS (Health of the Nation Outcome Scales) zur Erfassung des Verlaufs und des Schweregrads depressiver Symptomatik im stationären Setting. doi:10.1055/s-0043-105482
176. Pedersen AG, Ellingsen CL. Data quality in the Causes of Death Registry. *Tidsskrift for den Norske laegeforening : tidsskrift for praktisk medicin, ny raekke*. May 5 2015;135(8):768-70. doi:10.4045/tidsskr.14.1065
177. Vittinghoff E, McCulloch CE. Relaxing the Rule of Ten Events per Variable in Logistic and Cox Regression. *American Journal of Epidemiology*. 2006;165(6):710-718. doi:10.1093/aje/kwk052 %J American Journal of Epidemiology
178. R Core Team. R: A language and environment for statistical computing. . *R Foundation for Statistical Computing, Vienna, Austria*. 2020;
179. Whittemore R, Knafl K. The integrative review: updated methodology. *Journal of advanced nursing*. 2005;52(5):546-553.
180. Lakeman R, Fitzgerald M. The ethics of suicide research. *Crisis*. 2009;30(1):13-9. doi:10.1027/0227-5910.30.1.13
181. Fisher CB, Pearson JL, Kim S, Reynolds CF. Ethical Issues in including Suicidal Individuals in Clinical Research. *IRB: Ethics & Human Research*. 2002;24(5):9-14. doi:10.2307/3563804
182. Rothschild AJ. Challenges in the treatment of depression with psychotic features. *Biological Psychiatry*. Apr 15 2003;53(8):680-90.
183. Heslin M, Young AH. Psychotic major depression: challenges in clinical practice and research. *The British Journal of Psychiatry*. 2018;212(3):131-133. doi:10.1192/bjp.2017.43
184. Beauchamp TL, Childress JF. Principles of Biomedical Ethics. 7. Aufl New York. Oxford; 2013.
185. Baldwin CJJoAS. Narrative ethics for narrative care. 2015;34:183-189.
186. Fredriksen KJ, Schoeyen HK, Johannessen JO, Walby FA, Davidson L, Schaufel MA. Psychotic Depression and Suicidal Behavior. *Psychiatry*. 2017/01/02 2017;80(1):17-29. doi:10.1080/00332747.2016.1208002

187. Fredriksen KJ, Schaufel MA, Johannessen JO, Walby FA, Davidson L, Schoeyen HK. Preventing suicide among psychiatric inpatients with psychotic depression. *Psychiatric Quarterly*. 2020;91(1):223-236.
188. Fredriksen K, Bartz-Johannessen C, Schoeyen H, Vaaler A, Walby FP, Hegelstad W. Imminent and very short-term risk of death by suicide in 7000 acutely admitted psychiatric inpatients. *submitted, in review*. 2022;
189. Keilp JG, Sackeim HA, Brodsky BS, Oquendo MA, Malone KM, Mann JJ. Neuropsychological dysfunction in depressed suicide attempters. *American Journal of Psychiatry*. 2001;158(5):735-741.
190. Desmyter S, Van Heeringen C, Audenaert K. Structural and functional neuroimaging studies of the suicidal brain. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 2011;35(4):796-808.
191. Townsend J, Altshuler LL. Emotion processing and regulation in bipolar disorder: a review. *Bipolar Disorders*. 2012;14(4):326-339.
192. Baker JT, Holmes AJ, Masters GA, et al. Disruption of cortical association networks in schizophrenia and psychotic bipolar disorder. *JAMA Psychiatry*. 2013;
193. Keller J, Gomez R, Williams G, et al. HPA axis in major depression: cortisol, clinical symptomatology and genetic variation predict cognition. *Molecular Psychiatry*. 2017/04/01 2017;22(4):527-536. doi:10.1038/mp.2016.120
194. Oquendo MA, Galfalvy H, Russo S, et al. Prospective study of clinical predictors of suicidal acts after a major depressive episode in patients with major depressive disorder or bipolar disorder. *American Journal of Psychiatry*. 2004;161(8):1433-1441.
195. McGorry PD. Issues for DSM-V: clinical staging: a heuristic pathway to valid nosology and safer, more effective treatment in psychiatry. *Am J Psychiatry*. Jun 2007;164(6):859-60. doi:10.1176/ajp.2007.164.6.859
196. Leboyer M, Schurhoff F. Searching Across Diagnostic Boundaries. *Schizophrenia Bulletin*. 2014;40(5):946-948. doi:10.1093/schbul/sbu112
197. Østergaard SD, Bille J, Søltoft-Jensen H, Lauge N, Bech P. The validity of the severity–psychosis hypothesis in depression. *Journal of affective disorders*. 2012;140(1):48-56.
198. Forty L, Jones L, Jones I, et al. Is depression severity the sole cause of psychotic symptoms during an episode of unipolar major depression? A study both between and within subjects. *J Affect Disord*. Apr 2009;114(1-3):103-9. doi:10.1016/j.jad.2008.06.012
199. Ohayon MM, Schatzberg AF. Prevalence of depressive episodes with psychotic features in the general population. *American Journal of Psychiatry*. 2002;159(11):1855-1861.

200. Maj M, Pirozzi R, Magliano L, Fiorillo A, Bartoli L. Phenomenology and prognostic significance of delusions in major depressive disorder: a 10-year prospective follow-up study. *The Journal of clinical psychiatry*. 2007;68(9):1411.
201. Baumeister RF. Suicide as escape from self. *Psychological review*. 1990;97(1):90.
202. Li S, Yaseen ZS, Kim H-J, et al. Entrapment as a mediator of suicide crises. *BMC Psychiatry*. 2018/01/08 2018;18(1):4. doi:10.1186/s12888-018-1587-0
203. Bostwick JM, Pabbati C, Geske JR, McKean AJ. Suicide attempt as a risk factor for completed suicide: even more lethal than we knew. *American journal of psychiatry*. 2016;173(11):1094-1100.
204. Lester D. The role of shame in suicide. *Suicide and Life-Threatening Behavior*. 1997;27(4):352-361.
205. Wurmser L. Trauma, shame conflicts, and affect regression: Discussion of "wounded but still walking". *Psychoanalytic Inquiry*. 1999/01/01 1999;19(3):309-319. doi:10.1080/07351699909534252
206. Herman JL. *Trauma and recovery*. Basic Books; 1997.
207. Nelson WH, Khan A, Orr WW. Delusional depression: Phenomenology, neuroendocrine function, and tricyclic antidepressant response. *Journal of affective disorders*. 1984;6(3):297-306.
208. Miller F, Chabrier LA. The relation of delusional content in psychotic depression to life-threatening behavior. *Suicide Life Threat Behav*. Spring 1987;17(1):13-7. doi:10.1111/j.1943-278x.1987.tb00058.x
209. Hori M, Shiraishi H, Koizumi J. Delusional depression and suicide. *Psychiatry and clinical neurosciences*. 1993;47(4):811-817.
210. Deisenhammer EA, Ing CM, Strauss R, Kemmler G, Hinterhuber H, Weiss EM. The duration of the suicidal process: how much time is left for intervention between consideration and accomplishment of a suicide attempt? *J Clin Psychiatry*. Jan 2009;70(1):19-24.
211. Kvale S. Interviews: An Introduction to Qualitative Research Interviewing, Sage. *Thousand Oaks, CA*. 1996;
212. Miles MB, Huberman AM. *Qualitative data analysis: An expanded sourcebook*. Sage; 1994.
213. Leadholm AK, Rothschild AJ, Nolen WA, Bech P, Munk-Jorgensen P, Ostergaard SD. The treatment of psychotic depression: is there consensus among guidelines and psychiatrists? *J Affect Disord*. Feb 20 2013;145(2):214-20. doi:10.1016/j.jad.2012.07.036
214. Nome S, Holsten F. A prospective longitudinal study of utilization of a psychiatric hospital in Hordaland County, Norway, from 1985 to 2003. *Nordic journal of psychiatry*. Apr 2011;65(2):117-24. doi:10.3109/08039488.2010.504991

215. Bock C, Bukh JD, Vinberg M, Gether U, Kessing LV. Validity of the diagnosis of a single depressive episode in a case register. *Clinical Practice and Epidemiology in Mental Health*. 2009;5(1):4.
216. Kessing L. Validity of diagnoses and other clinical register data in patients with affective disorder. *European psychiatry*. 1998;13(8):392-398.
217. Hjelmeland H, Knizek BL. Why we need qualitative research in suicidology. *Suicide Life Threat Behav*. Feb 2010;40(1):74-80. doi:10.1521/suli.2010.40.1.74
218. van Os J, Reininghaus U. Psychosis as a transdiagnostic and extended phenotype in the general population. *World Psychiatry*. Jun 2016;15(2):118-24. doi:10.1002/wps.20310
219. Tamminga CA, Ivleva EI, Keshavan MS, et al. Clinical phenotypes of psychosis in the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP). *Am J Psychiatry*. Nov 2013;170(11):1263-74. doi:10.1176/appi.ajp.2013.12101339
220. Hacker PMS. *The intellectual powers: A study of human nature*. John Wiley & Sons; 2013.
221. Ness E, Skotte JR, Christensen TB, Andresen JFJTfDnl. Can we save more lives? 2020;
222. Oeye C, Bjelland AK, Skorpen A. Doing participant observation in a psychiatric hospital--Research ethics resumed. *Social Science & Medicine*. 2007;65(11):2296-2306.
223. Cukrowicz K, Smith P, Poindexter E. The effect of participating in suicide research: does participating in a research protocol on suicide and psychiatric symptoms increase suicide ideation and attempts? *Suicide Life Threat Behav*. Dec 2010;40(6):535-43. doi:10.1521/suli.2010.40.6.535
224. Deeley ST, Love AW. Does asking adolescents about suicidal ideation induce negative mood state? *Violence and victims*. 2010;25(5):677-88.
225. Mathias CW, Michael Furr R, Sheftall AH, Hill-Kapturczak N, Crum P, Dougherty DM. What's the harm in asking about suicidal ideation? *Suicide and Life-Threatening Behavior*. Jun 2012;42(3):341-51. doi:10.1111/j.1943-278X.2012.0095.x

# Appendices

The following articles make up the rest of the thesis, but cannot be included in Brage due to copyright. Access to the articles may be restricted.

1. Fredriksen, K. J., Schoeyen, H. K., Johannessen, J. O., Walby, F. A., Davidson, L., & Schaufel, M. A. (2017). Psychotic Depression and Suicidal Behavior. *Psychiatry*, 80(1), 17-29. DOI: 10.1080/00332747.2016.1208002

2. Fredriksen, K. J., Schaufel, M. A., Johannessen, J. O., Walby, F. A., Davidson, L., & Schoeyen, H. K. (2020). Preventing suicide among psychiatric inpatients with psychotic depression. *Psychiatric Quarterly*, 91(1), 223-236. DOI: 10.1007/s11126-019-09677-6

3. Fredriksen, K., Mellesdal, L., Gjestad, R., Walby, F., Anda, L., Oedegaard, K. J., & Schoeyen, H. (2022). High scores on the MADRS depression rating scale and psychotic symptoms predict suicide: -A prospective cohort study of psychiatric acute ward patients. *Journal of Clinical Psychiatry*, 2022, 83(5). DOI:10.4088/JCP.21m14018

4. Fredriksen, K., Bartz-Johannessen, C., Schoeyen, H., Vaaler, A., Walby, F. P., & Hegelstad, W. (2022). Imminent and very short-term risk of death by suicide in 7000 acutely admitted psychiatric inpatients. (Manuscript submitted).