Analysis protocol

Evaluating effects of acute referrals for patients with mental health problems in primary care out-of-hours services

Project group:

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Introduction

Individuals with severe mental illness frequently face recurring health crises, requiring decisions to be made about whether hospitalization is warranted or if alternative treatment options are viable.[1,2] Acute hospitalization typically begins with a referral decision made by a physician outside the receiving institution. These referrals, whether voluntary or involuntary, may be required in cases of elevated suicide risk, severe self-neglect or risk to self or others in the context of mental illness, or severe agitation due to bipolar disorder or psychosis.[3-5] The risk of self-harm with suicidal intent is a common reason for acute hospitalization, although predicting this risk remains challenging. [3-7]

Despite an awareness of these risks, the effects of hospital admission on patients in crisis, whether voluntary or involuntary, is unclear. Systematic reviews provide inconclusive evidence on whether inpatient admission or alternative treatments yield better health outcomes.[2 8] Additionally, some evidence suggests that hospitalization may potentially increase suicide risk.[3] This issue is further complicated by a limited range of treatment options, affecting voluntary care planning and care delivered in an involuntary context.

Ethical and practical considerations make it nearly impossible to perform randomized trials to evaluate acute referrals for patients with recurrent mental health problems. Therefore, our understanding of how acute voluntary and involuntary admissions causally affect outcomes referrals remains limited.[2]

Clinicians must evaluate the available evidence to balance treatment decisions' potential benefits and risks, leading to substantial variation in practice. Previous studies have identified considerable differences in doctors' treatment approaches, in referral practices and the choice of pharmacological treatments.[9-13] In Norway, individuals experiencing acute mental health crises often first seek help from out-of-hours service physicians[5]. These physicians frequently face dilemmas about whether to refer patients to the hospital. When symptoms are vague but potentially severe, some physicians may choose to refer patients. Alternatively, physicians might adopt a watchful waiting approach or advise patients to contact their general practitioner (GP) during regular hours or other alternatives within the primary care system. As a result, many patients' referral decisions are influenced by personal preferences and the threshold for intervening with the assessing physician. In the out-of-hours setting, these physician preferences, or referral thresholds, are unlikely to be related to the presenting symptoms of their current patient. Therefore, the probability of patients being referred to specialist care may differ substantially depending on which physician is working at the out-of-hours service at the time of their visit

In this study, we will study patients aged 18 or older, aiming to investigate two research questions:

1. What is the effect of acute hospital referrals from primary care out-of-hours services for patients with mental illness, and
2. given acute referral, what is the effect of voluntary versus involuntary referrals from primary care out-of-hours services?

We will study outcomes up to six months after the initial contact with out-of-hours primary care services.

Primary outcome:

1. health service use related to self-harm

Secondary outcomes:

2. direct discharge from hospital after referral from out-of-hours,
3. acute contacts with specialised health services for intoxications,
4. acute contacts with specialised health services for accidents,
5. acute somatic hospitalisations in total,
6. acute psychiatric admissions,
7. contacts with primary care physicians (GP and out-of-hours)
8. costs for using specialist health care services.

We will use a case-only design, following individuals with multiple out-of-hours service contacts. To overcome confounding by indication, we will use two analytical approaches. First, we will use a multivariable-adjusted within-patient approach to investigate outcomes after out-of-hours service contacts that end in a referral to hospital versus no referral and voluntary vs involuntary referral. Secondly, using an instrumental variable approach,[14] we will use physicians' preferences for referral as an instrument to estimate the effects of referral on the outcomes. Although the severity of the condition at different out-of-hours service visits is likely to vary, this is unlikely to be related to the physicians' working schedules at the out-of-hours service. Such instrumental variable analyses can provide valid estimates of the causal effects of referrals, even when there are residual differences in the severity of symptoms between the referred or non-referred.

Methods

Study Setting

The Norwegian healthcare system is characterised by universal access, minimal patient co-payments for GP services and outpatient specialist clinics, and no co-payment for hospital admissions. Out-of-hours primary care in Norway is primarily organized through GP cooperatives, which is the predominant model in Europe. These cooperatives handle most acute presentations for mental illnesses occurring outside regular office hours and, like scheduled GP care, provide gatekeeping services for secondary care.

The Admission Process in The Norwegian Health Care System

When primary care physicians decide to refer a patient to the hospital immediately, a hospital clinician will reassess the patient to determine if acute admission is necessary. The assessment is recorded as an acute outpatient specialist contact if the admission is deemed unnecessary or the situation was resolved immediately. In cases where a patient has both mental and

physical illnesses, the urgency of their respective conditions dictates the initial treatment facility used. For example, a patient referred for self-harm with physical injuries, toxicity, or alcohol intoxication may first be admitted to a somatic part of the hospital. This patient will then be evaluated for follow-up care or transfer to a psychiatric facility.

Involuntary or voluntary referral

The Norwegian system regulates involuntary admission under the Mental Health Care Act.[15] In case of an out-of-hours visit, the physician must first decide whether the patient should be referred to the hospital or can be supported appropriately through regular GP contact or, if possible, be referred to other available services in the municipality. The referring physician must also decide whether the referral should be voluntary or involuntary. Based on information from the medical examination from the out-of-hours physician and an assessment, a responsible professional at the hospital (a psychiatrist or a clinical psychologist) assesses whether the conditions for compulsory admission are met.[16]

Conditions for Involuntary Hospitalisation

After the assessment of the responsible clinician, involuntary hospitalisation can be categorised as for observation or admission.

Table 1 – Conditions for involuntary observation or admission to hospital [16]

Involuntary observation for max 10 days	*Involuntary admission*
- Voluntary mental health care has been attempted without success, or it is clearly futile to attempt this. - The patient has been examined by two physicians, one of whom must be independent of the responsible institution. - The patient lacks decision-making capacity - It is highly likely that the patient meets the criteria for compulsory mental healthcare. - The institution is professionally and materially capable of providing the patient with satisfactory treatment and care. - The patient has been given the opportunity to express their views.	Based on information from the medical examination, the responsible professional assesses whether the following conditions for compulsory mental health care are met: - Voluntary mental health care has been attempted without success, or it is clearly futile to attempt this. - The patient has been examined by two physicians, one of whom must be independent of the responsible institution. - The patient has a serious mental disorder, and the establishment of compulsory mental healthcare is necessary to prevent the following due to the mental disorder: o A significant reduction in their prospects of recovery or substantial improvement, or there is a high likelihood that their condition will significantly worsen in the very near future. o They pose an imminent and serious risk to their own life or the life or health of others. o The patient lacks decision-making capacity. This condition does not apply in cases of imminent and serious risk to the patient's own life or the life or health of others. - The institution is professionally and materially capable of providing the patient with satisfactory treatment and care and is approved. - The patient has been given the opportunity to express their views.

Even if the legal conditions are met, involuntary admissions can only be made if, after an overall assessment, they appear to be the best solution for the individual, unless they pose an imminent and serious risk to the life or health of others.

Study Population and Design

Reimbursement claims from out-of-hours contacts in Norway include patient ID, time, patient diagnoses, a unique physician identification number, and the type of contact (e.g. telephone, consultation, home visits, including a specific code for out-of-hours work). The study population in the current analysis represents all out-of-hours face-to-face or electronic contacts for patients aged 18 years and older who had more than one contact (with at least one of the refund codes 2AD, 2ED, 2AK, 2FK, 615, 2AE, 2AEK, 11AD or 11AK) with an out-of-hours physician in Norway with a diagnosis coded as related to mental health in the International Classification of Primary Care (ICPC) (Chapter P - Psychological) in the period from January 1, 2015, to December 31, 2021. Contacts at the out-of-hours service with the patient's own GP are excluded. This defines a sample of 72 328 patients, representing 347 941 out-of-hours contacts. Using a unique identification number, we link information on specialized health service use, primary care physician use, demographic information from Statistics Norway, and date of death from the Norwegian Cause of Death Registry. Information from the Norwegian General Practitioner Register is linked to each patient contact by a unique physician ID.

Data Sources

- Primary Care Data (KPR-KUHR): Information on out-of-hours service contacts and contact with GPs.
- Specialized Health Service Data (NPR): Hospital admissions and outpatient visits.
- Statistics Norway: Demographic data, including age, sex, place of residence.
- The Norwegian Cause of Death Registry (DÅR): Date and cause of death
- The Norwegian General Practitioner Register (FL): Background information on physicians

Patients visiting the same out-of-hours service

Although out-of-hours services are provided by municipalities, neighbouring municipalities may collaborate, especially in sparsely populated areas. As a result, the location of the service may change regularly or be centralized over time, and one out-of-hours office may serve multiple municipalities. Physicians typically work within a single out-of-hours service at a time, even if that service caters to multiple municipalities. Each patient contact is linked to the municipality code where the patient is registered (Statistics Norway). To determine the location of out-of-hours services for each contact, we use the most common (modal) municipality code among patients each physician sees per month. The municipality where most of a physician's patients reside is defined as the service location for that physician during that week. Patients visiting physicians with the same modal municipality code are redefined as belonging to the same service. We pick the largest municipality if the modal value is the same for two or more municipalities.

Exposure

- Primary exposures:
    - Referral to the hospital is defined as an unplanned hospital visit within 10 hours after an index contact with the out-of-hours services.
    - In cases of referral to hospital: the physician's decision on voluntary vs involuntary referral to the hospital.

Table 2 – Out-of-hours contacts for patients with >1 contact with an ICPC diagnosis indicating a mental health problem in 2015–2021. Number of contacts with and without an acute hospital referral.

year	acute_referral 0	1	Total
2015	33,175	10,456	43,631
2016	34,110	11,476	45,586
2017	36,379	12,973	49,352
2018	38,524	14,214	52,738
2019	40,829	14,720	55,549
2020	37,555	14,374	51,929
2021	35,913	13,243	49,156
Total	256,485	91,456	347,941

Table 3 – Out-of-hours contacts for patients with >1 contact with an ICPC-2 diagnosis indicating a mental health problem in the period 2015–2021. Number of contacts with and without an involuntary hospital referral.

year	involuntary_referral 0	1	Total
2015	40,065	3,566	43,631
2016	41,555	4,031	45,586
2017	45,183	4,169	49,352
2018	48,083	4,655	52,738
2019	50,597	4,952	55,549
2020	46,405	5,524	51,929
2021	43,875	5,281	49,156
Total	315,763	32,178	347,941

Outcomes

Primary Outcomes within 30 days and 180 days*:*

- Hospital admissions for diagnoses representing self-harm. Outcomes will be ascertained using diagnoses in the International Statistical Classification of Diseases and Related Health Problems (ICD-10),[17] registered after contact with specialized health services. Self-harm is indicated by codes X60-84 (suicide), X6n (intentional self-harm) and Y87 (Sequelae of intentional self-harm, assault and events of undetermined intent).

Secondary outcomes within 30 days and 180 days*:*

- Immediate discharge. The outcome of the hospital assessment is that the patient may either be admitted for inpatient treatment or discharged immediately. In cases of involuntary referral, the assessment could result in a voluntary stay or discharge immediately.

- Hospital admissions for diagnoses representing self-harm with expanded definition. There are reasons to assume the underdiagnosis of self-harm in Norwegian registries.[18] We will use the procedure from a Norwegian study, expanding the definition of deliberate self-harm by a proposed list of ICD-10 diagnostic codes.[19]
- Acute hospitalisations for intoxications (ICD-10 codes T4n-T50, T51-T60, T65, F10-19 [only code F1x.0]), accidents with undetermined cause (ICD-10 codes Y10-Y34) and transport accidents (ICD-10 codes V01-V99).
- Acute somatic hospitalisations in total.
- Acute psychiatric admissions.
- Contacts with primary care physicians (GP and out-of-hours).
- The costs for using specialist health care services.

Design – emulating a randomized cross-over trial

For all analyses, we will follow individuals with multiple out-of-hours service contacts with a mental health diagnosis in the International Classification of Primary Care (ICPC) (Chapter P - Psychological) from January 1, 2015, to December 31, 2021.

The study aims to emulate a randomized cross-over trial.[20] In a randomized cross-over trial, participants receive multiple interventions in a specific sequence. Each participant acts as their own control, receiving both the experimental and the control (or alternative treatments) at different times. The order in which participants receive the treatments is randomized to reduce confounding. This design allows direct comparison of the treatments within the same individuals, increasing the study's statistical power and reducing variability.

In this study, patients will be eligible for treatment each time they present at an out-of-hours service with a mental health problem. This means that the sequence of presentations may overlap with the follow-up periods after each presentation. To avoid selection bias, we will follow patients after each presentation, regardless of the timing of their next presentation.[21]

A concern with cross-over designs is the risk of carryover effects, where the treatment from the first period affects the subsequent period. In our study, an acute referral is likely to resolve a short-term crisis, which may reduce long-term carryover effects. We will use a washout period between treatments to address short-term carryover effects as a sensitivity analysis. For example, we will analyse out-of-hours contact without a previous acute hospital contact in the preceding month. Our study is based on the eligibility criteria of visiting an out-of-hours service, not a specific time sequence. Therefore, from a clinical perspective, the causal question of the effects of acute referral remains the same, regardless of previous hospital referrals.

Approaches to avoid confounding by indication

- Approach 1: Multivariable adjusted within-patient analysis. Comparing outcomes in out-of-hours visits where the patient is exposed vs not. This will account for all constant or slowly changing confounding. We will adjust for possible within-patient confounding, such as pre-exposure treatment, e.g. use of health services in the month before the out-of-hours service contact. This will be performed with dummy variables for different types of health services contacts: out-of-hours services, GPs, acute psychiatric, planned psychiatric, acute somatic and planned somatic. In addition, we will use fixed effects on patient ID as well as the out-of-hours-service location and date of contact.
- Approach 2: Instrumental variable analysis using the physician's preference for acute referral as an instrumental variable. This preference is calculated based on the

proportion of contacts for other patients with the same eligibility, which leads to an immediate unplanned hospital visit. We will use fixed effects on patient ID and consider place and time by a fixed effect on a combination of service and year.

Statistical Analyses

- We will use linear and Poisson regression estimators with fixed effects to study within-patient variability, adjusting for relevant time-dependent confounding variables. To account for dependency between observations, we will adjust standard errors for clustering within physicians and patients.
- We will use fixed effects instrumental variable regression to study within-patient variability. To account for dependency between observations, we will adjust standard errors for clustering within physicians and patients. We will use the physician's preference for referrals for other similar patients (defined with the same inclusion criteria) as candidate instruments.
    - IV 1: Physician's proportion of referrals of similar patients to hospital.
    - IV 2: Given referral: ratio of physician's involuntary vs. voluntary referrals of similar patients to the hospital. In this analysis, we will test if the IV is uncorrelated with the patient's probability of being referred to avoid collider bias. Since this analysis is contingent on referral, it will presumably have implications for statistical power. We, therefore, use only fixed effects for the patient ID in this analysis. Compared to the analysis of IV1, this strategy assumes that the ratio of the physician's involuntary vs. voluntary referrals is uncorrelated in different out-of-hours-services the patients may visit in different years.

- The data are based on complete registry information, but a small amount of missing data is to be expected. However, missing data on exposure and outcome are likely to be minimal.
- We anticipate non-differential misclassification of the primary outcome[18]. However, there are a few reasons to believe that patients are incorrectly registered with a self-harm episode as false positives. Therefore, we expect the relative risk estimates to be unbiased. However, the risk difference estimates are likely to be more conservative.

Assumptions for Instrumental Variable Estimation

1. Relevance: The instrumental variable must be strongly associated with the exposure (F-statistics > 10).
    - Preliminary analysis suggested F-statistics >100 for all candidate IVs.
2. Independence: No uncontrolled confounders of the instrumental variable-outcome relationship. We will evaluate this assumption with balance tests on possible time-varying confounders.
3. Exclusion Restriction: The instrument affects the outcome only through exposure. We will evaluate this by seeing if the instrument relates to other decisions, such as admission for a cardiovascular reason.
4. Point identification assumption - Monotonicity: Patients' likelihood of being referred should not decrease if they attend a high-referring physician versus a low-referring physician. Given this assumption, the analyses identify local average treatment effects.

Ethical approval and transparency

The Regional Committee for Medical and Health Research Ethics has approved the study, 2016/2159/REK Midt. All codes for preparing and analysing the data will be made available on Github.

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