Title:

Antipsychotic treatment of schizophrenia in Norwegian emergency wards, a cross-sectional national study.

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Abstract

Background

Surveys on prescription patterns for antipsychotics in the Scandinavian public health systems are scarce despite the prevalent use of these drugs. The clinical differences between antipsychotic drugs are mainly in the areas of safety and tolerability, and international guidelines for the treatment of schizophrenia offer rational strategies to minimize the burden of side effects related to antipsychotic treatment. The implementation of treatment guidelines in clinical practice have proven difficult to achieve reflected by major variations in the prescription patterns of antipsychotics between different comparable regions and countries.

Objective

To evaluate the practice of antipsychotic treatment of patients with schizophrenia at discharge from acute inpatient settings at a national level.

Methods

486 discharges from emergency inpatient treatment of patients with schizophrenia were selected from a large national study which covered 75% of hospitals receiving acute inpatients. Antipsychotic treatment, demographic variables, symptom scores (GAF and HoNOS), and information about comorbid conditions and prior treatment were analysed in order to look for predictors for non-adherence to guidelines.

Results

In 7.6 % of the discharges no antipsychotic treatment was given, of the remaining discharges 35.6% were prescribed antipsychotic polypharmacy, and 41.9 % first-generation antipsychotics (FGAs). The mean chlorpromazine equivalent dose was 450 (SD 347, range 25-2800). In the multivariate regression analyses younger age, inpatient
treatment the last 12 months or a comorbid diagnosis of personality disorder or mental retardation predicted antipsychotic polypharmacy, while inpatient treatment the last 12 months also predicted prescription of FGAs.

**Conclusions.**

Our national survey of antipsychotic treatment at discharge from emergency inpatient treatment reveal antipsychotic drug regimens that to some degree are at odd with current guidelines, with increased risk of side effects. Patients with high degree of recidivism, comorbid conditions and previous inpatient treatment are especially prone to receive deviating antipsychotic drug regimens.

**Background**

The clinical differences between antipsychotic drugs are mainly in the areas of safety and tolerability. International guidelines for the treatment of schizophrenia [1-4] offer rational strategies to minimize the burden of side effects related to antipsychotic treatment. These recommendations may be considered according to three dimensions: That of first- versus second generation antipsychotics, that of antipsychotic mono- versus polypharmacy, and that of optimal dosing of antipsychotics. The second generation antipsychotics (SGAs) are on a group level less associated with extrapyramidal symptoms (EPS) and hyperprolactinemia compared to the older first generation drugs (FGAs) and are recommended as first line treatment for schizophrenia [3]. Antipsychotic monotherapy is generally recommended, and doses should be between 300 and 1000 chlorpromazine equivalents in order to achieve maximum reduction of positive symptoms while avoiding EPS or use of anticholinergic medication [5].

The implementation of treatment guidelines in clinical practice have proven difficult to achieve [6], reflected by major variations in the prescription patterns of antipsychotics between different comparable regions and countries [7-9]. Prescribing a drug regime with
poorer tolerability may ultimately increase the risk of relapse, as the association between increasing side effects and poorer drug adherence is well established [10]. The goal to avoid relapses and hospital admissions for patients with schizophrenia is of major importance also in a cost-effectiveness perspective as readmissions represent one of the largest contributors to total treatment costs [11]. Surveys on prescription patterns for antipsychotics in the Scandinavian public health systems are scarce despite the prevalent use of these drugs. Studies addressing issues related to optimal antipsychotic treatment, as well as detection of predictors of non-compliance to guideline, are important. During admissions in psychiatric emergency wards the clinicians should evaluate and optimize the antipsychotic drug regime for the individual patient and these admissions represent unique opportunities to investigate the prescription patterns of antipsychotics.

The aims of this study were to evaluate the Norwegian practice of antipsychotic treatment of patients with schizophrenia at discharge from acute inpatient settings, compared with the international guidelines recommendations of monotherapy, choice of antipsychotics, and dosing. In addition, we wanted to study whether demographic or clinical factors at admission predicted non-compliance to guideline recommendations.

Methods
The data were collected in the Norwegian Multicenter study in Acute Psychiatry (MAP)[12] conducted by the Network for Evaluation of Acute Psychiatry, coordinated by SINTEF Health Research and financed in part by the Norwegian Directorate of Health and Social Affairs. The study was approved by the Regional Ethical committee, the Norwegian Directorate of Health and Social Affairs and the Norwegian Data Inspectorate. MAP is a cross-sectional observational study which included nineteen different hospitals with 37 emergency wards, and 3506 hospital admissions were recorded during three consecutive months in 2005. The 19
participating hospitals comprised approximately 75% of the Norwegian hospitals receiving patients for acute psychiatric inpatient treatment. From this material we have selected admissions with a diagnosis of schizophrenia at discharge (some patients had more than one admission and discharge in the study period). Data were recorded at admission and discharge. (Insert table 1 about here)

MAP collected data at admission and discharge from the emergency ward; the data included demography, information about treatment history, medication, and clinical measures including the Global Assessment of Function (GAF)[13], Health of the Nation Outcome Scales (HoNOS)[14]. HoNOS Item 1 (Overactive, aggressive, disruptive or agitated behavior) and HoNOS item 6 (hallucinations and delusions) were dichotomized to 0 (scores of 0, 1 or 2) or 1 (scores of 3 or 4). Training in HoNOS scoring was conducted at all the participating hospitals. The emergency wards were distributed in the five health regions of Norway, and the participating hospitals were both university hospitals and regional and local psychiatric hospitals. Clinical diagnoses according to the ICD 10 [15] were obtained from the medical records. Classification of antipsychotics in FGAs or SGAs and the computation of chlorpromazine-equivalent doses (CE) were done according to the literature and listed in table 2 [16-22]. The Defined Daily Dose is obtained from the WHO Collaborating Centre for Drug Statistics Methodology and is the assumed average maintenance dose per day for a drug used for its main indication in adults. In order to focus on prescriptions intended to treat psychotic symptoms, we excluded prescriptions of low-potency FGAs in doses below 100 CE from the analyses of prediction of polypharmacy and prediction of prescription of FGA at discharge. (Insert table 2)

Statistical analysis
All regression analyses used methods for clustered observations (GEE), since some patient had more than one hospitalization. For each drug, the change in prescriptions between admission and discharge was tested by logistic regression. The p-values were adjusted for multiple comparisons with the Benjamini-Hochberg method.

Univariate and multivariate logistic regression analyses with polypharmacy at discharge and use of FGA at discharge as dependent variables (after exclusion of prescriptions of low-potency FGAs in doses below 100 CE) were conducted with the following independent variables: Age, sex, GAF severity of symptoms at admission, HONOS item 1 and 6 (dichotomized) at admission, inpatient and outpatient treatment the last 12 months before admission (dichotomized), having a remitting/chronic or first-episode condition, and having a comorbid diagnosis of substance abuse, personality disorder or mental retardation. However, in the logistic regression with use of FGA at discharge as the dependent variable recurrent illness and a comorbid diagnosis of mental retardation had to be excluded from the analysis due to stability reasons. Results are presented as odds ratios with corresponding 95% confidence intervals and p-values.

The relationship between dosage and the independent variables above was analyzed using linear regression. Results were presented with p-values, and effects were reported with unstandardized regression coefficients and 95% confidence intervals. The relationships between type (university vs other) and region of the hospitals and use of polypharmacy and FGA were analyzed by logistic regression. SPSS Version 15 (SPSS Inc., Chicago, IL, USA) and R (The R Foundation for Statistical Computing, Vienna, Austria) were used for the statistical analyses.
Results
A total of 486 discharges of patients with a diagnosis of schizophrenia were identified and selected from the MAP database. The discharges were distributed among 412 patients where 352 patients had one hospitalization, forty-nine patients two hospitalizations, eight patients three hospitalizations, and 3 patients had four hospitalizations in the acute inpatient units in the 3 months study period. The background variables are given in Table 1.

Olanzapine was the single most frequently prescribed drug both at admission (25.1%), and at discharge (29.0%), followed by risperidone which was prescribed in 19.1% of the discharges. There was a significant increase in the prescription of olanzapine (p=0.049), and zuclopenthixol (p=0.049) from admission to discharge (See table 3). Depot antipsychotics were prescribed in 35.6%, and clozapine was prescribed in 8.0% of the discharges.

(Insert table 3 about here)

In 7.6% no antipsychotic medication was prescribed at discharge. In the remaining 449 discharges, antipsychotic polypharmacy was used in 160 cases (35.6%), and one or more FGA in 204 (41.9%) cases. In a subanalysis with exclusion of FGA in doses below 100 CE, antipsychotic polypharmacy was prescribed in 112 cases (24.9%) and FGA in 177 cases (36.4%).

Of the total of 449 discharges with antipsychotic treatment, monotherapy was prescribed in 289 (64.4%) of the cases, of these 203 (45.2%) were treated with SGAs. Among the 160 (35.6%) cases with polypharmacy, twenty-nine (6.5%) were treated with combinations of two or more FGAs, two or more SGAs were prescribed in 42 (9.4%) cases, and in 89 cases (19.8%) a combination including both FGA and SGA was prescribed. In 56 (12.3%) periods for patients treated with antipsychotic polypharmacy, one or more antipsychotics were started during the hospitalization, combined with one or more antipsychotic unchanged from admission to discharge. In twenty (4.5%) cases, patients received clozapine in combination with another SGA.
There were 15 cases with first-episode patients. Of these, 14 were treated with SGA monotherapy, and one had a combination of SGA with an FGA (25 mg levomepromazine). In seven of the nine discharges with a comorbid diagnosis of mental retardation, an FGA was prescribed. In the univariate analyses predictors for antipsychotic polypharmacy (excluding low-potency antipsychotics in doses below 100 CE) were found to be younger age, lower GAF-S score, recurrent illness, having had inpatient treatment last 12 months, a comorbid personality disorder and mental retardation. In the multivariate analyses younger age, inpatient treatment the last 12 months and a comorbid diagnosis of a personality disorder or mental retardation predicted antipsychotic polypharmacy (See table 4). Female sex and inpatient treatment the last 12 months were found to be predictors for prescription of FGA (excluding low-potency antipsychotics in doses below 100 CE) at discharge in the univariate analyzes. In the multivariate analyses only inpatient treatment last 12 months was found to predict FGA prescription.

(Insert table 4 about here)

Mean chlorpromazine equivalent dose at discharge was 450 CE (SD 347, range 25-2800)(See table 3). In the linear regression with dosage as the dependent variable, lower age, delusions/hallucinations at admission, recurrent illness, and inpatient treatment last year were found to predict higher dosages.

There were significant regional differences in the use of FGA (p=0.012), with more use of FGA in the southern (OR=3.21) and northern (OR=1.88) regions compared with the eastern region. No similar relationship was observed for the use of intended polypharmacy (p=0.412), and there were no significant differences between departments in university hospitals and other hospitals.
Discussion
The present study revealed a total rate of 35.6 % of polypharmacy with antipsychotics and a rate of 41.9 % first generation antipsychotics at discharge. The antipsychotic drug doses were within the recommended range in most cases. An argument for not classifying low-potency FGAs (levomepromazine, chlorpromazine, klorprotixene, thioridazine) at low doses as antipsychotics exists if the definition applies only to drugs prescribed for their antipsychotic properties. It is not uncommon to use low potency FGAs as hypnosedatives and in this regard they should not be classified as antipsychotics in the strict sense of the term. In practice, however, such a definition may prove difficult to validate retrospectively, as one would need to know the intent of each prescribing clinician to decide whether or not the drugs were prescribed for psychosis *per se*. When low potency FGAs in doses below 100 CE were excluded from the analyses in our sample, the rate of polypharmacy was reduced to 24.9%, and the proportion of periods prescribed FGA was 36.4 %. Regarding antipsychotic polypharmacy, our findings are comparable to those of other studies from Norway [7], Denmark [23], Italy [24] and North-America [25] in which rates have ranged from 27% to 48%. A study from Innsbruck reported only 12% antipsychotic polypharmacy at discharge, in this study low-potency FGAs were excluded from the analyses. An increasing trend of polypharmacy in recent years was also identified in that study [26], however. One previous study indicates that the level of polypharmacy decreases when patients are followed after discharge and that part of polypharmacy can be an intermediate situation [27]. The risk is, however, long-time continuation of polypharmacy after discharge from hospitalization because of sparse follow-up [28]. Nearly five percent have combinations of an SGA with clozapine, which could be in line with guideline recommendations in situations where clozapine monotherapy has been tried without success. The 2006 Update of the Texas Medication Algorithm for schizophrenia does recommend a trial of combination with another antipsychotic when there is partial or no response to clozapine, although the results from
RCTs in this field are inconsistent [29]. Our data did not give answers to the questions about treatment resistance, it is not unlikely, however, that the finding of a rate of polypharmacy of 35.6 % (24.9 when low-potency FGAs in doses below 100 CE are excluded) reflects a high rate of treatment resistance. This is also supported by the finding that 70.2 % had previous inpatient treatment last 12 months. Bearing this in mind, the finding that only 8.0 % of the cases were prescribed clozapine can indicate a too low prescription rate of clozapine. The finding of a rate of 6.5 % discharges with a combination of two or more FGAs, and 19.8 % with a combination of a FGA and an SGA are indications of guideline non-compliance.

More than 40% were prescribed FGAs at discharge in our study (36.4 % when FGAs in doses below 100 CE were excluded). This is indeed a very high rate compared to findings from USA, [30], while comparable to previous findings from European studies [7,24]. In the recent World Psychiatric Association Pharmacopsychiatry Section statement on comparative effectiveness of antipsychotics in the treatment of schizophrenia [5] the goal to achieve a maximum reduction of positive symptoms while avoiding EPS or the use of anticholinergic medication is emphasized, and while the possibility to achieve this with FGA treatment is noted, the probability of reaching this goal is more likely with SGA treatment. A newly published review finds FGA to be associated with more extrapyramidal side effects compared to SGAs [31], this is also the case for tardive dyskinesias [32]. The high rate of FGA prescription in our study could indicate suboptimal practice, leaving the patients at higher risk of EPS than necessary. In addition to this, the two most prescribed SGAs in our sample at discharge were olanzapine (29.0%) and risperidone (19.1%). These agents have both gained attention because of their side-effect profiles that include weight gain, dyslipidemia, and diabetogenic effect for olanzapine, and hyperprolactinemia and EPS for risperidone. The high prescription rates of FGAs, and of the SGAs olanzapine and risperidone may indicate that side-effects considerations are not prioritized in the planning of antipsychotic treatment. A
further indication is the significant rise in the prescription of the FGA zuclopenthixol between admission and discharge, as zuclopenthixol treatment has a high risk of extrapyramidal side effects.

Younger age, previous inpatient treatment the last 12 months, as well as comorbid disorders predicted polypharmacy at discharge, while inpatient treatment last 12 months predicted the prescription of FGA at discharge. Although a comorbid diagnosis of mental retardation had to be excluded from the regression with FGA as the dependent variable, there is a strong co-variation as we found that an FGA was prescribed in seven out of nine discharges with a comorbid mental retardation. Having in mind that our data do not give information about treatment resistance, a reasonable interpretation of these findings may be that psychiatrists working in acute inpatient units combine two or more antipsychotics when the mental illness is complex, chronic or remitting, while higher symptom burden measured by GAF or HoNOS at admission does not in itself predict neither polypharmacy nor FGA. This is in line with findings in a large study of Veteran Administration patients followed for one year [33]. The fact that younger age predicted polypharmacy is difficult to explain given treatment recommendation of lower doses for first-episode patients. One possible explanation may be that schizophrenia can be associated with more florid symptoms in younger patients. The clinical significance of the predictive effects of comorbidity with mental retardation is questionable, at least in our data, as the prevalence of this disorder is low. However, the finding of a very high prevalence of both polypharmacy and the use of FGAs in this group is worth to notice.

The recent statement from World Psychiatric Association Pharmacopsychiatry Section [5] also emphasizes dosing as a key variable in optimizing effectiveness of antipsychotic treatment. The dosages of antipsychotic treatment in the present study were largely in line with present guidelines. However, a substantial portion of discharged patients was treated
with doses below 300 chlorpromazine equivalents and even if CE is not an optimal measure
dosing could be suboptimal. Other measures for comparing antipsychotic equivalence exist
including defined daily doses (DDD)[34], which may give somewhat different results [16].
Each method has its flaws, however, and there is in the opinion of the authors no convincingly
better approach to compare doses in different antipsychotic drug regimens.

Regarding prescription patterns between different hospital sites, regional differences were
found. It was, however, due to lack of power not possible to control this finding in a
multivariate analysis. The existence of idiosyncratic and local drug practices is found in other
studies [35].

As data was obtained from 19 different departments with 27 different wards there can be
variations in the way HoNOS and GAF were scored, although efforts have been made to
minimize this variation. The use of clinical diagnoses at discharge has its limitations as in all
studies based on clinical diagnostic work. The evaluation at admission of seriously disturbed
psychotic patients can be difficult and give incomplete information about prior treatment, and
although we tried to collect information from other sources it is possible that some
information was missing. Another limitation in the present study is that a large portion (59.5
%) of the patients in our study was transferred to other inpatient treatment when discharged
from the acute ward, and thus, the prescription at the final discharge from inpatient treatment
can differ from our results. In twelve percent of the cases a new prescription was added to an
antipsychotic drug that was left unchanged during the hospitalization, and some of the cases
of antipsychotic polypharmacy may represent a cross-over period.

Conclusions
We conclude that our national survey of antipsychotic treatment from acute inpatient
treatment reveal drug regimens that to some degree are at odds with current guidelines, with
increased risk of side effects, and in the case of low rate of clozapine prescription, also with a
possibility of reduced antipsychotic effects. Patients with high degree of recidivism, comorbid conditions and previous inpatient treatment are especially prone to receive deviating antipsychotic drug regimens, this has also been found in other studies [36]. The fact that some aspects of the antipsychotic treatment were in total accordance with guideline recommendations, e.g. the prescription of monotherapy SGA to first-episode patients, could be an indication that the guidelines are well known to the psychiatrists. The reason for nonadherence to guidelines could be vague or missing guideline recommendations for the treatment of the most complex schizophrenic conditions, as underlined by Leucht [6]. This should be a target for future studies.

**Competing interests**

The authors declare that they have no competing interests.

**Authors' contributions**

RK and TR took part in the data collection, RK drafted the manuscript. RK and TWL did the statistical analyses, HAJ and EJ helped to draft the manuscript. All authors read and approved the final manuscript.

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References


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Additional files provided with this submission:

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