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Use of antipsychotics and benzodiazepines in connection to minimizing coercion and mechanical restraint in a general psychiatric ward

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ABSTRACT
Background:
Decrease in coercive measures can lead to increased exposure to antipsychotics and benzodiazepines. This is not desirable as these drugs are associated with harmful side effects and reduced life expectancy.

Aims:
To quantify and compare the use of antipsychotic and anxiolytic medications in connection with the implementation of a programme to reduce coercion and restraint.

Methods:
Observational study in a general psychiatric ward comparing psychopharmacological treatment after implementation of non-pharmacological interventions to reduce coercion and mechanical restraint with a historical reference cohort from the same ward.

Results:
Data from 101 admissions after implementation of interventions were compared with data from 85 admissions in a historical reference cohort. Mean defined daily doses of antipsychotics, benzodiazepines, or the total amount of both showed no difference before and after implementation of the programme. Standardized regression coefficients ($\beta$) from a mixed effects linear regression model, adjusted for age, gender, length of admission, involuntary admission and history of substance abuse showed that neither total dose of antipsychotics (adjusted $\beta$ 0.05, 95%CI: -0.20 to 0.31), total dose of benzodiazepines (adjusted $\beta$ -0.13 95%CI: -0.42 to 0.16), nor total amount of both drugs (adjusted $\beta$ 0.00 95%CI: -0.26 to 0.21) increased after implementation.

Conclusions:
Decrease in coercive measures from 2013 to 2016 has not lead to significant increases in the use of antipsychotic medication or benzodiazepines. The interventions are useful in establishing restraint-free wards, and careful monitoring of the psychopharmacological treatment is important for patient safety.
BACKGROUND

Coercion in psychiatry remains a controversial issue of close public and political interest due to its intrusive nature. Denmark has been criticised for its high numbers of coercive measures, especially mechanical restraint (Bak & Aggernæs, 2012). Restraint and other coercive measures can be necessary during psychiatric treatment to avoid self-harm or violence. However, these measures must be avoided whenever possible, both from an ethical perspective and from a treatment perspective. Patient satisfaction is especially important for our relation to patients with psychotic disorders, and satisfaction with in-patient treatment has been found to reduce the need for future involuntary admission (Setkowski, van der Post, Peen, & Dekker, 2016). Therefore, the Danish Government has set a goal: To reduce the use of mechanical restraint by 50% by the year 2020 (Ministry of Health, 2016). To meet this goal establishing "restraint-free wards" across Denmark is supported financially by the government (Ministry of Health, 2014). Six different psychiatric centres are participating in this project, and Department of Psychiatry in Aabenraa is participating with 2 out of its five general psychiatric wards. The clinical experience has so far been successful as the use of mechanical restraint has decreased from 20 episodes in 2014 over 18 episodes in 2015 to 9 episodes in 2016 (Defactum, 2016).

A considerable part of the patients treated at the wards have diagnoses of psychotic, mood, or personality disorders and are prone to be agitated at the time of admission. Therefore, many patients in the acute setting are treated with antipsychotic drugs or benzodiazepines to treat the underlying condition as they are effective means for treating agitation (Battaglia, 2005; Benjaminsen, 2014; Garriga et al., 2016). However, these drugs have potential acute as well as long-term adverse effects and thus need to be used sparingly and deliberately. Antipsychotics drugs are associated with increased mortality (Tiihonen, Mittendorfer-Rutz, Torniainen, Alexanderson, & Tanskanen, 2016), acute adverse effects as arrhythmias (Ray, Chung, Murray, Hall, & Stein, 2009) and long-term adverse effects as development of cardio-vascular disease (De Hert, Schreurs, Vancampfort, & Van Winkel, 2009). Benzodiazepines do not have the same cardiovascular effects as antipsychotics but are instead associated with cognitive impairment, dependency (Stewart, 2005) and increased mortality (Tiihonen et al., 2016).

Routine quality assurance data from, e.g. hospital pharmacies cannot provide exact figures for the use of psychotropic drugs (Defactum, 2016) and it is, therefore, crucial to assess the total use of medication when evaluating these interventions to reduce coercion.
Furthermore, data from this kind of studies will also allow effective interventions to be implemented without further delay if they prove to be effective (Munk-Jørgensen et al., 2015). The figures will also allow us to identify possible inexpedient practices. Therefore, we want to qualify and quantify the use of psychotropic medication during these efforts to reduce coercion.

We hypothesize that the expected decrease in coercive measures can lead to an unwanted increase in the use of psychotropic drugs, with a potentially accompanying negative impact on the physical health of the patients.

**Aims:**
To quantify and compare the use of antipsychotic and anxiolytic medications in connection with the implementation of a programme to reduce coercion and restraint.

**PATIENTS AND METHODS**

**Study design:**
A retrospective cohort study comparing psychopharmacological treatment after implementation of interventions (2016) to reduce coercion with a historical reference period (2013).

**Setting:**
The study was conducted at a general psychiatric department with a catchment area of approximately 94,000 inhabitants (Municipality of Haderslev and Tønder, Southern Denmark). The wards have changed physical location between the periods in comparison because of reorganisation, but the catchment area did not undergo any changes. Patients in the reference cohort (2013) were admitted to Ward P2 at Haderslev Hospital, Haderslev, Denmark, and patients in the intervention cohort (2016) were admitted to Ward 61/63 at the Department of Psychiatry in Aabenraa, Denmark.

**Intervention:**
Historical analyses of episodes of coercive measures in the project ward showed that patients at risk are often agitated at admission, have diagnoses of psychotic or personality disorders, are likely to have concurrent substance abuse, and that coercive episodes, most frequently, occur within the first four days after admission.
Based on these facts an intervention to reduce coercion in the ward was constructed of several different parts:

i) Early identification of patients at risk by consequent evaluation with Brøset Violence Checklist (BVC) (Woods & Almvik, 2002) at admission and three times daily, and continuously if scores of >1 were present.

ii) Individual contingency plan on relational and psychopharmacological treatment of patients with BVC-scores >1.

iii) Design of aggression profile on patients with high risk of violent behaviour by a psychologist.

iv) Systematic debriefing and analysis of all episodes, and near-episodes, of coercive measures.

v) Involvement of patients and relatives, e.g. by interviewing all patients at admission of their experience with coercive measures, and their ideas and proposals for management if they would become agitated.

vi) Improved staffing levels - including an occupational therapist to work with sensory integration (C. Andersen, Kolmos, Andersen, Sippel, & Stenager, 2017) (a non-pharmacological approach in reducing anxiety and agitation), a physiotherapist to facilitate daily physical activity, and a social worker to help patients with coordination of social situation e.g. housing and economic issues.

vii) Continuous training of staff in de-escalating techniques and handling of patients with substance abuse.

viii) Special attention to patients with concurrent substance abuse, including motivational approaches to rehabilitation.

**Sample:**
Patients were eligible for inclusion in the intervention cohort if they had been admitted to ward 61/63 between 1st January and 31st July 2016, and for inclusion in the reference cohort if they have been admitted to ward P2 between 1st January 2013 and 31st of July 2013.

**Inclusion criteria:**
Patients were included if they were discharged from the wards with a primary psychiatric diagnosis, according to World Health Organization ICD-10 research diagnostic criteria (World Health Organization, 1992) of:

ix) Organic mental disorders (F0x),
Use of antipsychotics and benzodiazepines

x) Mental disorders due to psychoactive substance use (F1x),
xi) Schizophrenia, schizotypal or delusional disorders (F2x),
 xii) Manic episodes or bipolar affective disorder (manic episode, severe depression with psychotic symptoms, mixed, other or unspecified episodes) (F30 and F31.0-.2, .5-.6, .8-.9),
 xiii) Specific personality disorders (F60.x)

Exclusion criteria:
Patients were excluded from further analysis if they had:

i) not stayed in the department (administratively admitted to psychiatric department, but physically admitted to a somatic ward for treatment of, e.g. delirium),
 ii) stayed less than 24 hours in the department (discharge before ward rounds, single-day treatment as electroshock therapy or intramuscular injection of antipsychotics), or
 iii) missing or insufficient prescription history.

Data sources:
Demographic and clinical data were collected from case records. Prescription history was collected from case records to obtain as exact measurement of exposure as possible: i) from admission history, ii) from administration forms, and iii) from discharge summary. For admissions longer than eight days, medication for the first seven days and the day of discharge was registered as most coercive episodes occur within the first four days of admission. All prescriptions of antipsychotics and benzodiazepines were recorded with Anatomical Therapeutic Chemical Classification-code (ATC-code (WHO Collaborating Centre for Drug Statistics Methodology, 2017)) and the administered dose. Antipsychotic medications were defined as ATC-group N05A except for lithium (ATC N05AN01). Benzodiazepines were defined as ATC-group N05BA including clonazepam (ATC N03AE01). Continuous treatment with more than one antipsychotic drug in fixed dosing was classified as antipsychotic polypharmacy. Cross-titration and pro necessitate dosing of another antipsychotic drug was exempted from classification as antipsychotic polypharmacy.
Statistics:
Anonymized data from the reviews of case records were entered into an electronic database. Data was structured with observations of daily doses nested as mean doses for the individual patient. The sample size was based on the ability to detect a difference of 20% in Defined Daily Doses (DDD) at a significance level of 5%. This necessitated a sample of minimum 567 admission days from each cohort. All doses of psychotropic medication were converted to DDDs according to World Health Organization DDD-index (WHO Collaborating Centre for Drug Statistics Methodology, 2017). For benzodiazepines (ATC N05B) doses were also converted to Diazepam Equivalents (DE) according to “The Ashton Manual” (Newcastle University, 2013) to investigate any possible difference in drug consumption between DDD and DE.

Descriptive statistics were calculated for patient characteristics, and cohorts were compared with Chi-Squared test for proportions and Wilcoxon signed-rank test for continuous measures. A 0.05 significance level was used.

We tested the hypothesis that the mean doses of antipsychotics and benzodiazepines were equal when comparing the two time periods. Mixed effects linear regression with random intercepts and robust standard error estimation was used. Standardized regression estimates (β) are reported.

Ethics:
This study followed the principles of the Declaration of Helsinki and was approved by the Danish Patient Safety Authority (No. 3-3013-1783). Data collection was approved by the Legal Department of the Region Southern Denmark on behalf of the Data Protection Agency (No. 2008-58-0035).

RESULTS
All 235 admissions to ward P2 during the 1st half of 2013 and 252 admissions to wards 61/63 during the 1st half of 2016 were assessed for eligibility. In 2013 the number of relevant diagnoses was 163 (69%), and in 2016 the number was 156 (62%). Of admissions with relevant diagnoses 97 was excluded from further analysis; 81 for admissions <24 hours, 4 for admission to a somatic ward and 12 for insufficient prescription history. See figure 1 for details on the selection of the sample.
Calculation of sample size had called for a minimum of 567 admission days from each cohort. Due to general differences in admission time, this amount was reached with sampling 85 consecutive admissions from 2013 and 101 admissions from 2016. Inclusion was terminated after the required sample size was reached.

Table 1 presents descriptive data of both cohorts. There were no significant differences between cohorts regarding age, gender, primary psychiatric diagnosis, intellectual disability, forensic status, type of admission, history of substance abuse. Mean length of admission differed significantly between time periods (2013: 22.9 days vs 2016: 24.3 days, p=0.03).

There were no missing data for the included patients regarding any variables. Patients excluded because of missing prescription history were in 2013: 3 males with substance dependency, three males with psychotic disorders and one male with a personality disorder. In 2016 patients with missing prescription history were one male and one female with alcohol dependency, one male and one female with psychotic disorders and one female with borderline personality disorder.

**Coercive measures:**
The number of episodes where mechanical restraint was used was 10 in 2013 and 2 in 2016 (difference -80%, p=0.01). For acute, involuntary medication with antipsychotics or benzodiazepines, the number of episodes was 6 in 2013 and 3 in 2016 (difference -50%, p=0.20).

**Psychopharmacological treatment:**
Table 2 presents data on the number of patients exposed to the most frequently used peroral antipsychotics, intramuscular depot-formulation antipsychotics and benzodiazepines and the mean and range of doses. The number of patients subject to antipsychotic polytherapy in 2013 was 37 (44%) and 30 (30%) in 2016. Antipsychotic polytherapy was highest in patients with F2x in both cohorts (57% resp. 40%).

Table 3 presents a comparison between cohorts as to mean doses of antipsychotics and benzodiazepines. We found no significant, nor substantial differences in mean doses for neither antipsychotics nor benzodiazepines or the total dose of both.
When testing for differences between the two cohorts with a mixed effects linear regression model we found no significant difference in neither total dose of antipsychotic, total dose of benzodiazepines (DDD or DE) nor the total amount of both drugs. The model was adjusted for age, gender, days of admission, involuntary admission and history of substance abuse. The standardised regression coefficients are shown in figure 2.

The upper confidence limit from the regression model regarding antipsychotics suggest that the mean DDD has not increased by more than 0.31 between 2013 and 2016. For benzodiazepines, the point estimates (both in DE and DDD) are below 0 indicating a non-significant drop in use. For the combined dose of antipsychotics and benzodiazepines, the point estimate is 0.00, and the upper confidence limit is 0.26. Overall, no significant, nor substantial increase in the use of these medications was observed when comparing admissions in 2016 with admissions in 2013. Confidence limits suggest that any true increase in the use antipsychotic medication or benzodiazepines are small, as upper confidence limits are < 0.31 in standardised terms.

DISCUSSION

We found no significant increase in the doses of antipsychotics, benzodiazepines or the total dose of both drugs when comparing patients admitted to the project ward with patients admitted to the former, ordinary ward. The use of mechanical restraint and involuntary medication decreased considerably when comparing the same two wards. In addition to this, we also found that the majority of patients were treated with recommended antipsychotic drugs, and that very few patients were subject to higher doses of antipsychotics or benzodiazepines than recommended.

We did not find any evidence of a substantial increase in the use of psychotropic medication after implementation of initiatives to reduce coercion as the point estimates from our regression model (figure 2) is very close to zero for all comparisons (-0.15 to 0.05). Moreover, the confidence limits of all comparisons suggest that any potential increase is not above 15-16% for benzodiazepines or 31% for antipsychotics.

We did not expect any increase in the use of psychotropic drugs, as no part of the intervention is based on psychopharmacological treatment. The core features of the intervention are relational and structural, and an important part of the approach is to avoid escalating situations to a point where coercive measures as involuntary medication or
mechanical restraint are necessary. To avoid escalation, the staff is trained to instruct patients in a wide array of non-pharmacological calming means (music, self-massage etc.) and hereby avoid extensive use of pro necessitate prescriptions. This might explain why we found no difference between the two periods, as the potential use of psychotropic medication has been replaced by other means.

A recent Dutch study (Noorthoorn et al., 2016) showed that decreases in seclusion were correlated to an increase in the use of involuntary medication. A similar trend has been seen in Denmark in the recent years were mechanical restraint seems to have been replaced with involuntary medication (Danish Health Authority, 2015).

A recent Danish study (K. Andersen & Nielsen, 2016) characterising different intra- and extramural factors in patients involved in coercive measures found that extramural factors as substance abuse and intoxication are strongly correlated to mechanical restraint.

The intervention in the project ward is based on the assumption that patients with concurrent substance abuse and psychotic disorder are in high risk of coercion and that this fact needs to be addressed by consequent evaluation of violence risk by BVC and by working to motivate patients to seek treatment for their substance abuse.

Four out of six of the most frequently used antipsychotic drugs were among the recommended 1st and 2nd line drugs from the national guidelines for antipsychotic treatment (Rådet for Anvendelse af Dyr Sygehusmedicin, 2015). These guidelines are based on evidence of efficacy and safety in the long-term treatment of psychoses and recommend that most patients should be treated with second-generation antipsychotics (SGA) as aripiprazole, quetiapine or risperidone because of their favourable side effect profile. Patients who do not respond properly to these SGAs should be treated with clozapine unless it is not an option for safety reasons. In this case other SGAs as olanzapine, or first-generation antipsychotics as haloperidol, perphenazine or zuclopenthixol should be considered. However, some of these 3rd line drugs (olanzapine and haloperidol) are recommended for use in the acute treatment of agitation (Benjaminsen, 2014). Antipsychotic polytherapy is not recommended for safety reasons, and we consider the decrease among patients with schizophrenia and other psychotic disorders (from 44% to 30%) a positive finding considering the widespread use of this approach among psychiatric patients in general (Baandrup et al., 2010).
Strengths and limitations:

One clear strength of the present analysis is that we were able to obtain an exact measure of drug consumption by a thorough review of case records. Prior attempts to estimate the use of psychotropic drugs in the participating wards have been based on department-level supply data from hospital pharmacies, and therefore it has not been possible to investigate the consumption in subgroups (Defactum, 2016).

However, there are some limitations to our study. Firstly, the project to create a restraint-free ward was initiated in the same period as other changes were made in the department: The wards changed their physical location from older hospital buildings in Haderslev to new state-of-the-art psychiatric facilities in Aabenraa as a part of restructuring the regional psychiatric services. Thus, a possible effect of this change in location and facilities cannot be separated from any effect of study interventions. However, the catchment area and the admission policy did not change either, so the associated patient population remained the same. The consultant psychiatrist in charge of the wards changed between reference and intervention period. There can be differences in the leader’s professional experience, attitude and preference, and this might have potential to alter clinical practice, but there were not made any other changes at management level or implemented any political directives.

Secondly, we choose only to sample from admissions during the 1st half of 2016, several months before the initiation of our study, even though this decision did limit the possible sample size. This decision was made to avoid any influence on clinical practice in the ward from this study’s attention on prescription practice. The reference cohort from 2013 was chosen for two reasons: i) to reflect psychiatric practice well before any national campaigns on coercion was initiated, and ii) because this year was selected as the baseline in other evaluations of restraint and other coercive measures (Defactum, 2016). To make the sample as representative as possible for a general psychiatric population, we included consecutive admissions and used as few exclusion criteria as possible to avoid selection bias. Thirdly, we did not use blinding in the review of case records, but to minimise information bias, all case records were reviewed by the same investigator. The investigator was not a member of the staff and had therefore not been involved in the treatment of any patients in the sample. Further, Brøset Violence Checklist was not used.
as a standard measure for agitation and violence risk in 2013, and we were therefore not able to conduct subgroup analyses based on this parameter.

Because the sample consists of consecutive admissions from many diagnostic categories, we consider the study population representative for many other general psychiatric wards across the country. In relation to the other wards participating in the national project, the generalizability may be limited as some are specialised wards for e.g. psychotic disorders (Defactum, 2016).

CONCLUSION
In conclusion, the decrease in coercive measures from 2013 to 2016 at the Department of Psychiatry in Aabenraa, Denmark has not lead to significant increases in the use of benzodiazepines or antipsychotic medication. Most patients were treated with recommended 1st or 2nd line antipsychotic drugs, and the majority of doses were within recommendations. However, other factors besides targeted interventions can contribute to the positive findings: Modern psychiatric facilities and the input from senior clinicians. As a clinical implication of our study, we suggest continuous monitoring of the prescription practice among patients at risk of coercive measures, as it is of importance in evaluating the efforts to establish restraint-free wards for the benefit of psychiatric patients.

DECLARATION OF INTERESTS
The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

FUNDING
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REFERENCES
Højlund et al. Use of antipsychotics and benzodiazepines


Table 1: Sociodemographic and clinical characteristics of patients and admissions during the study period

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>2013 (n = 85)</th>
<th>2016 (n = 101)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years, median (range)</strong></td>
<td>47 (18-69)</td>
<td>39 (20-67)</td>
<td>.06</td>
</tr>
<tr>
<td><strong>Sex, No (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>49 (58)</td>
<td>59 (58)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>36 (42)</td>
<td>42 (42)</td>
<td>.92</td>
</tr>
<tr>
<td><strong>Primary psychiatric diagnosis, No (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Organic mental disorders (F0)</td>
<td>0</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Psychoactive substance abuse (F1)</td>
<td>15 (18)</td>
<td>16 (16)</td>
<td></td>
</tr>
<tr>
<td>Schizophrenia (F2)</td>
<td>51 (60)</td>
<td>47 (47)</td>
<td></td>
</tr>
<tr>
<td>Mood disorders (F30-31)</td>
<td>6 (7)</td>
<td>14 (14)</td>
<td></td>
</tr>
<tr>
<td>Personality disorders (F60)</td>
<td>13 (15)</td>
<td>21 (21)</td>
<td>.14</td>
</tr>
<tr>
<td><strong>Intellectual disability, No (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retardation (F7x)</td>
<td>3 (4)</td>
<td>11 (11)</td>
<td></td>
</tr>
<tr>
<td>Inferior intellect (R41.8)</td>
<td>0</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td><strong>Forensic patients, No (%)</strong></td>
<td>3 (4)</td>
<td>5</td>
<td>.63</td>
</tr>
<tr>
<td><strong>Type of admission, No (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voluntary</td>
<td>78 (92)</td>
<td>91 (90)</td>
<td></td>
</tr>
<tr>
<td>Involuntary</td>
<td>7 (8)</td>
<td>10 (10)</td>
<td>.70</td>
</tr>
<tr>
<td><strong>Length of admission, days, mean (SD)</strong></td>
<td>22.9 (22.1)</td>
<td>24.3 (38.1)</td>
<td>.03</td>
</tr>
<tr>
<td><strong>History of substance abuse, No (%)</strong></td>
<td>34 (40)</td>
<td>28 (28)</td>
<td>.08</td>
</tr>
<tr>
<td>Alcohol</td>
<td>22 (26)</td>
<td>11 (11)</td>
<td></td>
</tr>
<tr>
<td>Cannabis</td>
<td>4 (5)</td>
<td>6 (6)</td>
<td></td>
</tr>
<tr>
<td>Stimulants</td>
<td>1 (1)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>7 (8)</td>
<td>11 (11)</td>
<td>.07</td>
</tr>
</tbody>
</table>

SD: Standard Deviations. Chi-squared test is used for categorical data. Wilcoxon signed-rank test is used for numerical variables.
Table 2: Summary of psychopharmacological treatment of patients admitted to the project ward during 1st half of 2016 regarding most frequently used drugs and doses.

<table>
<thead>
<tr>
<th>Drug Type</th>
<th>Drug</th>
<th>n</th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antipsychotics, peroral</strong></td>
<td>Chlorprothixene</td>
<td>20</td>
<td>68.4</td>
<td>15-200</td>
</tr>
<tr>
<td></td>
<td>Clozapine</td>
<td>15</td>
<td>300</td>
<td>75-650</td>
</tr>
<tr>
<td></td>
<td>Olanzapine</td>
<td>33</td>
<td>24.2</td>
<td>2.5-60</td>
</tr>
<tr>
<td></td>
<td>Quetiapine</td>
<td>57</td>
<td>346</td>
<td>25-1200</td>
</tr>
<tr>
<td></td>
<td>Risperidone</td>
<td>18</td>
<td>3.29</td>
<td>0.5-6</td>
</tr>
<tr>
<td></td>
<td>Aripiprazole</td>
<td>10</td>
<td>23.1</td>
<td>10-30</td>
</tr>
<tr>
<td><strong>Antipsychotics, intramuscular</strong></td>
<td>Perphenazine</td>
<td>4</td>
<td>203</td>
<td>108-270</td>
</tr>
<tr>
<td></td>
<td>Risperidone</td>
<td>4</td>
<td>48.8</td>
<td>25-50</td>
</tr>
<tr>
<td></td>
<td>Aripiprazole</td>
<td>2</td>
<td>400</td>
<td>400</td>
</tr>
<tr>
<td></td>
<td>Paliperidone</td>
<td>7</td>
<td>117</td>
<td>75-150</td>
</tr>
<tr>
<td><strong>Benzodiazepines</strong></td>
<td>Clonazepam</td>
<td>3</td>
<td>5.78</td>
<td>3-14</td>
</tr>
<tr>
<td></td>
<td>Oxazepam</td>
<td>26</td>
<td>39.5</td>
<td>7.5-135</td>
</tr>
<tr>
<td></td>
<td>Lorazepam</td>
<td>1</td>
<td>1.00</td>
<td>1</td>
</tr>
</tbody>
</table>

Recommended peroral maximum dosing ([pro.medicin.dk](pro.medicin.dk)):
Chlorprothixene 600mg/day, Clozapine 900mg/day, Olanzapine 40mg/day, Quetiapine 800mg/day, Risperidone 16mg/day, Aripiprazole 30mg/day, Clonazepam 6mg/day, Oxazepam 90 mg/day, Lorazepam 7.5mg/day.
Table 3: Comparison of psychopharmacological treatment by mean doses. Groups are compared by Wilcoxon signed-rank test.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>2013</th>
<th>2016</th>
<th>Z</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 85</td>
<td>n = 101</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Psychopharmacological treatment, Mean (SD)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antipsychotics [DDD]</td>
<td>1.67 (1.33)</td>
<td>1.78 (1.47)</td>
<td>0.43</td>
<td>.67</td>
</tr>
<tr>
<td>Benzodiazepines [DDD]</td>
<td>0.24 (0.72)</td>
<td>0.14 (0.32)</td>
<td>0.43</td>
<td>.67</td>
</tr>
<tr>
<td>Benzodiazepines [DE]</td>
<td>0.89 (2.53)</td>
<td>0.55 (1.82)</td>
<td>0.39</td>
<td>.69</td>
</tr>
<tr>
<td>Antipsychotics+Benzodiazepines [DDD]</td>
<td>1.91 (1.45)</td>
<td>1.92 (1.57)</td>
<td>0.05</td>
<td>.96</td>
</tr>
</tbody>
</table>

DDD: Defined Daily Doses; DE: Diazepam equivalents; SD: Standard Deviations
Figure 1: Flow diagram of study sample selection.
Figure 2: Standardized regression coefficients (beta estimates) for changes in use of psychotropic medication from 2013 to 2016 (n=1322 days) from mixed effects linear regression model with robust standard error estimation. Model is adjusted for age, gender, length of admission, substance abuse and involuntary admission. DDD: Defined Daily Doses; DE: Diazepam equivalents.