Reducing psychotropic pharmacotherapy in patients with severe mental illness: a cluster-randomized controlled intervention study

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Abstract

Background: Many patients with mental illness receive psychotropic medicine in high dosages and from more than one drug. One of the consequences of this practice is obesity, which is a contributing factor to increased physical morbidity and premature death.

Methods: Our study was a cluster-randomized intervention study involving 6 facilities and 174 patients diagnosed with severe mental illnesses (73% schizophrenia). The intervention period was 12 months and consisted of teaching sessions with the staff and evaluating the patients' intake of psychotropic medication. At index, 44% met criteria for obesity and 76% met criteria for overweight. Waist circumferences were 108 cm for men and 108 cm for women. Olanzapine, clozapine and quetiapine were the most common prescribed antipsychotics. Mean values of daily doses of antipsychotic were 2.5.

Results: The intervention showed no significant differences between the intervention and control group regarding psychotropic treatment. At follow up, independent of intervention, patients receiving antipsychotic polypharmacy had a larger waist circumference compared with patients receiving antipsychotic monotherapy of 9.8 cm (1.5–18.1) ($p = 0.028$).

Discussion and conclusion: We found both a high prevalence of obesity and that the patients received treatment with antipsychotic polypharmaceuticals in high dosages. Active awareness did not change practice and we must think of other ways to restrict treatment with psychotropics in this group of patients.

Keywords: cluster randomized intervention, mental illness, obesity, psychotropic polypharmacy

Introduction

Prescription of high doses and more than one antipsychotic drug to patients with mental illness is present in clinical practice regardless of the lack of approval by clinical treatment guidelines [Xiang *et al.* 2012; Moore *et al.* 2007; Goh *et al.* 2011; Procyshyn *et al.* 2010; Gardner *et al.* 2010; Tranulis *et al.* 2008]. The implications for patient's physical health could be unwanted side effects. The side effects and risk from antipsychotic drugs can be dose-related [Uchida *et al.* 2011] and it is important to use the lowest possible effective antipsychotic dose for prevention of relapse and to enhance overall treatment outcomes [American

Diabetes Association *et al.* 2004; Centorrino *et al.* 2004; Glick *et al.* 2006]. Long-acting antipsychotics can have advantages in reducing the severity of symptoms, a lower side effect profile and increasing patient compliance to medication [Lindenmayer *et al.* 2004].

Obesity is a major physical health problem in patients with severe mental illness [Leucht *et al.* 2007]. It has been explained by a sedentary lifestyle, unhealthy eating habits and the medication [Allison *et al.* 1999; Leucht *et al.* 2007]. In addition, patients with schizophrenia may have difficulty in changing an unhealthy lifestyle because of

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factors related to their illness and treatment [Hasnain and Vieweg, 2011]. Lower physical activity level could also be caused by negative symptoms, cardio-metabolic comorbidity, side-effects of antipsychotic medication and social isolation [Vancampfort *et al.* 2012].

Weight gain as a result of antipsychotic medication has been verified in clinical trials. While some antipsychotic agents are more likely than others to cause this side effect [Allison *et al.* 1999], the mean weight change found in clinical trials does not always mirror everyday observations. There is great individual variability regarding weight gain from antipsychotic products [(Allison *et al.* 1999; Parsons *et al.* 2009; Vanina *et al.* 2002)]. Furthermore, patients with severe mental illness do perhaps receive more than one drug, often in a higher dosage than recommended [Goh *et al.* 2011; Procyshyn *et al.* 2010]. Additionally, this group of patients typically uses antidepressants and anticonvulsants in combination with antipsychotics [Goh *et al.* 2011; Procyshyn *et al.* 2010]. Some of these psychotropics have been associated with weight gain [Vanina *et al.* 2002] and the total impact on the patient's weight can be considerable. Typical and atypical antipsychotics may lead to serious side effects such as extrapyramidal symptoms, tremor, rigidity, akathisia, sexual dysfunction, sedation and decreased physical activity, and rarer but nevertheless problematic side effects on the heart [Haddad and Anderson, 2002; Lindstrom *et al.* 2005].

Recommendations from the Danish National Board of Health concerning treatment with antipsychotic medication of patients with mental illness are intended to be a guide to clinicians and staff working in the area. The guidance advocates using antipsychotic monotherapy and as small dosage as possible in view of the effect and the side effects for the individual patient's psychiatric illness [Dons, 2007].

The present study was conducted in facilities where patients typically lived for several years. The results of the interventions on the physical health of patients are published in a separate paper [Hjorth *et al.* 2014]. The aim of the study was to quantify the use of psychotropic medication in patients with severe mental illness and to measure the effectiveness of an intervention to indirectly reduce psychotropic medication. In addition, the study investigated whether there was any

association between psychotropic medication and obesity in the included patients.

Methods

The study was designed as a cluster-randomized controlled-intervention study involving six facilities. All patients in the facilities were invited to participate in this 12-month study, which started in November 2009. Data were collected at index and this was repeated after 12 months. In cooperation with staff, the prescribed medication was registered before and after the intervention in order to secure accurate data about medication. Depot antipsychotics were included in the calculation of overall doses, taking dosing intervals into account. Data collection included all antipsychotics, antidepressants and mood stabilizers. Data on age, gender and diagnoses were obtained from the patient's charts. Patients' body mass index (BMI) and waist circumference were measured.

In order to be able to compare dosages of the various antipsychotics, measurement units were calculated by dividing the prescribed daily dose (PDD) by the defined daily dose (DDD). A PDD/DDD ratio >1.5 was defined as indication of an excessive dose [Nose *et al.* 2008]. Schizophrenia Patient Outcomes Research Team (PORT) recommended doses and DDD [Dixon *et al.* 2010] are given in Table 1.

The participants were 174 patients with severe mental illness living in six long-term facilities in Northern Jutland, Denmark, where they were offered specialized social psychiatric treatment for 24 hours a day. The participating patients had been mentally ill for years and it had not been possible for them to live in an acceptable way in their own home with external psychiatric help and nursing. The intervention was based on cluster-randomization of the six facilities. Three facilities were randomized into the intervention group and three facilities were randomized into the control group.

The patients in our study had previously been diagnosed by a psychiatrist, the most frequent diagnoses being schizophrenia (72% and 73% in the intervention and control groups, respectively). The remaining patients suffered from other severe mental illnesses, for example bipolar disorder, with equal distribution of disorders in the intervention and control groups. All patients were Danish nationals, the majority of Caucasian race

Table 1. DDDs and the Schizophrenia Patient Outcomes Research Team (PORT) recommended dose ranges of antipsychotic drugs for the maintenance treatment of schizophrenia.

Drug	DDD	PORT recommended dose range
Olanzapine	10 mg	10–20 mg
Clozapine	300 mg	300–800 mg
Quetiapine	400 mg	300–750 mg
Apripiprazole	15 mg	10–30 mg
Ziprasidone	80 mg	120–160 mg
Risperidone	5 mg	2–8 mg

except three patients, two being Inuit and one Indian.

All patients in the facilities were invited to participate in the study but some declined. The 77 who did not take part in the study were on average 11 years older than the participants. We had only limited data from this group of nonparticipants and it was not possible to say if or how they differ from the participating group. The nonparticipants were distributed among the interventions and control group with 42% and 46%, respectively.

Primary outcome variables were the number of DDDs of antipsychotics and changes in DDD during the intervention period. Secondary outcomes variables were DDDs of antidepressant medication and DDDs of mood stabilizer medication. Furthermore, we calculated the degree of polypharmacy and changes during the study period.

The randomization was done on facility level. The facilities were matched by the project leader based on the best fit of homogeneity with the size of the facility and the patients' diagnoses. The resulting pairs were randomized to either the intervention or the control group. Randomization was performed by a person with no knowledge or interest in facilities, patients or the study.

The intervention consisted of the following elements.

1. The project leader collected information about all participating patients' medication. The total daily doses and the degree of polypharmacy were presented to the leaders of the facilities and the staff in a discussion of medication to the patients.

2. Staff, the consulting psychiatrist and the project leader of this study reviewed each patient's medication compared with guidelines from the Danish National Board of Health [Dons, 2007] and the patient's physical health status. The intention was that educating the staff about psychotropics would enhance the cooperation between the staff and the consulting psychiatrists and, as a result, reduce treatment with psychotropics. The psychiatric consultants were not part of the staff but visited the facilities for psychiatric supervision and treatment. They were therefore peripheral to the intervention programme.
3. The project leader provided training lectures to the staff about the use of antipsychotic medicine according to guidelines from the Danish National Board of Health [Dons, 2007]. The staff had close contact with patients and therefore had the opportunity to evaluate the effectiveness and side effects of the medication on the individual patients and to pass their observations on to the psychiatrist in charge of the medication.
4. Focus group discussions were carried out with patients and staff members separately (each with 5–8 participants). The topics were health problems and methods for improving physical health.
5. Individual sessions were held with the patients to collect index data.
6. During the first third of the study period, 3 group sessions of 1.5 hours each with the staff were provided by the project leader about how to promote smoking cessation among patients and staff.
7. On the visits to the facilities the project leader constantly provided guidance to the staff on healthy food and about ways to maximize the patient's physical activity in daily living.

The control group received the usual treatment and no intervention took place except for initial collection of the patient's data.

For the dichotomous outcome (polypharmacy), we assumed that the frequency was 30% [Procyshyn *et al.* 2010]. Furthermore, we anticipated that the natural variation through the study period would involve a change of 10% of the patients from polypharmacy to

Table 2. Summary of patient characteristics at index ($n = 97$).

	Intervention		Control		p value
	Male (SD)	Female (SD)	Male (SD)	Female (SD)	Male/Female
Gender	58.8%	41.2%	50.5%	49.5%	0.262 (male + female)
Age	48.0 (13.6)	47.8 (11.1)	41.5 (12.4)	45.0 (17.9)	0.014/0.415
Years at facility	5.8 (4.9)	8.2 (8.2)	5.6 (4.5)	6.1 (6.1)	0.898/0.195
Fat (%)	26 (9)	41 (8)	31 (9)	42 (9)	0.019/0.779
Waist (cm)	106 (14)	108 (21)	112 (17)	109 (18)	0.032/0.845
BMI (kg/m ²)	27.9 (4.9)	31.9 (8.6)	30.0 (5.5)	31.6 (8.4)	0.050/0.916
Smokers	76%	66%	78%	52%	0.855/0.214
Cigarettes *	28 (11)	23 (10)	28 (17)	28 (11)	0.894/0.803
*Number of daily cigarettes among smokers. BMI, mass body index; SD, standard deviation.					

treatment with one drug or vice versa. We calculated that 80 patients in each of the two arms of the study would provide sufficient power on the 80% level for detection of a reduction in the intervention group of 18%. We anticipated some dropout from the study and assessed that a dropout of 20% would still provide sufficient power.

Initially, we compared men and women in the intervention and control groups with respect to different index characteristics. For dichotomous variables we used the chi-squared test of association while t -tests, or the nonparametric equivalent Wilcoxon rank sum test, were applied for continuous variables. The mean number of index DDDs in the intervention and control groups were compared in each of three primary drug classes (antipsychotics, antidepressants and mood stabilizing) as well as in the overall psychotropic drug class by either t -tests or Wilcoxon rank sum tests. We also compared the number of different types of medication in each drug class between the two groups using Fisher's exact test.

The difference in DDDs between index and follow up were analysed to determine if any change had occurred. In order to account for the study being cluster-randomized, we corrected these analyses by calculating intraclass correlation coefficients (ICCs) and adjusting the corresponding p values. Finally we performed linear regression analyses of several outcome measures with age, gender and antipsychotic polypharmacy as explanatory variables as well as a logistic regression analysis of antipsychotic polypharmacy with age, gender and smoking status as explanatory variables. All

regression analyses were adjusted in order to account for the study being cluster-randomized.

The statistical analyses were carried out using the statistical software Stata version 11 (StataCorp LP, College Station, Texas, USA); the chosen level of significance was 5%.

The study followed the Helsinki II Declaration and was approved by the North Jutland Committee on Biomedical Research Ethics (N-2008004MCH) and the Danish Data Protection Agency. All enrolled patients provided a written statement of informed consent.

Results

Of 174 patients, 97 participated; 12 dropped out during the 12-month study period, 3 died and 3 moved from the facilities. Six patients wanted to leave the study for various personal reasons. There were no differences in dropout rates between the intervention and control groups. The characteristics of included patients at index are given in Table 2.

Men and women were equally represented. Mean age was 45.2 years [standard deviation (SD) 14.5] and years of stay at the facilities were 5.6 years (SD 5.8). Of the patients, 44% were obese and the mean waist circumference ($\bar{x} = 108.4$ cm for men and 107.9 cm for women) was above the recommended values for men and for women. The men in the intervention group were on average 6.5 years older than those in the control group ($p = 0.014$). The men in the intervention group had lower percentages of body fat compared with those in the control group ($p = 0.02$).

Table 3. DDDs and percentages of excessive dosing at index.

DDD*	Intervention			Control			<i>p</i>
	<i>n</i>	Mean	SD	<i>n</i>	Mean	SD	Value
Antipsychotic	43	2.50	1.65	44	2.59	1.73	0.858
Antidepressant	21	1.77	0.76	33	1.76	0.83	0.986
Mood stabilizer	10	0.87	0.50	19	1.03	0.68	0.836
Psychotropic	44	3.49	1.88	49	3.90	2.02	0.241
PDD/DDD >1.5 ^a	28 (65.1%)			29 (65.9%)			0.937
*Patients with DDD = 0 are excluded.							
^a Antipsychotics medicine.							
DDD, defined daily dose; PDD, prescribed daily dose; SD, standard deviation.							

Medication

The number of DDDs of psychotropic medicine and percentages of excessive dosing of antipsychotic were measured at index (Table 3).

The mean ratios of antipsychotic PDD/DDDs were >2.5 and the mean ratios of PDD/DDD of antidepressants were 1.8. There were no statistical significant differences between the DDD in the intervention and control groups. The overall rate of antipsychotic excessive dosing, defined as a PDD/DDD ratio >1.5, was more than 65% for both intervention and control groups.

The percentages of numbers of psychotropic drugs at index are shown in Table 4.

Antipsychotic polypharmacy was associated with excessive dosing since the mean PDD/DDD ratio for patients receiving polypharmacy (3.25, SD 1.74) was higher than the mean in the group of patients receiving antipsychotic monotherapy (1.55, SD 0.93; $p < 0.001$).

Antipsychotic doses according to age group at index were calculated and the antipsychotic doses varied within the three age groups. Patients aged 40–60 years received, on average, 1 DDD more than younger or older patients. Patients over 60 received, on average, 2 DDDs of antipsychotic medication. Of the prescribed antipsychotic medicine, 71% was olanzapine, clozapine or quetiapine.

Linear regression analysis on follow-up data showed that the waist circumference of patients receiving antipsychotic polypharmacy was 9.8 cm (1.5–18.1) larger than those receiving antipsychotic monotherapy ($p = 0.028$). The increase in the BMI value in the group receiving

antipsychotic polypharmacy was 3.14 kg/m² (–0.18 to 6.46) ($p = 0.059$).

Logistic regression analysis on follow-up data of antipsychotic polypharmacy *versus* monotherapy and the status of smoker *versus* nonsmoker showed that smokers had an elevated risk of receiving polypharmacy of 3.0 (1.1–8.11) ($p = 0.028$). This finding was gender specific with an odds ratio for female gender of 0.3 (0.1–1.02) ($p = 0.054$).

Intervention results

We found no significant results, as there were no differences between the intervention and control groups.

The results of the analyses from index to follow up are presented in Tables 5 and 6.

Discussion

Findings

A high prevalence of obesity was found in the patients participating in the study and the use of antipsychotic medication with a known risk of side effect induced weight gain was common. The patients received antipsychotic polypharmacy to a great degree and in high dosages. Furthermore, we found that patients receiving polypharmacy were also at higher risk of obesity and, as a consequence, had an enhanced risk of related health problems such as type 2 diabetes and cardiovascular disease. The intervention, consisting of teaching sessions to the staff and evaluating the patients' intake of psychotropic medication according to guidelines from the Danish Board of Health, did not reduce the degree of polypharmacy or lower the total amount of psychotropic medication.

Table 4. Percentages of psychotropic medication at index.

Number and type of drugs	Intervention		Control		<i>p</i> values	
	<i>n</i>	%	<i>n</i>	%	chi-squared test	Fisher's test
0 antipsychotic	1	2.3	5	10.2	0.122	
1 antipsychotic	12	27.3	24	49.0	0.032	
2 antipsychotic	25	56.8	16	32.7	0.019	
3 antipsychotic	6	13.6	3	6.1	0.221	
4 antipsychotic	0	0.0	1	2.0	0.346	0.023
>1 antipsychotic	31	70.5	20	40.8	0.004	
0 antidepressant	23	52.3	16	32.7	0.056	
1 antidepressant	18	40.9	29	59.2	0.078	
2 antidepressant	3	6.8	4	8.2	0.799	0.163
0 mood stabilizer	34	77.3	30	61.2	0.094	
1 mood stabilizer	10	22.7	16	32.7	0.283	
2 mood stabilizer	0	0	3	6.1	0.096	0.532
0 psychotropic	0	0	0	0	-	
1 psychotropic	5	11.4	6	12.2	0.896	
2 psychotropic	17	38.6	19	38.8	0.989	
3 psychotropic	15	34.1	13	26.5	0.428	
4 psychotropic	5	11.4	10	20.4	0.236	
5 psychotropic	2	4.6	1	2.0	0.494	0.726
>1 psychotropic	39	88.6	43	87.8	0.896	

*Nonmedicated patients excluded.

Table 5. Changes in medication (DDD) between index and follow up.

Type of medication	Intervention		Control		ICC	Design effect	<i>p</i> value
	Mean	SD	Mean	SD			
Antipsychotic	0.05	1.01	-0.01	1.18	0.005	1.08	0.786
Antidepressant	0.10	0.53	0.13	1.34	0*	1.00	0.507
Mood stabilizer	-0.01	0.23	0.18	0.67	0.065	2.07	0.445
Psychotropic	0.15	1.22	0.22	2.00	0*	1.00	0.778

*ICC truncated at zero.

DDD, defined daily dose; ICC, intraclass correlation coefficient; SD, standard deviation.

In a recent review of the metabolic syndrome in patients with schizophrenia, the rate of obesity was in the range of 45–55% [De Hert *et al.* 2009]. This is in accordance with our finding of 44%. Studies of antipsychotic polypharmacy in outpatient settings have found rates ranging from 4 to 47% [Procyshyn *et al.* 2010]. In our study, there were rates of 72% and 46% in the intervention and control groups, respectively. A study from Singapore [Goh *et al.* 2011] showed that it was possible to lower the average number of DDDs of antipsychotic medicines from 2.9 to 2.3, although the latter number is high

and far from recommendations. Our study found the average number of antipsychotic DDDs to be 2.5 and 2.6 in the intervention and control groups, with no reduction as a result of intervention.

One rationale for antipsychotic polypharmacy could be that using lower doses of two agents with different receptor profiles and different side effect profiles could possibly achieve efficacy with less severe side effects than would be expected from higher dosage of a single agent. This was not seen in our study, where the mean PDD/DDD ratio for patients

Table 6. Changes in no polypharmacy/polypharmacy between index and follow up.

	Intervention		Control		<i>p</i> value
	<i>n</i>	%	<i>n</i>	%	
Antipsychotic					
Poly-> no poly	5	11.4	4	8.2	0.227
no change	38	86.4	39	79.6	
no poly-> poly	1	2.3	6	12.2	
Antidepressive					
Poly-> no poly	1	2.3	2	4.1	>0.999
no change	43	97.7	46	93.9	
no poly-> poly	0	0	1	2.0	
Mood stab					
Poly-> no poly	0	0	0	0	0.527
no change	44	100	48	98	
no poly-> poly 0	0	0.0	1	2.0	

receiving antipsychotic polypharmacy (3.25, SD 1.74) was higher than the mean dose for antipsychotic monotherapy (1.55, SD 0.93) ($p < 0.001$).

Patients receiving antipsychotic polypharmacy had an increased value of waist circumference of 9.81 cm (1.54–18.08) compared with those receiving antipsychotic monotherapy ($p = 0.028$). Regarding BMI, the increase was 3.14 kg/m² (-0.18 to 6.46) ($p = 0.059$).

The high prevalence of smoking among patients in our study may increase the need for medication at a higher level in view of the fact that smoking is a potent inducer of CYP1A2 enzyme activity. Additionally, we found that smokers *versus* non-smokers had an elevated risk of receiving polypharmacy, with an odds ratio of 3.02 (1.13–8.09) ($p = 0.028$). Thus it will be of importance to prevent smoking and to achieve smoking cessation among patients as part of the effort to reduce the total amount of psychotropic medication.

Strengths and limitations

Data on medication were collected by the project leader in close cooperation with the staff in charge of the individual patients. The data represent the actual intake of medicine, since adjustment was made for deviations from the prescribed medication.

For some control group patients, the project leader found a level of medication above any recommended level. For professional and ethical reasons this was discussed with the psychiatric

consultant and staff to ensure there were relevant indications. This interference in the control group may have influenced the results.

The study did not succeed in reaching the planned number of 80 patients in each arm of the study and the assumption of 18% reduction of degree of polypharmacy in the intervention group may have been too optimistic. Absence of statistical power could possibly be one of the reasons for some of the results in our study not reaching statistical significance.

Comparison of our study findings with those of other studies must be made with caution due to differences in study design, intervention and population. We must, nevertheless, be aware of these findings. The excessive doses associated with antipsychotic polypharmacy should raise concern about the potentially serious side effects.

Perspectives

Of interest is that the economic incentive to minimize overuse of medication was limited in this Danish context, as there was no cost associated with psychotropic medicines, either to the individual patients or to the facility, because the Danish healthcare system in practice subsidises medication to this group of patients. Nevertheless, polypharmacy ultimately adds a cost burden to taxpayers [Zhu *et al.* 2008]. This is seen in a study of US Medicaid programmes, where cost savings from limiting antipsychotic polypharmacy could be considerable [Valuck *et al.* 2007]. Another study

within the California Medicaid programme showed that antipsychotic polypharmacy was the most expensive form used in the programme [Stahl and Grady, 2006].

The problem with obesity and the high dosing of psychotropic medication to patients who in many ways are dependent on professional help and guidance is of importance. This study found that the patients treated with antipsychotic polypharmacy in high dosages had a high prevalence of obesity. It is thus essential in the overall treatment and care plan to enhance the physical health of patients with severe mental illness. As the intervention tested did not work, we must think of new ways to restrict the use of psychotropic medicine, perhaps introducing sanctions from the national health boards to counteract overuse. Furthermore, the treatment and care of this group of patients is multifaceted and complex, and does not only consist of medication. Cognitive and behavioural therapies are an integral part of the treatment effort and it is important to include these therapies in the overall treatment programme to the patients. This study has shown that it is relatively easy to register and monitor data on the usage of psychotropic medication. This would be an essential start in managing the use of psychotropic medication in a desirable way in the future.

Conclusion

We found high prevalence of obesity and that the patients received antipsychotic polypharmaceuticals in high dosages. Active awareness did not change practice and we must think of other ways to restrict treatment with psychotropics to this group of patients.

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Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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