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Changes in antipsychotic and other psychotropic drugs during a 30-month lifestyle intervention among outpatients with schizophrenia

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Abstract

Background

Patients with schizophrenia have high risk of early death from diabetes and cardiovascular diseases, partly because of poor lifestyle and partly because of long-lasting exposure to antipsychotic treatment.

Aims

To investigate the influence of a lifestyle intervention programme on changes in psychotropic medication in a non-selected cohort of patients with schizophrenia.

Methods

Observational study of outpatients in the Central Denmark Region during a 30-month lifestyle programme.

Results

One hundred and thirty-six patients were enrolled and 130 were available for analysis. Median follow-up time was 15.9 months (range 1–31 months). Nineteen patients (15%) were not treated with antipsychotic drugs during the study period. 54% of the 111 patients exposed to antipsychotics were subject to monotherapy at index and at follow-up. The median defined daily dose (DDD) of antipsychotics was 1.33 at index (interquartile range (IQR) 0.67–2.00) and 1.07 at follow-up (IQR 0.40–1.50). 52% of the patients experienced a decrease in DDD during the study period (median change –0.33; IQR –1.00 to 0.43). There were no significant differences between the patients with decreased, stable or increased DDD with regard to age, sex, follow-up time and time since diagnosis. The number of prescriptions was significantly higher in the patients who decreased their DDD and the proportion of antipsychotic depot formulation was higher in those who increased their DDD.

Conclusions

Most patients decreased or stabilised their total dose of antipsychotic medication during the study period. Many patients were subject to antipsychotic polypharmacy. The extent of participation in the lifestyle intervention programme did not correlate with the changes in dosing of antipsychotic medication.

Keywords: Schizophrenia, Antipsychotics, Polypharmacy, Morbidity, Lifestyle intervention

Background

Excess mortality among patients with schizophrenia is well documented [1, 2, 3, 4, 5]. This population has a threefold higher risk of dying from complications from diabetes and cardiovascular diseases (CVD) than the general population [5]. This is partly because of poor lifestyle with inactivity, smoking, excess caloric intake and substance abuse, and partly because of long-lasting exposure to antipsychotic treatment, which can induce obesity, dyslipidaemia and metabolic syndrome [6, 7]. All these risk factors lead to CVD and premature death if they are not treated [8], and both the positive and negative symptoms of schizophrenia themselves might complicate treatment of somatic comorbidities and the necessary changes in lifestyle.

High doses of antipsychotic medication and psychotropic polypharmacy is part of clinical everyday life in Denmark [9]. In particular, second-generation antipsychotics may result in weight gain and subsequent metabolic syndrome [6, 10], whereas others have more acute effects, such as prolongation of QT interval [11]. Polypharmacy is a common treatment approach in the attempt to stabilise the symptoms of schizophrenia and to avoid side effects, but is generally not recommended, owing to lack of evidence of both efficacy and safety [12, 13, 14].

Inspired by European and Danish initiatives [15, 16, 17], a lifestyle modification project was initiated in the Central Denmark Region. The overall purpose of this project was to improve the physical health among people with severe mental illness and thereby lower the risk of early death from somatic causes [18]. The project is also an attempt to apply effective interventions to routine clinical practice for the benefit of the patients [19]; for example, weight loss has been proved to be attainable through group-based intervention [15], psychosocial interventions [20] and physical exercise [21] have been suggested effective in reducing psychiatric symptoms among patients with schizophrenia.

Our hypothesis for the present substudy to the overall programme [18] is that the lifestyle intervention programme could possibly lower the need for antipsychotic medication through positive impact on psychotic symptoms from physical exercise [21] and psychosocial interventions [20]. Data from this project provide us with a unique view of actual medication practice and changes during a focused intervention against modifiable risk factors of CVD.

Aims

The aim of this study was to investigate the influence of a lifestyle intervention programme on changes in antipsychotic medication and psychotropic polypharmacy in a non-selected cohort of patients recently diagnosed with schizophrenia.

Material and methods

Design:

This was a 30-month observational study of patients with schizophrenia referred to one of two outpatient psychosis units (OPUS) in the Central Denmark Region. The present study is a substudy to the overall programme [18].

Sample:

The sample included patients referred to one of the two participating OPUS centres. All participating patients had their diagnosis of schizophrenia validated by psychiatric specialists according to World Health Organization Diagnostic Research Criteria [22]. Some patients were not diagnosed with schizophrenia at the time of referral, as they had only been seen by general practitioner, physicians in the emergency department, or at other departments of the hospital, but were referred to the clinic on the suspicion of schizophrenia or schizophrenia-spectrum disorders. These patients were diagnosed with schizophrenia during the study period. Patients were enrolled from January 2013 to March 2015 and follow-up was completed in June 2015. The treatment at OPUS centers is a specialized early intervention program treating patients with a first episode of psychosis for 2 years following diagnosis. It consists of assertive community treatment, psychoeducational family intervention and social skills training, in addition to the ordinary psychiatric treatment [23].

Intervention:

Intervention began at enrolment and consisted of three different parts: i) individual consultations with a health professional, consisting of registration, and motivational interviewing regarding dietary habits (21), physical exercise, alcohol consumption and smoking cessation; ii) exercise groups with running, walking or other physical activities conducted by staff; and iii) group sessions held weekly with 8–10 patients consisting of both education and discussion of the same topics as the individual consultations (only at one centre). All patients were continuously scheduled for monthly consultations during the entire project period.

Data:

All data were collected at clinical interviews. The interviews were conducted at first visit in the outpatient clinic (index date) and at subsequent, scheduled consultations. Information on age, sex, diagnosis (psychiatric and somatic) and medical prescriptions were obtained from the case records. Both fixed and pro necessitate doses were recorded. The type and extent of the different interventions were recorded in conjunction with the intervention.

Statistical analysis:

Descriptive statistics regarding patient demographics and clinical characteristics were calculated for all patients. Follow-up time was defined as time from first to last visit at the outpatient clinic in relation to the project. Drug consumption was recorded as number of prescriptions and intake method. All doses of psychotropic medication were converted to daily defined doses (DDD) according to the World Health Organization tables [24], and changes in total doses of antipsychotic drugs were calculated as difference between index and last follow-up visit. Patients were stratified into groups of decrease, stability and increase of antipsychotics based on their change in total dose from index to follow-up, with decrease and increase defined as change of more than -0.25 DDD and $+0.25$ DDD, respectively, from total dose at index.

In order to analyse if there was any relation between participation in the interventions and drug consumption, we used different analysis methods: several tests for equal proportion of patients in each group (decrease, stable, increase) were performed, for example the hypothesis that an equal proportion of patients in each group received depot medication. The chi-square goodness-of-fit test for contingency tables was used, for example testing the hypothesis of equal chance that a patient is in one of the four groups. Usual the Kruskal–Wallis test for non-normal data was used for various hypotheses, for example testing if the mean drug consumption was equal for each group. All calculations were performed with STATA version 12.1 (StataCorp, College Station, TX, USA) and R version 3.1.1.

Ethics:

The study followed the principles of the Declaration of Helsinki and was approved by the Science Ethics Committee in the Central Denmark Region as a quality insurance study (No. 197/2012). The database was approved by the Data Protection Agency (No 2007-58-0010).

Results

All 136 patients treated at the outpatient clinics during the inclusion period agreed to participate in the programme. Seventy-two patients were enrolled from centre 1 (53%), and 64 from centre 2 (47%). Of these, 133 (98%) had a diagnosis of schizophrenia (F20) at the time of enrolment, and the remaining three (2%) were diagnosed with schizophrenia during the study period. Ten patients (7%) received another formal diagnosis than schizophrenia at discharge, mainly substance abuse, anxiety or personality disorders. Six patients were lost to follow-up and therefore were not included in further analyses. The median follow-up time was 15.9 months (range 1–31 months), and the mean number of consultations during the project period was 4.1 (SD 5.1). Data on age, sex and time since diagnosis are provided in Table 1.

Medication:

Twenty-seven patients (21%) did not receive antipsychotic treatment at index. At follow-up the number of patients not receiving antipsychotic treatment was also 27 (21%). Some of these patients may have been prescribed antipsychotics at an earlier or later time point in the follow-up period. The number of patients who did not receive any antipsychotic treatment at any time during the study period was 13 (10%). Six patients did not have sufficient data on type or dose of antipsychotic prescriptions, leaving 111 patients with prescriptions for further analysis. Most patients (54%) received one antipsychotic drug at both index and follow-up, and antipsychotic polypharmacy was present in 33% of the patients at follow-up (Table 2). Antidepressants (citalopram, sertraline and venlafaxine) and mood stabilisers (lamotrigine and pregabalin) were the most used adjuvants (39% and 19%, respectively). Only a small number of patients were exposed to benzodiazepines (5%) and non-benzodiazepine hypnotics (10%) at any time during the study period (Table 2). In the patients receiving antipsychotic monotherapy throughout the study period, most remained on the same drug. Among these patients the most commonly prescribed drugs were aripiprazole, quetiapine and risperidone. For patients changing drugs during the study period, this switch was most often to aripiprazole in low to moderate doses (5-20mg/day). In patients prescribed quetiapine, most patients switched from fixed to a lower, flexible dosing (50-700mg/day). Among all patients the median antipsychotic dosing in prescribed daily doses was 1.33 DDD at index (interquartile range (IQR) 0.67 to 2.00) and 1.07 DDD at follow-up (IQR 0.40 to 1.50) with a median change of -0.33 DDD (IQR -1.00 to 0.43) and little difference between centres (see Figure 1 and Table 2). Among patients

receiving antipsychotic monotherapy at index the median prescribed daily dose at index was 1.07 DDD (IQR 0.60 to 1.67) with a median change of 0.00 DDD (IQR -0.67 to 0.53) during the project period (mean change -0.09 DDD (SD 0.88)).

Subgroup analysis:

Fifty-eight patients had a decrease of more than 0.25 DDD and were allocated to the “decrease” group. Seventeen patients had changes within ± 0.25 DDD during the study period and were allocated to the “stable” group. Lastly, 36 patients had increases of more than 0.25 DDD and were allocated to the “increase” group. Subsequent analyses of the extent of participation in the interventions revealed no significant difference between mean total numbers of interventions received (Table 3).

Subgroups were compared regarding possible confounders, such as presence of psychotropic polypharmacy other than antipsychotics, antipsychotic polypharmacy, numbers of psychotropic prescriptions, number of antipsychotic prescriptions, antipsychotic medication in depot formula, age at enrolment, male sex, follow-up time, and time since diagnosis. These comparisons did not reveal any significant trend except for the number of prescriptions of psychotropics and antipsychotics (Table 3).

Discussion

In this naturalistic study among patients with schizophrenia, subject to a lifestyle intervention program, we found that most patients experienced a decrease or no change in their antipsychotic treatment. The proportions of patients with decreasing or stable doses differed somewhat between centres. This is a positive finding when taking the potential side effects of antipsychotics into account. We also found that there was no specific association between changes in antipsychotic treatment and extent of participation in the intervention.

Most of the patients were subject to antipsychotic monotherapy, but one-third of the patients received more than one antipsychotic drug at follow-up. As most of these patients are newly diagnosed, and might be in an acute phase of their illness, we would expect a higher degree of antipsychotic polypharmacy, high doses and/or frequent changes of drugs in order to lower the psychotic symptoms and improve general functioning. We would have expected a higher degree of polypharmacy in the subgroup with increasing doses of antipsychotic drugs, but found no significant difference in the proportion of

antipsychotic polypharmacy, but instead an unexpected significantly lower mean number of antipsychotic prescriptions (table 3). Monotherapy, in approved doses, is recommended in the national guidelines, and the use of more than one antipsychotic drug is only recommended in the case of treatment-resistant schizophrenia, after failure to treat with clozapine [25, 26, 27]. The rationale behind this algorithm is that combinations are not properly examined [28, 29], and that combinations generally lead to higher total dose with the subsequent risk of adverse effects [26]. Polypharmacy has not been clearly associated with increased mortality [30], but evidence is generally conflicting or insufficient [13]. In this light the practice of polypharmacy is not desirable, and we find it positive that the proportion is not greater than the present numbers.

The use of other psychotropic adjuvants was also present in up to one-third of the patients. Antidepressants and mood stabilisers were the most common drugs used, and this might be because these patients were recently diagnosed, and had been treated for other psychiatric disorders before the diagnosis of schizophrenia was established. Selective serotonin reuptake inhibitors are recommended in antipsychotic treatment when schizophrenia is dominated by negative symptoms, but the evidence of efficacy is only modest [26, 31, 32, 33]. Evidence of mood stabilisers as an effective adjuvant is limited [27], and they are generally not recommended [26]. Only a small number of patients were exposed to benzodiazepines, and this proportion did not change during the study period. The number of exposed patients was too small to examine the relationship with changes in antipsychotic dose. We would have expected a larger proportion of benzodiazepine exposure in the “increase” group. Benzodiazepines are valuable in the treatment of schizophrenia as they have a multitude of uses from treatment of agitation to management of akathisia [27]. Long-lasting benzodiazepine use has, besides well known problems with dependency, been associated with both increased mortality [30] and dementia [34], and is therefore not desirable.

We found no significant difference in the number or type of interventions received when comparing patients with decrease, stability or increase in doses of antipsychotic medication. It is possible that the interventions have a general impact on the doses of antipsychotic medication across groups, which we, however, were not able to assess. Other studies of lifestyle interventions have found that both extent and type are associated with the effect on different parameters: Size of weight loss has been correlated to the number of interventions [15, 35], and effect on psychiatric symptoms have been correlated

to type and duration of exercise interventions [21]. From the findings of this present study, we cannot conclude if the lifestyle intervention has positively influenced the symptoms of schizophrenia, and hereby lead to lower exposure to antipsychotic drugs. We know from other substudies within this framework that the lifestyle intervention in this project has the ability to heighten quality of life – both in patients with severe mental illness and concurrent substance abuse [36], but also in patients with schizophrenia specifically [37]. We also know that the ability to improve physical health has been limited with the intervention in its present form [38], and that this calls for further development of lifestyle interventions for this group of patients.

Possible confounders for the course of psychosis did not differ significantly between groups, except for the number of prescriptions and the proportion of depot formulation of antipsychotic treatment, which was largest in the “increase” group. No single factor has been clearly associated with remission of schizophrenia or with effect of antipsychotic treatment. Male sex and young age at diagnosis have been suggested to correlate negatively with prognosis and effect of treatment [39, 40].

Strengths and limitations:

The naturalistic design provides us a unique and detailed view of psychopharmacological treatment of schizophrenia in a non-selected population. A relatively long study period was possible in this project because of the set-up within routine work at regional clinics. This allowed us to include as many relevant subjects in the geographical area as possible, thus reflecting real-life clinical practice. The dropout rate during the study period was remarkably low, when taking into account the fact that patients with psychotic disorders can show low adherence to treatment in general.

We did not have any information on disease severity and of the sufficiency of the prescribed antipsychotic medication. Our prerequisite is that the treatment is based on the psychiatrist's clinical judgement, and therefore is as sufficient as possible. Registered prescriptions is not an exact measure of exposure, but, practically, is the most obtainable measure when working with outpatients who do not have their medication administered by hospital staff. Cross-titration when switching antipsychotic treatment would, wrongly, be classified as polypharmacy, and therefore we only assessed this parameter at index and at follow-up, to avoid false large numbers. Cut-off values for stratification based on changes in antipsychotic treatment were arbitrary, but was considered a relevant approach because

of the exploratory nature of this study. As a real-life quality assurance programme we were not allowed to contact the patients after discharge. It is our ambition to ask the science ethical committee for permission to perform a long-term follow-up at a later occasion.

Conclusions

This study demonstrates that most patients will need lower doses of antipsychotics over time, and that many are prescribed adjuvants such as antidepressants and mood stabilisers during treatment in an outpatient psychosis unit.

The extent of lifestyle intervention is not clearly associated with a decreasing need for antipsychotic medication. The effect of lifestyle intervention might have an impact on other parameters, which other, on-going subprojects in this framework project will show.

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Disclosure of interest

None of the authors have any conflicts of interest to declare.

Table 1: Summary of patient characteristics at baseline (N = 136)

<i>Variable</i>		
Mean age, years (range)	28	(20-53)
Sex, No. (%)		
Male	86	(63)
Female	50	(37)
Psychiatric diagnosis at index, No. (%)		0
Schizophrenia (F20)	133	(98)
No psychiatric diagnosis	3	(2)
Time since diagnosis, years (range)		
Mean (N=126)	3.47	(0-26)
Centre, No. (%)		
Centre 1	72	(53)
Centre 2	64	(47)

Table 2: Summary of psychopharmacological treatment during study period (N=111)

<i>Variable</i>	<i>Index</i>		<i>Follow-up</i>	
Type of antipsychotic treatment, No. (%)				
Any	100	(90)	98	(88)
Oral	90	(81)	71	(64)
Depot	14	(13)	29	(26)
Pro necessitate	33	(30)	33	(30)
Dose of antipsychotic treatment				
PDD of antipsychotics, median (IQR)	1.33	(0.67-2.00)	1.07	(0.40-1.50)
Excessive dosing*, No. (%)	36	(32)	24	(22)
Number of prescriptions, No. (%)				
1 antipsychotic [§]	60	(54)	60	(54)
2 antipsychotics	30	(27)	32	(28)
3 antipsychotics	10	(9)	6	(5)
>1 antipsychotic	40	(36)	38	(33)
1 psychotropic [%]	40	(36)	36	(32)
2 psychotropics	33	(30)	32	(29)
3 psychotropics	17	(15)	18	(16)
4 psychotropics	10	(9)	7	(6)
>4 psychotropics	5	(5)	7	(6)
Non-antipsychotic co-medication, No. (%)				
Antidepressant (N06A)	37	(33)	31	(28)
Mood stabiliser (N03)	15	(14)	19	(17)
Hypnotic (N05C)	6	(5)	6	(5)
Benzodiazepine (N05B)	3	(3)	3	(3)
Psychostimulant (N06B)	3	(3)	4	(4)
Substance abuse treatment (N07B)	2	(2)	5	(5)
Anticholinergic (N04)	3	(3)	4	(4)
PDD: Prescribed Daily Dosing.				
IQR: Interquartile Range.				
* Excessive dosing is defined as total prescribed daily dose > 150% of WHO daily defined dose (DDD)				
§ Antipsychotics is defined as prescriptions from ATC-group N05A				
% Psychotropics is defined as prescriptions from any subgroup within the ATC-group N				

Table 3: Comparison of groups based on changes in prescribed daily dose (PDD) of antipsychotic medication between baseline and follow-up (N=111)

Variable	Decrease (N=58)		Stable (N=17)		Increase (N=36)		p-value
	Mean	Range	Mean	Range	Mean	Range	
Total number of interventions	4.31	0-32	3.94	0-12	5.19	0-19	0.63%
Psychotropic* polypharmacy, No. (%)	58	100 %	17	100 %	30	83 %	0.001\$
Antipsychotic§ polypharmacy, No. (%)	26	39 %	5	29 %	9	25 %	0.12\$
Antipsychotic§ depot formulation, No. (%)	19	28 %	2	12 %	14	39 %	0.13\$
Number of psychotropic* prescriptions, mean (range)	5,0	2-14	3.8	2-8	2.8	0-8	<0.001%
Number of antipsychotic§ prescriptions, mean (range)	1.6	1-3	1.3	1-2	1,0	0-3	0.003%
Age, mean (range)	26.6	18-51	26.2	19-41	23.6	18-33	0.26%
Male sex, No. (%)	35	60 %	8	47 %	26	72 %	0.19_
Follow-up time, Mean (range)	1.4	0-2.6	1,4	0.2-2.4	1,5	0.5-2.5	0.76%
Time since diagnosis, Mean (range)	5.9	0.9-28.9	5.1	0.5-17.0	4.1	1.0-16.0	0.21%

PDD: Prescribed Daily Dosing. Change in PDD during study period is <-0.25DDD for decrease, -0.25 to 0.25DDD for stable, and >0.25DDD for increase group.

* Psychotropics is defined as prescriptions from any subgroup within the ATC-group N

\$ Antipsychotics is defined as prescriptions from ATC-group N05A

% Kruskal–Wallis test

§ Proportionality test

_ Goodness of fit

Figure 1: Changes in total prescribed daily doses (PDD) of antipsychotic medication between baseline and follow-up in total (upper half) and at both centres (lower half).

